3rd EDITION

ASPEN
Pediatric Nutrition Support
Core Curriculum

EDITOR-IN-CHIEF Mark R. Corkins, MD

ASSOCIATE EDITORS Elizabeth Bobo, MS, RD · Michael L. Christensen, PharmD · Catherine Larson-Nath, MD · Robin Nuse Tome, MS, RD · Steve Plogsted, PharmD

ASPEN PEDIATRIC NUTRITION SUPPORT CORE CURRICULUM, 3rd Edition

ASPEN PEDIATRIC NUTRITION SUPPORT CORE CURRICULUM, 3rd Edition

EDITOR-IN-CHIEF

Mark R. Corkins, MD, FAAP, FASPEN
Division Chief of Pediatric Gastroenterology
University of Tennessee Health Science Center/Le Bonheur Children's Hospital
Memphis, TN

ASSOCIATE EDITORS

Elizabeth Bobo, MS, RD, LDN, CNSC, FAND
Senior Clinical Dietitian
Department of Gastroenterology and Nutrition
Nemours Children's Health
Jacksonville, FL

Michael L. Christensen, PharmD, BCNSP
Professor Emeritus
University of Tennessee Health Science Center
Memphis, TN

Catherine Larson-Nath, MD, CNSC
Associate Professor, Pediatric Gastroenterology, Hepatology, and Nutrition
University of Minnesota Medical School
Minneapolis, MN

Robin Nuse Tome, MS, RD, CSP, LDN, CLC, FAND
Senior Clinical Dietitian
Department of Clinical Nutrition Services
Nemours Children's Health
Wilmington, DE

Steve Plogsted, PharmD, FASPEN
Nutrition Support Pharmacist
Dublin, OH

AMERICAN SOCIETY FOR PARENTERAL AND ENTERAL NUTRITION

Copyright © 2025 by the American Society for Parenteral and Enteral Nutrition (ASPEN). All rights reserved. Except as permitted under the United States Copyright Act of 1976, no part of this publication may be reproduced or distributed in any form, including but not limited to, the process of scanning and digitization, or stored in a database or retrieval system, without prior written permission from the publisher.

Published by ASPEN, 8401 Colesville Road, Suite 510, Silver Spring, MD 20910
https://www.nutritioncare.org
aspen@nutritioncare.org

Library of Congress Cataloging-in-Publication Data

LCCN 2024001591 (print)
LCCN 2024001592 (ebook)

LC print book record available at https://lccn.loc.gov/2024001591
LC ebook record available at https://lccn.loc.gov/2024001592

ASPEN is a scientific society whose members are dietitians, nurses, pharmacists, physicians, scientists, students, other health professionals, and researchers who envision an environment in which every patient receives safe, efficacious, and high-quality nutrition care. ASPEN's mission is to improve patient care by advancing the science and practice of clinical nutrition and metabolism.

NOTE: This publication is designed to provide accurate authoritative information regarding the subject matter covered. It is sold with the understanding that the publisher is not engaged in rendering medical or other professional advice. Trademarked commercial product names are used only for education purposes and do not constitute endorsement by ASPEN.

This publication does not constitute medical or professional advice and should not be taken as such. Use of the information published herein is subject to the sole professional judgment of the attending health professional, whose judgment is the primary component of quality medical care. The information presented herein is not a substitute for the exercise of such judgment by the health professional.

ISBN: 9781889622569
eISBN: 9781889622576

Contents

List of Tables and Figures

Preface

Acknowledgments & Dedication

PART I
INTRODUCTORY AND BASIC PHYSIOLOGY

1. Mechanics of Nutrient Intake
Mark R. Corkins, MD, CNSC
Carol G. McKown, DDS, MS, PC
Memorie M. Gosa, PhD, CCC-SLP, BCS-S

2. Principles of Feeding and Gastrointestinal Motility
Molly Dienhart, MD
Jane Balint, MD
Desale Yacob, MD

3. Carbohydrates
Suzanna L. Attia, MD, MScPH

4. Fats
Peggy R. Borum, PhD

5. Protein Digestion, Absorption, and Metabolism
Oscar R. Herrera, PharmD
Richard A. Helms, PharmD

6. Minerals

Winston Koo, MBBS, FACN, CNS
May Saba, PharmD, BCNSP
Letitia Warren, RD, CSP
Mirjana Lulic-Botica, PharmD, BCPS

7. Water-Soluble Vitamins and Related Compounds

Winston Koo, MBBS, FACN, CNS
Judith Christie, RN, MSN
May Saba, PharmD, BCNSP
Letitia Warren, RD, CSP
Mirjana Lulic-Botica, PharmD, BCPS

8. Fat-Soluble Vitamins

Winston Koo, MBBS, FACN, CNS
May Saba, PharmD, BCNSP
Mirjana Lulic-Botica, PharmD, BCPS
Judith Christie, RN, MSN

9. Fluids and Electrolytes

Gerald L. Schmidt, PharmD, BCNSP

PART II
AGE-SPECIFIC NUTRITION FOR GROWTH AND DEVELOPMENT

10. Nutrition and Early Development

Ricardo Rueda, MD, PhD
Paula Soriano, MSc
Esther Castanys-Muñoz, PhD
José M. López-Pedrosa, PhD
Yen-Ling Low, PhD

11. Human Milk Feeding and Clinical Considerations

Christina J. Valentine, MD, MS, RD, FAAP, FASPEN
Amy Gates, PhD, RDN, LD

12. Infant Formulas and Complementary Feeding

Kelly Green Corkins, MS, RD, LDN, CNSC, FAND, FASPEN
Lindsey Lee, MS, RD, LDN, CSP

13. Enteral Formulas

Kelly Green Corkins, MS, RD, LDN, CNSC, FAND, FASPEN

14. Childhood Overweight and Obesity: Efficacy and Safety of Popular Diets and Weight-Control Programs

David Freestone, DO

15. Lipid Disorders

Elizabeth L. Wright, MS, RDN, CSP, LDN, FAND, CLC
Danielle H. Campbell, MS, RDN, LDN
James Gherardi, BS, DTR

PART III
DISEASE STATES AND NUTRITION

16. Severe Neurological Impairment

Gina Rempel, MD, FRCPC, FASPEN

17. Eating Disorders

Mary Pat Turon-Findley, MEd, RD, CMHIMP, LD

18. Food Allergies

Mary Beth Feuling, MS, RD, CSP, CD
Leslie M. Gimenez, MD
Nicole M. Martin, RD, CSP, CD
Praveen S. Goday, MBBS

19. Diabetes Mellitus and Other Endocrine Disorders

Michelle Reed, MS, RD, CSP, LDN, CDCES

20. Inborn Errors of Metabolism

Sandy van Calcar, PhD, RD, LD

21. Cardiac Disease

Kavisha Shah, MD

22. Renal Disease

Christina L. Nelms, MS, RD, LMNT/LD
Marisa Juarez-Calderon, MPH, RD, CSP, LD
Bradley A. Warady, MD

23. Gastrointestinal Disease

Jill Dorsey, MD, MS
Donald George, MD
Elizabeth Bobo, MS, RD, LDN, CNSC, FAND

24. Hepatic Disease

Julie Bonn, MD
Samuel A. Kocoshis, MD

25. Intestinal Failure

Vikram Raghu, MD, MS
Kishore R. Iyer, MBBS, FRCS (Eng), FACS

26. Pulmonary Disorders

Laura Padula, MS, RD, LDN
Rachel Kofsky, MA, RD, CSP, LDN, CLC
Maria Mascarenhas, MBBS

27. Pediatric Oncology and Hematopoietic Stem Cell Transplant Patients

Hannah Williams, RD, LDN, CSP, CSO
Bethany Squillante, MS, RD, CSP, LDN
Darielle Wilhelm, RD, LDN, CNSC
Karen Smith, MS, RD, CSO, LD/LDN
Erika May Murphy, PharmD, BCPPS
Susan Rheingold, MD

28. Trauma and Burns

Arlet G. Kurkchubasche, MD

29. Surgery

Arlet G. Kurkchubasche, MD

PART IV
NUTRITION CARE

30. Assessment of Nutrition Status by Age and Determining Nutrient Needs

Ellen Wagner, MD
Timothy Sentongo, MD

31. Nutrition Access

Katina Rahe, RN, BSN, CPN

32. Enteral Nutrition Support

Jessica Monczka, RD, CNSC
Sarah Simental, MS, RD, CSNC, CSPCC

33. Parenteral Nutrition Support

Kathleen M. Gura, PharmD, FASHP, FPPA, FASPEN, FMSHP, BCNSP
Catherine M. Crill, PharmD, FCCP, BCPS, BCNSP

34. Evaluation and Monitoring of Pediatric Patients Receiving Specialized Nutrition Support

Elaina Szeszycki, PharmD, CNSC
Wendy Cruse, MMSc, RDN, CSPCC
Clare McLaughlin, RDN, CSPCC

35. Ethical Issues in Providing Nutrition

Kelly Cronin Komatz, MD, MPH, FAAP, FAAHPM

Contributors

Reviewers

List of Tables and Figures

TABLES

TABLE 1-1. Primary Teeth by Age of Eruption

TABLE 1-2. Permanent Teeth by Age of Eruption

TABLE 1-3. Varibar Products and Equivalent IDDSI Framework Level/Name

TABLE 5-1. Gastrointestinal Regulatory Peptides

TABLE 5-2. Essential, Nonessential, and Conditionally Essential Amino Acids in Human Nutrition

TABLE 5-3. Modification of Amino Acid Classification in Humans

TABLE 5-4. Functions of Amino Acids and Protein

TABLE 5-5. Protein Requirements

TABLE 6-1. Dietary Reference Intake for Calcium, Phosphorus, and Magnesium

TABLE 6-2. Proportion by Weight of Elemental Calcium or Magnesium in Related Compounds

TABLE 7-1. Water-Soluble Vitamin Content per Unit Dose of Multivitamin Preparations for Parenteral Nutrition

TABLE 7-2. Dietary Reference Intake of Water-Soluble Essential Micronutrients in Pediatric Populations

TABLE 7-3. Characteristics of Water-Soluble Essential Micronutrients
TABLE 7-4. Potential Nutrient–Nutrient and Nutrient–Drug Interactions of Water-Soluble Essential Micronutrients
TABLE 8-1. Dietary Reference Intake for Fat-Soluble Vitamins
TABLE 8-2. Fat-Soluble Vitamins Content per Unit Dose of Multivitamin Preparations for Parenteral Nutrition
TABLE 9-1. Distribution of Total Body Water as a Percentage of Total Body Weight
TABLE 9-2. Calculating Estimated Fluid Requirements (Holliday-Segar Formula/4:2:1 Shortcut)
TABLE 9-3. Estimated Insensible Water Losses in Preterm Infants in Different Environments in the First 24 to 48 Hours
TABLE 9-4. Clinical Assessment and Treatment of Dehydration in Infants and Adolescents
TABLE 9-5. Oral Electrolyte Requirements by Age
TABLE 9-6. Medications Affecting Potassium and Magnesium
TABLE 10-1. Recommended Daily Nutrient Intakes During Pregnancy
TABLE 11-1. Selected Components From Human Milk
TABLE 11-2. Nutrient Comparison of Preterm MOM and DHM
TABLE 12-1. Infant Formula Manufacturer Websites
TABLE 12-2. Increasing Caloric Concentration With Formula Concentrate

TABLE 12-3. Increasing Caloric Concentration With Powder Infant Formula—Standard Dilution 20 kcal/oz
TABLE 13-1. Enteral Formulas
TABLE 13-2. Enteral Formula Manufacturer Websites
TABLE 14-1. Weight Recommendations According to Age and BMI Percentile
TABLE 14-2. Diagnostic Criteria for the Metabolic Syndrome in Pediatrics
TABLE 14-3. Laboratory Testing Guidelines Based on Age, BMI Percentile, and Risk Factors Present
TABLE 15-1. Interpretation of Lipid Profile
TABLE 15-2. Summary of Nutrition and Physical Activity Recommendations for Specific Lipid Abnormalities
TABLE 16-1. World Health Organization Equations for Determining Energy Needs
TABLE 16-2. Measuring Anthropometrics in Children With NI Who Are Unable to Stand
TABLE 16-3. Red Flags for Undernutrition in Children With NI
TABLE A16-1. Growth Parameters at Initial Visit
TABLE A16-2. Growth Parameters at Follow-Up Visit
TABLE 17-1. Eating Disorder/Feeding Disorder Summary From the Diagnostic and Statistical Manual of Mental Disorders
TABLE 17-2. Additional Disordered-Eating Presentations
TABLE 17-3. Timeline for Prevention of and Therapy for Refeeding Syndrome
TABLE 18-1. Common Terms Frequently Used With Food

Allergies
TABLE 18-2. Clinical Food Allergy Syndromes Associated With IgE or Non-IgE Immune-Mediated Mechanisms
TABLE 18-3. Early Peanut Introduction Guidelines
TABLE 18-4. Case Scenario
TABLE 18-5. Key Micronutrients of Common Food Allergens and Alternative Food Substitutes
TABLE 18-6. Food Allergy Resources
TABLE 18-7. Major Types of Pediatric Formulas
TABLE 18-8. Nutrient Comparison of Enriched Unflavored Milk Substitutes/Beverages
TABLE 18-9. Common Sources of Hidden Food Allergens
TABLE 18-10. Allergen-Free Multivitamins
TABLE 18-11. Allergen-Free Calcium and Vitamin D Supplements
TABLE 18-12. Ages for Tolerance of Common Food Allergens
TABLE 20-1. Recommended Daily Nutrient Intakes for Phenylketonuria
TABLE 20-2. Example of a Daily Meal Plan for Classical Phenylketonuria
TABLE 20-3. Phenylketonuria Summary
TABLE 20-4. Methylmalonic Acidemia Summary
TABLE 20-5. Ornithine Transcarbamylase Deficiency Summary
TABLE 20-6. Very Long-Chain Acyl-CoA Dehydrogenase Deficiency Summary

TABLE 20-7. Classical Galactosemia Summary
TABLE 20-8. Common Nutritional Supplements Prescribed for Various Mitochondrial Disorders
TABLE 21-1. Factors Contributing to Growth Failure in Congenital Heart Disease
TABLE 21-2. Infant Feeding and Nutrition Checklist for Congenital Heart Disease
TABLE 21-3. Types of Pediatric Cardiomyopathies
TABLE 21-4. Classification of Total and LDL Cholesterol Levels in Children and Adolescents From Families With Hypercholesterolemia or Premature Cardiovascular Disease
TABLE 22-1. NKF KDOQI Classification of the Stages of Chronic Kidney Disease
TABLE 22-2. Transplant Primary Diagnosis
TABLE 22-3. Nutrition Assessment
TABLE 22-4. General Nutrition Management of Patients With Renal Dysfunction
TABLE 22-5. Nutrition for Kidney Stone Management
TABLE 22-6. Summary of Nutritional Needs for Common Kidney Disorders
TABLE 23-1. Mechanisms of Nutrition Deficiency
TABLE 23-2. Gastrointestinal Nutrient Deficiencies
TABLE 23-3. Potential Effects of Medications Used for Gastroesophageal Reflux Disease
TABLE 23-4. Presentation of Celiac Disease
TABLE 23-5. Grains and Gluten

TABLE 23-6. Low FODMAP Diet
TABLE 24-1. Etiology and Pathophysiology of Malnutrition in Chronic Liver Disease
TABLE 24-2. Fat-Soluble Vitamin Recommendations
TABLE 25-1. Causes of Intestinal Failure in Children
TABLE 26-1. Pancreatic Enzyme Formulations
TABLE 27-1. Nutrition-Related Side Effects of Radiation Therapy
TABLE 27-2. Complications of Select Chemotherapy and Targeted Therapies Agents
TABLE 27-3. Components of a Nutrition Assessment for Pediatric Oncology and HSCT Patients
TABLE 27-4. Nutrition Strategies for Treatment-Related Symptom Management
TABLE 27-5. Calorie and Protein Requirements of Pediatric Patients Undergoing HSCT
TABLE 27-6. Side Effects of Some of the Drugs Commonly Used During HSCT
TABLE 27-7. Suggested Schedule for Monitoring Blood Biochemical and Other Indices During Early Stages of HSCT
APPENDIX 27-1. SCAN Tool for Assessing Malnutrition Risk in the Pediatric Oncology Patient
APPENDIX 27-2. Correction for Amputation Type and % Body Weight Lost Based on Segmental Weights
TABLE 30-1. Key Domains to be Encompassed During Pediatric Nutrition Assessment
TABLE 30-2. Classification of Preterm and Newborn Infants

by Birth Weight and Growth Percentile
TABLE 30-3. Gross Motor Function Classification System
TABLE 30-4. Primary Indicators for Pediatric Malnutrition When Only Single Data Point is Available
TABLE 30-5. Nutrition Concerns Based on Physical Examination
TABLE 30-6. Primary Indicators for Pediatric Malnutrition When 2 or More Data Points are Available
TABLE 30-7. CDC and WHO Classification of Pediatric and Adult Obesity
TABLE 30-8. Clinical Features Encountered During Evaluation of Pediatric Obesity
TABLE 30-9. Protein and Energy Intakes Needed to Achieve Fetal Rates of Weight Gain for Preterm Infants
TABLE 30-10. Recommendations for Adequate Dietary Calcium (elemental) Intake in the United States
TABLE 30-11. Progression of Biochemical Indicators or Iron Status
TABLE 31-1. Comparison of Feeding Tubes and Troubleshooting Issues
TABLE 31-2. Comparison of Techniques Used to Obtain Blood Samples From a VAD
TABLE 31-3. Prevention of CLABSIs
TABLE 31-4. Intestinal Failure Anticipatory Suggestion Sheet
TABLE 32-1. Indications for Enteral Nutrition
TABLE 32-2. Examples of Drug-Nutrition Interactions
TABLE 32-3. Room Temperature Formula Stability

TABLE 32-4. Components of Home Enteral Nutrition Education
TABLE 33-1. Recommendations for Initiation and Advancement of Macronutrients in Parenteral Nutrition
TABLE 33-2. Comparison of Commercially Available Pediatric Amino Acid Products
TABLE 33-3. Composition and Properties of ILE Products
TABLE 33-4. Parenteral Nutrition Electrolyte and Mineral Dosing Guidelines
TABLE 33-5. Dosing Recommendations for Pediatric Parenteral Multivitamins
TABLE 33-6. Comparison of Multitrace Element Products
TABLE 33-7. Pediatric Trace Element Requirements
TABLE 33-8. Comparison of Parenteral Iron Products
TABLE 33-9. Recommendations From ASPEN Parenteral Nutrition Safety Consensus
TABLE 34-1. Suggested Monitoring for Infants and Children Receiving Specialized Nutrition Support
TABLE 34-2. Parameters to Evaluate Adequacy of Parenteral Nutrition Volume
TABLE 34-3. Factors Affecting Total Nutrient Admixture Stability
TABLE 34-4. Doses of Calcium and Phosphorus Dosing for Prevention/Treatment of Metabolic Bone Disease
TABLE 34-5. Frequency of Short-Term and Long-Term Metabolic Monitoring
TABLE 34-6. Frequency of Long-Term Nutrition-Related Monitoring

TABLE 34-7. Enteral Dosing Options for Trace Metals
TABLE 34-8. Effect of Disease and Clinical Status on Iron Studies
TABLE 34-9. Drug-Induced Metabolic Adverse Effects

FIGURES

FIGURE 1-1. Normal Swallow Sequence of a Bottle-Feeding Infant
FIGURE 1-2. Typical Feeding Development in the First 12 Months of Life
FIGURE 2-1. Normal Gastric and Small Bowel Motility During a Fasting State With All 3 Phases of MMC
FIGURE 2-2. Increased Antroduodenal Motility in the Postprandial Period
FIGURE 3-1. Classification of Carbohydrates
FIGURE 3-2. Digestion and Absorption of Dietary Carbohydrates
FIGURE 3-3. Lactase Development With Age and Type of Feeding
FIGURE 4-1. 18-Carbon Steric Acid
FIGURE 4-2. Classification of Fatty Acids Based on Degree of Chain Saturation and Chain Length
FIGURE 4-3. Critical Functions of Fat
FIGURE 4-4. Oxidation of Medium-Chain, Long-Chain, and Very-Long-Chain Fatty Acids in Mitochondria
FIGURE 4-5. Schematic of the Steps Leading to Lipotoxicity
FIGURE 5-1. Pancreatic Enzyme Activation

FIGURE 5-2. Overview of Protein Digestion and Absorption
FIGURE 5-3. The Transport of Amino Acids
FIGURE 5-4. Transsulfuration Pathway in the Metabolism of Methionine
FIGURE 5-5. Urea Cycle With Enzymes and Substrates
FIGURE 9-1. Fluid Distribution of 100 mL Dextrose 5% in Water
FIGURE 9-2. Fluid Distribution of 100 mL of 0.9% Sodium Chloride
FIGURE 9-3. Laboratory Assessment
FIGURE 9-4. Electrolyte Replacement Assessment Algorithm
FIGURE 9-5. Maintenance Electrolyte Replacement Flow Chart
FIGURE 9-6. Evaluating Hyponatremia
FIGURE 9-7. Evaluation of Hypernatremia
FIGURE 10-1. Scheme of the Role That Programming of the Fetal Hypothalamic–Pituitary–Adrenal Axis During Development Plays in the Link Between Fetal Growth and Long-Term Disease in Adulthood
FIGURE 11-1. Lactogenesis Stages and Staff Priorities
FIGURE 11-2. Secretory IgA in Human Milk
FIGURE 11-3. Hospitalized Infant: Parent-Centered Feeding Algorithm at Discharge
FIGURE 11-4. Maternal Diet Nutrients That Impact Human Milk Composition
FIGURE 18-1. Algorithm for the Evaluation of Suspected Food Reactions

FIGURE 18-2. Suggested Algorithm for the Management of Hypersensitivity to Parenteral Nutrition
FIGURE 20-1. Phenylketonuria Results From Phenylalanine Hydroxylase Deficiency With Elevated Phenylalanine Concentrations and Tyrosine Deficiency
FIGURE 20-2. Calculating a Low Phenylalanine (Phe) Formula
FIGURE 20-3. Methylmalonic Acidemia Caused by a Defect in Methylmalonyl Coenzyme A Mutase
FIGURE 20-4. Nitrogen Metabolism in the Urea Cycle
FIGURE 20-5. Fatty Acid Oxidation and Very Long-Chain Acyl-CoA Dehydrogenase Deficiency
FIGURE 20-6. Classical Galactosemia is Caused by Galactose-1-phosphate Uridyltransferase Deficiency
FIGURE 20-7. The Electron Transport Chain Produces Adenosine Triphosphate From ADP by Oxidative Phosphorylation
FIGURE 21-1. Recommendations for Preoperative Feeding
FIGURE 21-2. Recommendations for Postoperative Enteral Feeding
FIGURE 21-3. Transition to Postoperative Oral Feeding
FIGURE 21-4. Interstage Feeding Guidelines
FIGURE 21-5. Diagnosis and Management of Chylothorax After Pediatric Cardiac Surgery
FIGURE 28-1. Metabolic/Endocrine Effects of Trauma and Burns
APPENDIX 30-1. Fenton 2013 Growth Charts for Preterm Girls

APPENDIX 30-2
APPENDIX 30-3.a
APPENDIX 30-3.b
APPENDIX 30-4. Percentiles of Mid-Upper Arm Circumference
APPENDIX 30-5. Triceps Skinfold Percentiles
APPENDIX 30-6. Estimating Nutrient Needs
APPENDIX 34-1. Neonatal and Pediatric Nutrition Monitoring Form
APPENDIX 34-2. Long-Term Lab Tracking Sheet
APPENDIX 34-3. Example Pediatric Patient >40 kg Nutrition Monitoring Form

EXHIBITS

EXHIBIT 3-1. Selected Disorders Associated with Carbohydrate Malabsorption
EXHIBIT 7-1. Predispositions to Deficiency of Water-Soluble Essential Micronutrients
EXHIBIT 8-1. Clinical Effects of Vitamin A Deficiency
EXHIBIT 15-1. Screening Guidelines
EXHIBIT 15-2. Laboratory Testing
EXHIBIT 17-1. Interview Process Template Guide Decision Tree
APPENDIX 17-1. Eating Disorder Case Study 1
APPENDIX 17-2. Eating Disorder Case Study 2
APPENDIX 17-3. Eating Disorder Case Study 3
APPENDIX 17-4. Eating Disorder Case 4

EXHIBIT 18-1. Important Questions for Determining the Degree of Nutrition Risk in Children With Food Allergies

EXHIBIT 20-1. Foods and Ingredients Containing Lactose and/or Galactose That Are Eliminated in the Diet for Classical Galactosemia

EXHIBIT 20-2. Common Mitochondrial Myopathies

EXHIBIT 21-1. Two Major Categories of Congenital Heart Disease

EXHIBIT 21-2. Nutrients That Augment Myocardial Energy Production in Adults

EXHIBIT 26-1. Clinical Features and Manifestations of Cystic Fibrosis

EXHIBIT 34-1. Factors Negatively Affecting Calcium and Phosphorus PN Solubility

EXHIBIT 34-2. Factors Associated With Increased Risk for Metabolic Bone Disease in Neonates

Preface

Since it was first published in 2009, the editorial team has been continuously pleased with how well the ASPEN Pediatric Core Curriculum has been received. The text is used in classrooms around the world to teach the basics of pediatric nutrition support, serves as a valuable resource to practicing clinicians, and is a popular study tool for individuals sitting for certification exams.

The authors and associate editors for this edition are a mixture of experts who helped create the earlier versions and some new voices. We learned a lot during the creation of the previous two editions, which allowed us to refine the information further in the third and produce a text with the information readers care the most about. As a result, we expanded coverage in some areas and condensed others.

This book is designed to start with basic nutrition physiology before progressing through the principles for nutrition in specific disease states. It ends with the "nuts and bolts" for daily care. This curriculum is not intended to provide in-depth coverage of neonatal nutrition, although some of this is covered in the context of the physiology of development. This book is not designed to be exhaustive in its coverage of nutrition in the various disease states but is rather meant to be the pediatric "core" curriculum; to be a disease-specific specialist will require study beyond this starting point.

It is my hope that this book helps to create a firm foundation of pediatric nutrition support principles that anyone can build on in any way they wish.

Mark R. Corkins, MD, FAAP, FASPEN
Editor-in-Chief

Acknowledgments & Dedication

Pulling together a text such as the *ASPEN Pediatric Nutrition Support Core Curriculum, 3rd Edition* is a team effort. I have to thank the associate editors, Elizabeth Bobo, Michael Christensen, Catherine Larson-Nath, Robin Nuse Tome, and Steve Plogsted, for helping guide the creation of this new edition. The job of updating the *Curriculum* for a third edition was a tremendous undertaking, requiring hours upon hours of dedication and hard work from all involved. Thank you all for volunteering your time to the pursuit of this revision and balancing this work in with your countless other obligations to family, careers, and other activities.

Thank you to the many authors who revised the text for the third edition, as well as to the authors of the first two editions from which it was built. Thank you to the peer reviewers who contributed their expertise to ensure that this publication and the data contained within are as scientifically sound as possible. And of course, we couldn't have done it without ASPEN's publications staff.

This book is dedicated to all of the folks who taught me through the years—my mentors and faculty at every level, the nurses, pharmacists, and dietitians I worked with, and especially the patients. Last and most important, I have to dedicate this to the coauthor of my life, Kelly Green Corkins, who loaned me to ASPEN for over a year to work on this revision.

Mark R. Corkins, MD, FAAP, FASPEN
Editor-in-Chief

PART I

Introductory and Basic Physiology

1. Mechanics of Nutrient Intake

Mark R. Corkins, MD, CNSC
Carol G. McKown, DDS, MS, PC
Memorie M. Gosa, PhD, CCC-SLP, BCS-S

2. Principles of Feeding and Gastrointestinal Motility

Molly Dienhart, MD
Jane Balint, MD
Desale Yacob, MD

3. Carbohydrates

Suzanna L. Attia, MD, MScPH

4. Fats

Peggy R. Borum, PhD

5. Protein Digestion, Absorption, and Metabolism

Oscar R. Herrera, PharmD
Richard A. Helms, PharmD

6. Minerals

Winston Koo, MBBS, FACN, CNS
May Saba, PharmD, BCNSP
Letitia Warren, RD, CSP

Mirjana Lulic-Botica, PharmD, BCPS

7. Water-Soluble Vitamins and Related Compounds

Winston Koo, MBBS, FACN, CNS
Judith Christie, RN, MSN
May Saba, PharmD, BCNSP
Letitia Warren, RD, CSP
Mirjana Lulic-Botica, PharmD, BCPS

8. Fat-Soluble Vitamins

Winston Koo, MBBS, FACN, CNS
May Saba, PharmD, BCNSP
Mirjana Lulic-Botica, PharmD, BCPS
Judith Christie, RN, MSN

9. Fluids and Electrolytes

Gerald L. Schmidt, PharmD, BCNSP

Mechanics of Nutrient Intake

Mark R. Corkins, MD, CNSC; Carol G. McKown, DDS, MS, PC; and Memorie M. Gosa, PhD, CCC-SLP, BCS-S

Learning Objectives

1. Describe how social and behavioral influences guide food consumption.
2. Describe the psychological, mechanical, biochemical, and hormonal inputs that determine appetite and intake.
3. Outline the developmental stages in deglutition and corresponding changes in appropriate feedings in children.

Introduction

Nutrition support in the pediatric population typically focuses on the biological and physiological needs of patients. However, unlike other areas of medicine that are directed by genetic programming and environmental factors, there are emotional components associated with nutrition right from the start. The original source of nutrition is food, yet food is so much more than nutrition. It is symbolic, from the stalk of wheat in the American Society for Parenteral and Enteral Nutrition (ASPEN) logo to the traditional birthday cake.

In her 2007 ASPEN Presidential Address, Marion Winkler shared a story about her mother when she was dying from cancer and the foods she requested. It was clear that the requests were about more than just food, stating, "It was always about the nostalgic stories that surrounded the food, the memories, the social aspects, and the companionship of the sharing of meals."[1] Of course, many of the nonbiologic factors are not quantifiable or easy to describe. Therefore, the focus of this pediatric nutrition support core curriculum is on the science and clinical experiences that are useful in everyday practice. This chapter begins with an overview of the factors that influence appetite and intake. We discuss dentition, which has a direct impact on the type of dietary intake possible, and the chapter concludes with a review of the mechanisms of swallowing.

Appetite

When we begin to explore the desire to eat, we realize that appetite has a cultural aspect.[2] Part of this derives from the environment; certain foods are more available in different geographic regions, and one culture's delicacy may be unacceptable in another. Children's memories and associations will thus influence their intake.[3] Also, human beings will eat some foods just because they taste good. The reward of taste stimulates feeding even in the absence of a true energy deficit.[4] It is very difficult to separate appetite due to homeostatic (biologic) needs and hedonic (pleasurable) desires from each other when discussing food intake.[5]

Critical periods of infant feeding development hinge upon exposure to new tastes and textures. Genetic input affects the sense of taste itself, including the strength of the response to sweet, salty, bitter, and sour.[6] Studies show that breastfed infants have a greater willingness to try new tastes, possibly because of their exposure to various flavors in human milk.[2,7] Early exposure to tastes determines later taste and food preferences before a child develops neophobia.[2] Neophobia is the developmental stage from 18 months to 2 years of age when children resist trying new foods.[2,6] The more a child is exposed to a taste, the more likely he or she will accept it as a preferred taste later.[6,7] Studies indicate that it may take 5 to 10

exposures before a food becomes an "accepted" taste.[7] Also, there appears to be a critical period for beginning solid foods, due to their texture, which is before 10 months of age. Northstone et al reported on long-term feeding problems related to acceptance of the taste and texture of foods.[8] Feeding difficulties identified by 9360 parents were found to occur more often among children for whom solid foods were delayed until after 10 months of age.[8]

Food preferences are also altered by the modeling that children observe in their parents and peers.[2,6] Eating with others positively influences the feeding behaviors and the food selections that children ultimately develop.[7] Adolescents alter their diet to an even greater degree based on social influences.[9] They are aware of the health concerns related to dietary intake but are not motivated by issues in the "distant future."[10] One study on influences and attitudes toward diet in adolescents indicated that parent attitudes had a statistically significant negative effect on healthy food intake.[11]

Appetite Regulation

An individual's final appetite is the result of many complex interactions between the brain and the gastrointestinal tract. The brain's appetite regulation begins with Agouti-related protein-expressing (AGRP) neurons in the hypothalamus that drive the appetite for food intake.[5,12] The activity of these neurons varies depending on homeostatic and hedonic input.[12] Endocrine cells in the stomach produce ghrelin, which acts on the AGRP neurons to stimulate appetite; ghrelin levels are high when the stomach is empty and fall after eating.[5,12,13] The level of appetite is also inversely influenced by the amount of leptin, a hormone produced by the body's adipose tissue.[5,13] The levels of blood glucose and insulin produced by the pancreas in response to serum glucose also influence the general appetite level.[13]

In addition to the AGRP neurons, the lateral hypothalamus (LH) is also tied to appetite behaviors.[5] This is the area of the brain responsible for the preconsumption responses to feeding. This concept was first presented by Ivan Pavlov. Pavlov demonstrated that dogs could be conditioned to salivate

at the ringing of a bell once they developed an association between the sound and feedings.[14] A variety of studies have shown that visual, olfactory, gustatory, tactile, and auditory inputs lead to activity in the salivary glands, gastrointestinal tract, pancreas, and cardiovascular and renal systems.[15] These responses are quick and prepare the body to digest and absorb the anticipated meal.[15] The LH makes food intake a rewarding experience by responding to taste stimuli and preferences and integrating the hedonic input with the homeostatic signals that also drive appetite.[5]

The other area of the brain important for appetite regulation is the calcitonin gene-related peptide neurons in the parabrachial nucleus (PBN).[5,12] The PBN is the source of the sense of satiety that suppresses appetite. The PBN neurons are a relay point for signals about taste, metabolism, and visceral sensations.[5] Therefore, unpleasant sensations such as nausea or fullness from stomach distention give feedback to decrease appetite. The PBN is modified by inputs from a wide variety of signaling hormones that are released into the circulation. These peptides act to decrease appetite and are released in proportion to the amount of various nutrients ingested.[4,12] These include peptide YY, glucagon-like peptide 1, oxyntomodulin, cholecystokinin, and pancreatic polypeptide.[4,5,12]

The hypothalamus neurons integrate all these signals to regulate appetite. The heightened appetite drive in pediatric patients that increases the caloric intake to support growth is not well understood. This drive may derive from programming within the hypothalamus itself or from signals indicating increased nutrient needs due to growth.

Mastication/Dentition

An important part of digestion is the initial homogenization of food that takes place in the mouth. Mastication, or the act of chewing, depends on the teeth to make foods a uniform consistency. Human beings are born toothless, which necessitates a reliance on liquid feedings. The muscles used in mastication are the temporalis, the masseter, and the medial and lateral pterygoids. The trigeminal nerve is the primary nerve involved in mastication. The act of chewing involves 2 sets of teeth, the anterior teeth

(incisors and canines) and the posterior teeth (premolars and molars). The anatomy of the incisors and canines with their single cusps and anterior position in the mouth allow them to tear food. The anatomy of the premolars and molars with multiple cusps and their posterior position in the mouth allow them to grind and chew food, preparing it for swallowing.[16]

The primary dentition, or the development and eruption of teeth, consists of 20 teeth, all of which begin development at 13 to 20 weeks in utero. Teething, the act of tooth eruption, may cause infants malaise, with increased drooling plus stomach or bowel changes, but it is not associated with fevers.[17] The mandibular central incisors are the first teeth to erupt at ages 6 to 10 months. The next teeth to erupt are the maxillary central incisors, between ages 8 and 12 months. Over the next 2 years, the other primary teeth come in as shown in Table 1-1.

TABLE 1-1. Primary Teeth by Age of Eruption

Primary Teeth	Age of Eruption
Mandibular central incisors	6–10 mo
Maxillary central incisors	8–12 mo
Maxillary lateral incisors	9–13 mo
Mandibular lateral incisors	10–16 mo
Maxillary first molars	13–19 mo
Mandibular first molars	14–18 mo
Maxillary canines	16–22 mo
Mandibular canines	17–23 mo
Second molars	2–3 y

The primary dentition stays intact until ages 5 to 7 years, when the permanent dentition begins to erupt. As the root end of the permanent tooth develops in the bone, it causes the crown of the tooth to emerge, which resorbs the root of the primary tooth, leaving only the crown. The crown of the primary tooth is then shed, allowing the permanent tooth to erupt. The mandibular central incisors and mandibular and maxillary first molars are

the first permanent teeth to erupt between ages 6 and 7 years. Their hard tissue formation begins shortly after birth. The subsequent progression of permanent tooth acquisition is shown in Table 1-2. The permanent third molars, or wisdom teeth, are the most commonly missing teeth and normally erupt between ages 17 and 21 years.

TABLE 1-2. Permanent Teeth by Age of Eruption

Permanent Teeth	Age of Eruption
Mandibular central incisors	6–7 y
Mandibular first molars	6–7 y
Maxillary first molars	6–7 y
Maxillary central incisors	7–8 y
Mandibular lateral incisors	7–8 y
Maxillary lateral incisors	8–9 y
Mandibular canines	9–10 y
Maxillary premolars	10–11 y
Mandibular premolars	10–12 y
Maxillary second premolars	10–12 y
Mandibular second premolars	11–12 y
Maxillary canines	11–12 y

Feeding Development and Swallowing

The process of swallowing has historically been described as 3 distinct physiological phases occurring in 3 distinct anatomic locations: (a) oral phase, (b) pharyngeal phase, and (c) esophageal phase. Safe and effective swallowing depends on the coordination of functional anatomy and neurophysiology of the muscles for feeding and respiration. For academic purposes, swallowing is typically broken down into distinct phases. However, it is widely recognized that the act of swallowing involves highly coordinated muscle activity that is often happening simultaneously or within milliseconds of a proceeding event throughout the upper aerodigestive tract.

Oral Phase

During the oral phase, bolus consistencies are prepared (masticated if necessary) and transported through the oral cavity with movement of the bolus posteriorly through the oral cavity. Infants take human milk or formula into the mouth by either breast or bottle and the liquid bolus is deposited directly on the back third of the tongue. In infancy, this is an involuntary action as the infant reflexively suckles. As the infant experiences physical growth and maturation, the depository position of the liquid and eventual semisolid and solid food boluses changes to a more anterior position to allow for greater manipulation of boluses with more complex textures. At this point in development, the oral preparatory stage transitions from a reflexive to a volitional process. The eruption of teeth and the downward forward growth of the mandible facilitate the transition from a purely liquid diet to a diet that includes purees, semisolids, and solids. Experience with spoon-feeding facilitates activity of the lips during the oral phase. Skills such as taking puree off a spoon and drinking through a straw, both of which require the lips, will occur in the latter half of the first year of life.[18,19]

Pharyngeal Phase

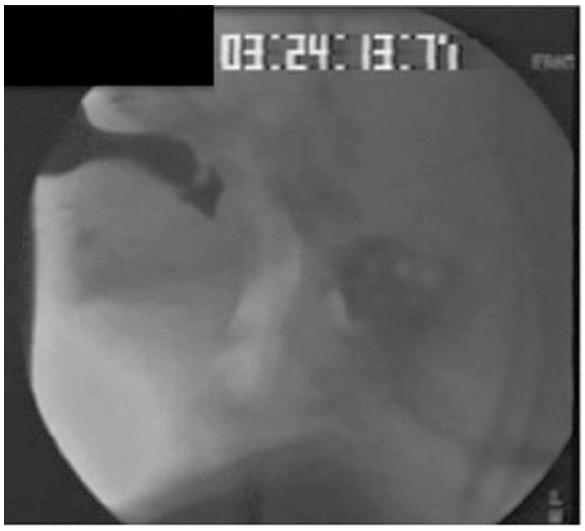
The pharyngeal phase consists of the liquid or food moving through the pharynx towards the esophagus. The soft palate and uvula lift so that liquid/food will not pass into the nasopharynx. The larynx closes by muscle contractions, superior and anterior movement of the hyolaryngeal complex, and the retroflexion of the epiglottis over the entrance to the larynx. Respiration ceases briefly (deglutition apnea), and after the food has started its descent, expiration and then inspiration will occur. In the infant, the swallow can occur during any part of the respiratory cycle, and it is variable.[20] The pharyngeal phase is involuntary, but the speed and strength of muscular action in this phase is influenced by sensory characteristics of the bolus material being swallowed.

Esophageal Phase

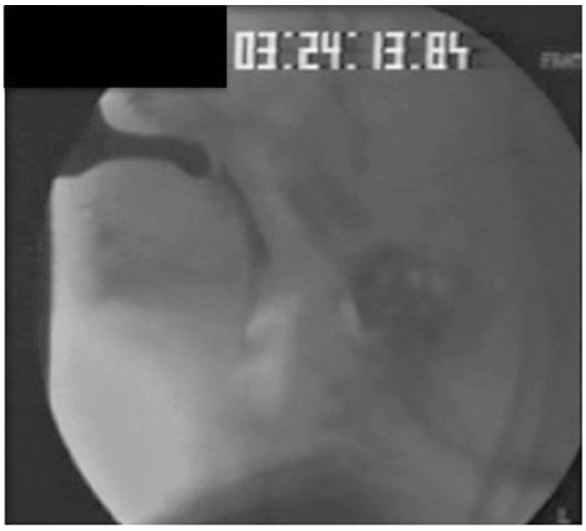
The esophageal phase is also involuntary but can be influenced by bolus characteristics such as volume. At the beginning of the esophageal phase,

the upper esophageal sphincter opens by a combination of muscle relaxation and biomechanical forces (through hyolaryngeal excursion) so that the food can enter the esophagus. Food travels to the stomach by esophageal peristalsis. Successful swallowing depends on all these structures, muscles, and neurological and respiratory systems working in coordinated millisecond timing.[21,22] Anatomical or physiological abnormalities within these systems will affect feeding effectiveness and efficiency. Figure 1-1 illustrates the typical swallow sequencing in a bottle-feeding infant.

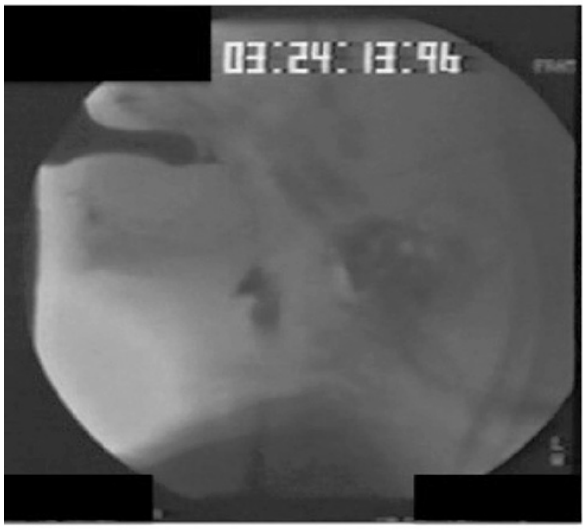
FIGURE 1-1. Normal Swallow Sequence of a Bottle-Feeding Infant



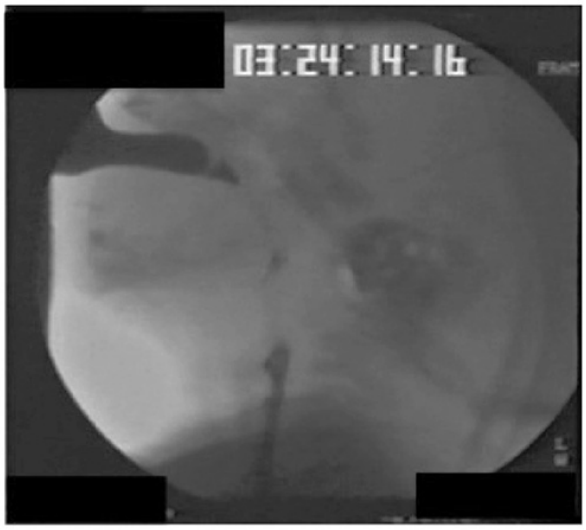
Oral Preparatory Stage
- Bolus material is sucked from bottle
- Bolus is collected on posterior 1/3 of tongue



Oral Transit Stage
- Bolus is moved through the oral cavity towards the pharynx



Pharyngeal Phase
- Bolus is moved through the pharynx by sequential, peristaltic-like contraction of the superior, middle, and inferior pharyngeal constrictors
- Larynx closes to prevent airway compromise



Esophageal Phase
- Upper esophageal sphincter is opened through relaxation of the cricopharyngeus and biomechanical forces
- Fluid moved through esophagus towards the stomach via peristalsis

Images courtesy of Memorie M. Gosa.

Feeding Skills in the First Year

The typical newborn is ready to feed shortly after birth. The reflexive root allows the infant to open the mouth, turn toward the food source, latch, and begin to suckle. The newborn will suckle, swallow, and breathe in a rhythmic sequence. This pattern is established through early reflexes that develop in utero, and the efficiency of this pattern improves by the third day of life.[23] The rooting reflex is among the most important and is activated by a light touch on or near the infant's mouth. Once latched onto the nipple, the infant's tongue and jaw work together to express milk.[24] The infant will feed in a burst-pause pattern that is usually quite regular, with the bursts being suck-swallow-and-breathe cycles and the pauses being brief and regular rest periods. Bursts of 8 sucks or more are seen in the typical newborn.[25] Sensing changes in the nipple, the infant can vary the sucking pressure quite easily to control the flow of milk. During early infancy, the infant will increase the rate of expression per minute with age. Studies have varied on the changes in the volume of expression; however, it ranges from 0.26 to 0.4 mL per suck.[26,27] In a typical newborn, 1 suck-swallow-breathe cycle including all 3 swallowing phases lasts approximately 1 second.[26] As infants' oromotor skills develop, the increase in control and efficiency of intake allows them to take in more milk in less time.

Pacifier sucking differs from sucking for nutritional intake. In pacifier sucking (nonnutritive sucking), the suck rate is twice as fast as nutritive sucking.[25] The infant only has to balance breathing and swallowing until a critical volume of saliva has been collected that will trigger a pharyngeal swallow response. Therefore, infants participating in nonnutritive sucking swallow with significantly less frequency as compared to swallowing frequency during nutritive sucking. This also means that infants sucking on a pacifier do not have to tolerate a swallow apnea with every suck, thus explaining why many nonfeeding infants can non-nutritively suck but have difficulty when a nipple introduces liquid.

Readiness for transitioning to spoon feeding has been debated, and recommendations have changed over the years. Brain growth, neural development, and anatomical changes in the oropharynx support development of a larger variety of oromotor movements. The tongue no

longer moves in a forward-backward patterned response due to the expansion of the oral cavity with forward and downward growth of the mandible, reabsorption of fat pads, and eruption of primary teeth. The tongue can stay in the mouth, not thrust out, and move side to side in response to stimulation, such as mouthing on fingers or the hand. The infant no longer has a single oral response of suck-swallow-breathe or bursts of sucking without swallowing as in pacifier sucking.

At 5 to 6 months of age, infants typically have some sitting balance and want to feed in an upright position. They anticipate food and will open their mouth for the spoon. The lips will close on the spoon to pull the food off.[28] The food is moved all around in the mouth, not strictly kept over the center of the tongue for propulsion back for swallowing. The tongue and the jaw no longer work only as a single unit. The gag is diminished to allow for nonliquids and will continue to be modulated as the experience with textures continues.[29] The critical period for introducing infants to new tastes to expand their flavors of accepted foods is between 4 and 6 months of age, which coordinates with the infant's physiological changes that allow for a greater variety of intake.[30]

When infants begin to pick up objects at age 6 to 7 months, they instinctively put them into their mouths. As the tongue can move in multiple directions and mouth objects, the parent introduces meltable solids and foods with greater texture (lumps) for the infant to handle. In late infancy, the infant begins to "munch" or use an up-down motion of the jaw to manipulate foods of increasingly complex and firm textures. These prechewing skills increase in efficiency with age.[31] Soft solid foods are then provided with small, single bite-size pieces for the infant to move around in the mouth and eventually swallow. This feeding has less rhythm compared to nutritive sucking. The movements are volitional and no longer directed by reflex. Early reflexes are fading at 4 to 8 months and volitional patterns of oromotor skills are emerging.[32] The critical period for texture advancement coincides with the anatomical and physiological changes occurring between 6 and 7 months of age.[33]

By 9 months of age, with the development of the fine-motor skills of reach, grasp, and release, self-feeding is established. Now the infant is skillful at watching others, communicating interests in foods, and eating.

Drinking from a cup and straw begins as the infant is guided by a parent. The infant will open his or her mouth to accept liquids from the cup. At this age, both breastfeeding and bottle-feeding begin to diminish as the infant takes in a greater proportion of liquids by cup and solids by spoon or hand.[29] Opportunities for oral exploration of various tastes and textures during these critical periods of feeding development are necessary to ensure advanced feeding behavior and skill development. Figure 1-2 outlines feeding development during the first year of life.[33]

FIGURE 1-2. Typical Feeding Development in the First 12 Months of Life

0–4 Months of Age

- Exclusive bottle/breast feeding
- Reflexive suckling pattern dominates intake of fluid from breast or bottle
- Newborns eat on demand every 1.5–2.0 hours
- 1–4 months of age, baby eats on demand every 2–3 hours

4–6 Months of Age

- Continue bottle or breast feeding on demand, usually every 3–4 hours
- Transitions from reflexive suckling to learned, mature sucking pattern between 4–6 months of age
- Introduction of baby cereal from a spoon when baby has:
  - Steady head control
  - Sits independently for 10–30 seconds
- Typical for baby to use suckling motion on spoon until they learn to use tongue and lips to clean bolus from spoon and swallow without loosing the bolus out of the front of the mouth
- Learning to spoon feed is messy- it is not necessary or desirable to clean baby's mouth after every bite or to scoop the food from around the mouth and re-feed it to baby

6–9 Months of Age

- Continue bottle or breast feeding on demand, usually every 3.5–4 hours
- Introduction of baby food- Stage 1 as baby uses mature spoon feeding skills
- Transition to Stage 2 foods around 8 months
- Transition to soft, mashed table foods at 9 months
- Baby begins hand to mouth play at ~6 months, sits independently for more than 3–5 minutes at 6–7 months, and has stable head control with no head bobbing by 6–7 months

9–11 Months of Age

- Continue bottle or breast feeding on demand, usually every 4–6 hours
- Introduction of foods for oral play at 9 months of age; foods should be almost impossible for baby to bite through and should be administered with strict supervision
- Introduction of foods that dissolve easily at 10 months of age
- Introduction of foods that are easily chewed at 11 months of age
- Baby begins munching and moving food from side to side in mouth around 9 months of age as they are learning a mature chewing pattern

11–12 Months of Age

- Continue bottle or breast feeding on demand, usually every 6–8 hours
- Introduction of single ingredient soft foods at 11 months (like avocado)
- Introduction of multiple ingredient soft foods & Stage 3 foods at 12 months (like Mac & Cheese)
- Baby's chewing skills advance to a circular pattern, tongue actively moves food from side to side in mouth

Information derived from Birch and Fisher,[7] Morris and Klein,[19] Bosma,[21] Ayano et al.[28] Toomey and Ross,[33] and Arvedson et al.[49] Photos courtesy of Memorie Gosa.

Problems in Infant Feeding Skills

Neurological disorders, prematurity (and its resulting sequelae), craniofacial anomalies, gastrointestinal disorders/diseases, aerodigestive anomalies, and pulmonary disorders/diseases may result in at least transient dysphagia in pediatric populations.[34] Dysphagia describes skill-based problems that compromise the safety, efficiency, and adequacy of oral intake.[35] This definition includes difficulty with oral preparation such as transferring liquid from the breast or bottle to the mouth, trouble with chewing food sufficiently for safe pharyngeal transit, and incoordination of breathing and swallowing that can result in airway compromise.

Infants may have difficulty with oral feeding that is not solely due to skill-based deficits. Difficulties with oral intake that result from more than skill-based deficits are termed feeding disorders. A unified definition of pediatric feeding disorder (PFD) was introduced in the literature in 2019. Goday and colleagues (2019) provide a multidisciplinary, consensus-based definition that makes use of the World Health Organization's *International Classification of Functioning Disability and Health Framework* to define PFD as "impaired oral intake that is not age appropriate, and is associated with medical, nutritional, feeding skill, and/or psychosocial dysfunction."[36] In 2022, the *International Classification of Diseases* (11th rev ed) was updated to include a diagnosis code for acute and chronic PFD. Acute PFD is defined as occurring for fewer than 3 months (coded R63.31) and chronic PFD is defined as occurring for longer than 3 months (coded R63.32). The PFD codes can be used in consort with previously established codes for dysphagia (R13.1 series), when applicable, to comprehensively document the medical necessity of treatment that will result from that diagnosis.[37]

Craniofacial anomalies are largely congenital but may also include damage acquired during eustachian tube placement or nerve damage sustained during cardiac surgery. These anomalies may affect the structures and muscles of feeding and swallowing, as well as the physiological timing and efficiency of feeding, leading to poor oral intake. In extreme cases, dysphagia can be seen. Classically, cranial nerve abnormalities, such as those seen in Mobius syndrome, cause dysphagia. Neurodevelopmental problems in infants, such as muscle tone abnormalities, persistence of early reflexes, or abnormal oral reflexes, can also lead to dysphagia.[38] Infants

with hypotonia (sometimes seen in infants with Down's syndrome) may have significant oromotor dysfunction, dysphagia, and aspiration, which is the passage of liquid or solids into the airway during swallowing.[39] Even infants with normal development can have difficulty feeding if they have abnormal respirations, cardiac disorders, or gastroesophageal reflux. They may tire easily and self-limit their intake, or they may have difficulty with the suck-swallow-breathe sequence and self-limit due to aspiration.[40]

Preterm infants frequently have feeding difficulties because of respiratory problems, neurodevelopmental problems, or both. Early birth does not allow for the typical developmental sequence of oral skills. Poor growth, especially in the youngest gestational age infants, may not allow neural pathways to mature. Many preterm infants have difficulty with "newborn" skills when they are at a "term-adjusted age" and may have significant feeding problems. Preterm infants with bronchopulmonary dysplasia may have abnormal development of suck patterns.[41] Infants who had significant limitations in oral feeding attempts because of severe illness or respiratory disorders may display aversion to oral feeding attempts because of illness or interruptions in typical feeding development.[42,43] In other infants, a persistent rapid breathing rate can interfere with establishing an efficient feeding rhythm. Lower gestational ages at birth and higher rates of neonatal morbidity are significantly correlated with longer transitions to full oral feeding in preterm infants.[44] In modern neonatal intensive care nurseries, it is more common for preterm infants to have respiratory complications than neurologic complications because of advancements in neonatal medicine in the last 20 years

Evaluation of the infant who is not feeding appropriately is ideally accomplished by a multidisciplinary team consisting of a physician, nurse, occupational therapist, speech-language pathologist, dietitian, and/or psychologist trained in and experienced with the aspects of normal and abnormal infant feeding development. There is not a single, comprehensive assessment that can be administered to fully evaluate all 4 domains of PFD (medical, nutritional, psychosocial, and feeding skills).[45] As a result, the evaluation will typically span a myriad of assessments including medical history, developmental history, a neurological examination, as well as an oromotor assessment including a feeding/attempt.[46] Pediatric specialists in

gastroenterology, neurology, rehabilitation, development, and other fields may be needed. The evaluation, under the direction of a physician, may include radiologic testing such as a feeding study (video fluoroscopic swallow study [VFSS] and/or flexible endoscopic evaluation of swallowing [FEES]), esophagram, or studies for reflux or gastric emptying.[47] Neurological studies of the central nervous system may be needed for the diagnosis of neurodevelopmental abnormalities. Studies of respiratory function and sufficiency of ventilation may be needed to provide optimal respiratory support for feeding.[48] It is important to determine the safety of feeding and ensure that the infant is not aspirating because of underlying problems.[47,49]

Aspiration cannot be accurately diagnosed from bedside assessment. It requires objective evaluation from an instrumental assessment.[47] When evaluating for dysphagia, a VFSS and FEES are both commonly used with pediatric patients. The goal of an instrumental assessment is not solely to confirm or deny the presence of dysphagia symptoms (eg, laryngeal penetration or aspiration), but also to determine the physiologic cause of the symptoms and then identify the most appropriate treatment strategies to provide the safest and least restrictive method of caloric intake for infants and children. When choosing which instrumental assessment to provide, the practitioner must consider the differences between the VFSS and the FEES and hypothesize which stage of the swallow is the cause of the feeding problems. Specifically, the VFSS allows visualization of a bolus as it moves from the mouth into the upper esophageal sphincter, providing the clinician with information about swallowing function across all four phases of the swallow (oral preparation, oral transit, pharyngeal transit, and esophageal), but it requires that the child drink barium and be able to tolerate the exam in a radiology suite.[44] In contrast, the FEES exam only provides visualization of the larynx before and after the swallow, giving specific information about the pharyngeal phase of swallowing function, but it can be performed at the bedside, utilizes actual food substances with food-safe dye added to improve visualization of the bolus before and after the swallow, and can be performed while the infant is breastfeeding (the VFSS cannot be performed during breastfeeding).[50] These considerations help the practitioner decide

which test will provide the desired information about the patient's swallowing function.[51,52]

Sometimes, despite extensive evaluations, the etiology of the feeding difficulty is never discovered. In some situations, the precipitating cause may have resolved, but the resulting behavior has become established. Once the cause and extent of poor feeding are understood, a treatment plan can be initiated to target improved oral feedings and/or to provide supplemental feedings through a nonoral means (such as nasogastric tube feeding) for the safety and growth of the infant. Such treatment plans should be drafted with the parents by a team of medical and therapy providers.

Feeding Skills in the Second Year

Toddlers typically need to expand their acceptance of foods and master self-feeding, including biting and chewing, while simultaneously developing greater independence and asserting more control over their environment. Most toddlers (from 1–3 years of age) enter this stage of eating "table foods." By their first birthday, they have successfully transitioned to eating some of the foods their families eat.[53] Due to their immature oromotor skills, toddlers need their foods diced, chopped, or cut into small bite-sized pieces. This continues until they become skillful at biting a single mouthful of food. Only then can a parent be assured that the toddler is not likely to choke. During this period, chewing improves and changes from the up-down munching motion to the rotary chewing that allows the toddler to grind meat fibers by 3 years of age. The toddler will increase chewing efficiency until 5 years of age.[54] Through careful trial and error, the parents will supply the toddler with small bites of their own foods and expand the toddler's diet. Meltable solids will be exchanged for nonmeltable solids that require biting off and chewing as the parent sees the child is ready for the single bite. Gradually, the diet will reach the level of a preschooler.

The toddler may initially allow the parent to assist with providing bites, but this will diminish, and by 18 months, the child will likely prefer self-feeding. The use of utensils can start as early as 15 months but is generally not perfected until much later. Initially, sticky foods will be given to help with self-spoon feeding; later the child will learn to spear food with a fork

as well, particularly soft foods. Using their fingers to assist the utensil feeding will continue until preschool age. Also, the child can now drink independently from an open cup.[29]

Behavior during mealtimes can be challenging as the toddler will seek to exert control over this environment as well. The way in which parents model and reinforce appropriate behavior to diminish unwanted behavior can affect not only eating but also sleeping habits and play interactions. Routine meals and snacks that are eaten with the child are the best times to teach appropriate mealtime behavior. As the toddler's ability to understand language increases, the parents need to demonstrate and explain desired mealtime behavior. Praise for sitting and eating with the family is necessary in addition to the repetitive teaching of desired behaviors. Watching the toddler's cues is important, as throwing or playing with food may signal that the child is full. Ellyn Satter describes mealtime in a series of roles for parents and children.[55] She suggests that it is the child's job to decide what and how much to eat, and the parent's job is to decide when to eat and what to offer the child. Problems in mealtime behavior can often be traced back to crossing roles between parents and children. This is illustrated when the parent tries to force the child to eat beyond when he or she is finished or when the child tries to eat throughout the day (grazing) instead of eating when the parent offers food at a structured meal or snack time.[55] As with all behaviors, routine and consistency will teach both the easy feeder and the difficult feeder.

Challenges of the Toddler Feeder

Challenges that affected an infant's feeding may still be present in toddlerhood. Problems such as anatomical anomalies, neurodevelopmental problems, gastrointestinal difficulties, and cardiorespiratory concerns require ongoing medical and therapeutic intervention. However, even toddlers who had normal feeding skills in their first year may have new behaviors affecting feedings or an aversion to advancing to a variety of flavors and textures. In one population study, parents reported that 20% of toddlers had feeding problems.[56] At times, a sentinel event can be recalled ("he had his tonsils out and couldn't eat"); other times, subtle problems with advancing textures in infancy were present but not well recognized.

Still other issues include behavioral problems that become more evident at this age, such as short attention span, oppositionality, or slow learning. As in infancy, we again see that the precipitating factor that triggered feeding difficulties may resolve but that undesirable feeding behaviors persist.

Evaluating new feeding problems in the toddler begins with a thorough feeding history of who feeds the child and what, when, where, how, and how much he or she is fed. Often, through this history, the initial therapeutic interventions can be determined. A review of the anthropometric measures since birth will identify inadequate growth, and a physical examination will determine the need for additional cardiac, respiratory, or gastrointestinal evaluation. The neurological and developmental examination can determine the need for feeding studies or further psychological or developmental evaluation.[46]

Most therapeutic plans include a mealtime routine and modeling of desired eating behavior by parents and caregivers. Parents and practitioners need to keep in mind that "picky eating" can be part of typical feeding development. As toddlers strive for autonomy and independence between 24 and 36 months of age, their behaviors in relation to new foods may become increasingly frustrating to parents.[57] Choosing a variety of nutritious foods for meals and snacks will expand the toddler's feeding experience and decrease pickiness.[57–60] It is important to ascertain the toddler's baseline abilities with oromotor function, fine motor development, and cognitive function to determine the level at which to begin. Identification of the problem or problems as well as the parents' goals for feeding will direct the therapist's plans, dietary plans, and home intervention. For toddlers with medical comorbidities, weight loss, worsening feeding problems, extended mealtimes (greater than 30 minutes), or significant family stress, referral to a multidisciplinary feeding team—including a psychologist, occupational/speech therapists, and a dietitian—to provide behavioral plans, therapy, and dietary advice, can be helpful.

Dysphagia and Pediatric Feeding Disorder (PFD)

As previously discussed, dysphagia refers to skill-based difficulties that compromise the safety, efficiency, and adequacy of oral intake,[35] whereas PFD refers to impaired oral intake that is not age appropriate and is associated with dysfunction in one or more of the following domains: feeding skill (as also seen in dysphagia), psychosocial, nutrition, and/or medical.[36] In the infant and young child, feeding proceeds in the developmental sequence previously discussed in this chapter, and abnormalities in feeding abilities need to be evaluated for their underlying physiological cause.

During the VFSS, the infant or child is ideally provided standardized radiopaque diagnostic barium products specifically designed for use with the VFSS (such as Varibar®, E-Z-EM Canada, Bracco Diagnostics Inc., https://www.varibar.mbs.com) that matches their expected dietary intake level (ie, liquid, puree, and solid as appropriate).[61] During an FEES, liquids, purees, or solids are typically colored with food dye so that the ingested substance is distinguishable from the soft tissue of the pharynx. At some institutions, swallowing studies can be done with pulse oximetry to see the effect of respiratory effort or deglutition apnea on the total saturation of oxygen. The real-time images are observed by the feeding/swallowing specialist (usually a speech-language pathologist), referring physician, and related specialist (such as the radiologist or otolaryngologist).[46] Further assessment (such as neurologic evaluation) to determine the underlying cause of dysphagia should be initiated by the physician when warranted.

During both a VFSS and FEES, the clinician is responsible for identifying the physiologic cause of dysphagia and determining effective compensatory strategies that will assist the infant or child in swallowing without airway compromise immediately. Therapeutic plans typically include a combination of direct interventions to improve swallowing function over time (informed by the physiologic cause of swallowing dysfunction) and/or compensatory strategies (confirmed as effective during the VFSS) to allow for immediate safe oral intake despite deficient feeding skills. Direct interventions typically include combinations of motor,

sensory, and behavioral approaches to improve feeding abilities.[62] One of the most common compensatory strategies for pediatric dysphagia is the use of thickened liquids.[64]

Historically, liquids have been classified as either thin, half-nectar, nectar, honey, or pudding consistency during dysphagia management.[63] These classifications were from the consensus-based National Dysphagia Diet (NDD), which categorized liquids and food based on subjective criteria.[64] The Varibar[65] line of standardized VFSS barium stimuli includes matched barium products to the thin, nectar, thin honey, honey, and pudding consistencies. The International Dysphagia Diet Standardization Initiative (IDDSI) was formed in 2013 and published their framework for describing thickened liquids and texture-modified foods in 2016. Along with the IDDSI Framework, the IDDSI Task Force also recommended a series of inexpensive clinical testing methods that can be performed at the patient's bedside to confirm that prescribed liquids and foods meet the desired therapeutic properties to alleviate airway compromise during swallowing. The IDDSI Framework describes liquids as thin (level 0), slightly thick (level 1), mildly thick (level 2), moderately thick (level 3), and extremely thick (level 4).[61] The Varibar products continue to use the liquid descriptors (thin, nectar, honey, etc.) from the NDD; however, the Varibar products have been mapped to the IDDSI Framework and results are provided in Table 1-3.[65] The IDDSI Framework is quickly being adopted across settings that treat infants and children for PFD and/or dysphagia as it provides an objective, consistent way to classify texture-modified food and liquids used for therapeutic management and it facilitates communication between professionals involved in dysphagia/PFD management across different settings.[61,63]

TABLE 1-3. Varibar Products and Equivalent IDDSI Framework Level/Name

Varibar Product	IDDSI Level/Name
Thin Liquid Barium	0/Thin
Nectar Thick Barium	2/Mildly Thick
Thin Honey Barium	3/Moderately Thick
Honey Thick Barium	≥ 4/Extremely Thick
Pudding Barium	≥ 4/Pureed

Data from Steele.[65]

Typical therapeutic plans may include the following:

- Physical, occupational, and speech therapy to advance skills.
- Thickness/texture modifications of liquids or foods offered.
- Selection and/or adaptation of bottles/nipples, cups, and utensils for feeding.
- Positioning assistance to obtain an optimal feeding position to facilitate safe and adequate oral intake.
- Diet adaptation to meet caloric, nutrition, and volume goals.
- Nutrition support through gastrostomy feedings.
- Diagnosis and treatment of gastroesophageal reflux.
- Medications (ie, to increase appetite).
- Referral to other medical specialists, additional instrumental assessments, or both.

The goals of therapy are to normalize tone and posture, particularly around head control and seating for feeding, and foster feeding development in the typical sequence as determined by the child's level of function and feeding safety. For example, an infant who has had brain damage from meningitis may have dysphagia and might require relaxation techniques to decrease hypertonicity and foster normal positioning. This infant may require a feeder seat for good positioning and may need to be offered purees if liquids are aspirated. This infant may need dietary assistance with increased caloric density to decrease the volume of intake needed by tube feeding or may need small and frequent feedings if large

gastrostomy feeding volumes are not tolerable. Once again, a team approach is needed in the feeding care of infants or children with dysphagia.[66]

Feeding Teams

Pediatric institutions that form feeding teams draw from the professional expertise at their organizations. With that in mind, each team will determine the problems they feel are appropriate in their setting and for their population. The usual team members include the following:

- child and parents
- physician (eg, developmental pediatrician, gastroenterologist, general pediatrician, pediatric psychiatrist)
- coordinator, who may be in social work, psychology, or nursing
- child psychologist
- speech-language pathologist and/or occupational therapist
- dietitian
- social worker

For the feeding team to be successful, parents must identify their goals clearly and be willing to make changes and work with the team members. Each professional must also be willing to work with team members and support the parents and patient during the process. Setting clear goals with the team and reviewing those goals is an important part of a feeding team program. For example, “Abby” is a young toddler who has an aversion to eating because of severe respiratory problems caused by prematurity. Her respiratory status is significantly improved, and she needs only occasional bronchodilators. She is gastrostomy fed and is very sensitive to the rate of feedings. Her mother has cut back on her feedings, so Abby is also malnourished. The team members have many goals, and progression of the goals may vary. The family hopes to shorten feeding times and increase Abby’s oral feedings so she can eventually stop gastrostomy feedings. These goals are appropriate for the child and the team members; however, they are long-term goals, and the progress is incremental and variable. The parents, with the team’s help, determine the daily schedule for feeding and

continue the routine of feedings. The physician and dietitian may work on a short-term goal of improving Abby's weight gain while trying to shorten her feeding times. The therapists may start by improving her ability to stay at the table at mealtime and touch food for short time periods. The dietitian and therapists may use a "chaining" technique to select foods that are similar to foods Abby likes to slowly broaden her food choices. At each follow-up visit with the team, the goals are reassessed, and the plan of care is revised based on the child's progress.[67] Referral to a feeding team is generally made by the child's primary care provider and reviewed by the coordinator for appropriateness to the team.

Summary

A patient's desire for food—or appetite—is driven by both biology and mental processes. The inputs are combined from the gastrointestinal tract and the brain to develop an appetite for intake. A factor in the intake is also the patient's dentition because it directly affects the ability to take in certain foods. Finally, for the ingested nutrition to get safely to the stomach, safe and coordinated swallowing skills are needed. There are many children who have unsafe swallowing and require a variety of interventions, from thickening to feeding tubes, to safely receive the nutrition they require to grow and develop.

Test Your Knowledge Questions

1. Appetite is suppressed by which of the following?
   A. Sensory stimulus before eating
   B. Ghrelin release by the stomach
   C. Intestinal release of glucagon-like peptide 1
   D. Low leptin levels
2. An abnormal swallow contains which of the following?
   A. Lift of the soft palate and uvula
   B. Continued respirations
   C. Closure of the epiglottis
   D. Opening of the upper esophageal sphincter

3. Chewing that allows the intake of higher texture foods requires which of the following?
   A. Rotary chewing
   B. Forward-backward patterning
   C. Suck-swallow-breathe cycles
   D. Up-down motion of the jaw

References

1. Winkler MF. American Society for Parenteral and Enteral Nutrition presidential address: food for thought: it's more than nutrition. *JPEN J Parenter Enteral Nutr.* 2007;31(4):334–340. https://doi.org/10.1177/0148607107031004334
2. Harris G. Development of taste and food preferences in children. *Curr Opin Clin Nutr Metab Care.* 2008;11:315–319. https://doi.org/10.1097/mco.0b013e3282f9e228
3. Lupton D. *Food, the Body and the Self*. Sage Publications; 1996.
4. Druce M, Bloom SR. The regulation of appetite. *Arch Dis Child.* 2006;91:183–187. https://doi.org/10.1136/adc.2005.073759
5. Sternson SM, Eiselt AK. Three pillars for the neural control of appetite. *Annu Rev Physiol.* 2017;79:401–423. https://doi.org/10.1146/annurev-physiol-021115-104948
6. Scaglioni S, Salvioni M, Galimberti C. Influence of parenteral attitudes in the development of children eating behavior. *Brit J of Nutr.* 2008;99(suppl. 1):S22–S25. https://doi.org/10.1017/s0007114508892471
7. Birch LL, Fisher JO. Development of eating behaviors among children and adolescents. *Pediatrics.* 1998;101:539–549. https://doi.org/10.1542/peds.101.S2.539
8. Northstone K, Emmett P, Nethersole F. The effect of age of introduction to lumpy solids on foods eaten and reported difficulties at 6 and 15 months. *J Hum Nutr Dietet.* 2001;14:43–54. https://doi.org/10.1046/j.1365-277x.2001.00264.x
9. Blakemore SJ, Mills KL. Is adolescence a sensitive period for sociocultural processing? *Annu Rev Psychol.* 2014;65:187–207.

https://doi.org/10.1146/annurev-psych-010213-115202
10. Bassett R, Chapman GE, Beagan BL. Autonomy and control: the co-construction of adolescent food choice. *Appetite.* 2008;50(2–3):325–332. https://doi.org/10.1016/j.appet.2007.08.009
11. Baker K, Figueroa R. Motivation, attitudes, and diet quality among US parents and adolescents. *Am J Health Behav.* 2021;45(1):125–137. https://doi.org/10.5993/ajhb.45.1.10
12. Andermann ML, Lowell BB. Toward a wiring diagram understanding of appetite control. *Neuron.* 2017;95(4):757–778. https://doi.org/10.1016/j.neuron.2017.06.014
13. Zanchi D, Depoorter A, Egloff L, et al. The impact of gut hormones on the neural circuit of appetite and satiety: a systematic review. *Neurosci Biobehav Rev.* 2017;80:457–475. https://doi.org/10.1016/j.neubiorev.2017.06.013
14. Pavlov IP. The centrifugal (efferent) nerves to the gastric glands and the pancreas. In: Thompson WH, ed. *The Work of the Digestive Glands*. Charles Griffin and Co; 1910:48–59.
15. Mattes RD. Physiologic responses to sensory stimulation by food: nutritional implications. *J Am Diet Assoc.* 1997;97(4):406–413. https://doi.org/10.1016/s0002-8223(97)00101-6
16. McDonald RE, Avery DR, Dean JA. *Dentistry for the Child and Adolescent.* 8th ed. Mosby; 2004:176–178.
17. Massignan C, Cardoso M, Porporatti AL, et al. Signs and symptoms of primary tooth eruption: a meta-analysis. *Pediatrics.* 2016;137(3):e20153501. https://doi.org/10.1542/peds.2015-3501
18. Logemann JL. Anatomy and physiology of normal deglutition. In: Logemann JL, ed. *Evaluation and Treatment of Swallowing Disorders.* 2nd ed. Pro-Ed; 1998:13–52.
19. Morris SE, Klein MD. *Pre-feeding Skills: A Comprehensive Resource for Feeding Developement.* 2nd ed. Therapy Skill Builders; 2000.
20. Kelly BN, Huckabee ML, Jones RD, Frampton CM. The first year of human life: coordinating respiration and nutritive swallowing. *Dysphagia.* 2007;22(1):37–43. https://doi.org/10.1007/s00455-006-9038-3
21. Bosma JF. Development of feeding. *Clin Nutr.* 1986;5(5):210–218.

22. Derkay CS, Schechter GL. Anatomy and physiology of pediatric swallowing disorders. *Otolaryngol Clin of North Am.* 1998;31(3):397–404. https://doi.org/10.1016/s0030-6665(05)70060-8
23. Weber F, Woolridge MW, Baum JD. An ultrasonographic study of the organisation of sucking and swallowing by newborn infants. *DevMed Child Neurol.* 1986;28(1):19–24. http://dx.doi.org/10.1111/j.1469-8749.1986.tb03825.x
24. Tamura Y, Horikawa Y, Yoshida S. Co-ordination of tongue movements and peri-oral muscle activities during nutritive sucking. *Dev Med Child Neurol.* 1996;38(6):503–510. https://doi.org/10.1111/j.1469-8749.1996.tb12111.x
25. Wolff PH. The serial organization of sucking in the young infant. *Pediatrics.* 1968;42(6):943–956.
26. Qureshi MA, Vice FL, Taciak VL, Bosma JF, Gewolb IH. Changes in rhythmic suckle feeding patterns in term infants in the first month of life. *Dev Med Child Neurol.* 2002;44(1):34–39. https://doi.org/10.1017/s0012162201001621
27. McGowan JS, Marsh RR, Fowler SM, Levy SE, Stallings VA. Developmental patterns of normal nutritive sucking in infants. *Dev Med Child Neurol.* 1991;33(10):891–897. https://doi.org/10.1111/j.1469-8749.1991.tb14798.x
28. Ayano R, Tamura F, Ohtsuka Y, Mukai Y. The development of normal feeding and swallowing: Showa University study of the feeding function. *Int J Orofacial Myology.* 2000;26:24–32.
29. Gesell A, Ilg FL. *Feeding Behavior in Infants: A Pediatric Approach to the Mental Hygiene of Early Life.* J.B. Lippincott, Co; 1937.
30. Skuse D. Identification and management of problem eaters. *Arch Dis Child.* 1993;69(5):604–608. https://doi.org/10.1136%2Fadc.69.5.604
31. Gisel EG. Effect of food texture on the development of chewing of children between six months and two years of age. *Dev Med Child Neurol.* 1991;33(1):69–79. https://doi.org/10.1111/j.1469-8749.1991.tb14786.x
32. Sheppard JJ, Mysak ED. Ontogeny of infantile oral reflexes and emerging chewing. *Child Dev.* 1984;55(3):831–843.
33. Toomey K, Ross E. *Picky Eaters Versus Problem Feeders: Sequential Oral Sensory Approach to Feeding Therapy.* Seminar Spring; 2007.

34. Lefton-Greif MA. Pediatric dysphagia. *Phys Med Rehabil Clin N Am.* 2008;19(4):837–851, ix. https://doi.org/10.1016/j.pmr.2008.05.007
35. Dodrill P, Gosa MM. Pediatric dysphagia: physiology, assessment, and management. *Ann Nutr Metab.* 2015;66(suppl 5):24–31. https://doi.org/10.1159/000381372
36. Goday PS, Huh SY, Silverman A, et al. Pediatric feeding disorder: consensus definition and conceptual framework. *J Pediatr Gastroenterol Nutr.* 2019;68(1):124–129. https://doi.org/10.1097/mpg.0000000000002188
37. World Health Organization. *International Classification of Diseases.* 11th rev ed. WHO; 2018.
38. Arvedson JC. Dysphagia in pediatric patients with neurologic damage. *Semin Neurol.* 1996;16(4):371–386. https://doi.org/10.1055/s-2008-1040996
39. Frazier JB, Friedman B. Swallow function in children with Down syndrome: a retrospective study. *Dev Med Child Neurol.* 1996;38(8):695–703. https://doi.org/10.1111/j.1469-8749.1996.tb12139.x
40. Mercado-Deane M-G, Burton EM, Harlow SA, et al. Swallowing dysfunction in infants less than 1 year of age. *Pediatr Radiol.* 2001;31:423–428. https://doi.org/10.1007/s002470100456
41. Gewolb IH, Vice FL. Abnormalities in the coordination of respiration and swallow in preterm infants with bronchopulmonary dysplasia. *Dev Med Child Neurol.* 2006;48:595–599. https://doi.org/10.1017/s0012162206001241
42. Illingworth RS, Lister J. The critical or sensitive period, with special reference to certain feeding problems in infants and children. *J Pediatr.* 1964;65:839–848. https://doi.org/10.1016/s0022-3476(64)80006-8
43. Bingham PM. Deprivation and dysphagia in premature infants. *J Child Neurol.* 2009;24(6):743–749. https://doi.org/10.1177/0883073808329530
44. Dodrill P, Donovan T, Cleghorn G, McMahon S, Davies PS. Attainment of early feeding milestones in preterm neonates. *J Perinatol.* 2008;28(8):549–555. https://doi.org/10.1038/jp.2008.56
45. Marshall J, Gosa MM, Dodrill P. Patient-reported outcome measures that describe the feeding skills domain for pediatric feeding disorder: a

clinimetric review. *J Pediatr Gastroenterol Nutr.* 2023;77(1):137–145. https://doi.org/10.1097/mpg.0000000000003798
46. Gosa MM, Dodrill P, Lefton-Greif MA, Silverman A. A multidisciplinary approach to pediatric feeding disorders: roles of the speech-language pathologist and behavioral psychologist. *Am J Speech Lang Pathol.* 2020;29(2s):956–966. https://doi.org/10.1044/2020_ajslp-19-00069
47. Tutor JD, Gosa MM. Dysphagia and aspiration in children. *Pediatr Pulmonol.* 2012;47(4):321–337. https://doi.org/10.1002/ppul.21576
48. Tutor JD, Srinivasan S, Gosa MM, Spentzas T, Stokes DC. Pulmonary function in infants with swallowing dysfunction. *PLoS One.* 2015;10(5):e0123125. https://doi.org/10.1371/journal.pone.0123125
49. Arvedson J, Rogers B, Buck G, Smart P, Msall M. Silent aspiration prominent in children with dysphagia. *Int J Pediatr Otorhinolaryngol.* 1994;28(2–3):173–181. https://doi.org/10.1016/0165-5876(94)90009-4
50. Miller CK, Reynolds J, Kelchner LN, Scarborough D, Langmore S, Gosa M. Tutorial on clinical practice for use of the fiberoptic endoscopic evaluation of swallowing procedure with pediatric populations: part 2. *Am J Speech Lang Pathol.* 2023;32(1):55–82. https://doi.org/10.1044/2022_ajslp-22-00057
51. Benson J, Lefton-Greif MA. Videofluoroscopy of swallowing in pediatric patients: a component of the total feeding evaluation. In: Tuchman DN, Walter RS, eds. *Diagnosis of Feeding and Swallowing in Infants and Children: Pathophysiology, Diagnosis, and Treatment.* Singular Publishing Group; 1994:187–200.
52. Newman LA. Optimal care patterns in pediatric patients with dysphagia. *Semin Speech Lang.* 2000;21(4):281–291. https://doi.org/10.1055/s-2000-8382
53. Briefel RR, Reidy K, Karwe V, Jankowski L, Hendricks K. Toddlers' transition to table foods: Impact on nutrient intakes and food patterns. *J Am Diet Assoc.* 2004;104(suppl 1):S38–S44. https://doi.org/10.1016/j.jada.2003.10.025
54. Gisel EG. Chewing cycles in 2- to 8-year-old normal children: a developmental profile. *Am J Occup Ther.* 1988;42(1):40–46. https://doi.org/10.5014/ajot.42.1.40

55. Satter E. *Child of Mine: Feeding with Love and GOOD SENSE.* Bull Publishing Company; 2000.
56. Wright CM, Parkinson KN, Shipton D, Drewett RF. How do toddler eating problems relate to their eating behavior, food preferences, and growth? *Pediatrics.* 2007;120(4):e1069–e1075. https://doi.org/10.1542/peds.2006-2961
57. Carruth BR, Skinner J, Houck K, Moran J, 3rd, Coletta F, Ott D. The phenomenon of "picky eater": a behavioral marker in eating patterns of toddlers. *J Am Coll Nutr.* 1998;17(2):180–186. https://doi.org/10.1080/07315724.1998.10718744
58. Gidding SS, Dennison BA, Birch LL, et al. Dietary recommendations for children and adolescents: a guide for practitioners. *Pediatrics.* 2006;117(2):544–559. https://doi.org/10.1542/peds.2005-2374
59. Satter E. *How to Get Your Kids to Eat: But Not Too Much.* Bull Publishing Company; 1987.
60. Jana L, Shu J. *Food Fights: Winning the Nutritional Challenges of Parenthood Armed With Insight, Humor, and a Bottle of Ketchup.* American Academy of Pediatrics; 2008.
61. Steele C, Martin B, Gosa M, Allen S. Diagnosis and management of swallowing physiology: standardized contrast, the MBSImP™, & the IDDSI Framework. *Appl Radiol.* 2021. https://appliedradiology.com/articles/diagnosis-and-management-of-swallowing-physiology-standardized-contrast-the-mbsimp-the-iddsi-framework
62. Gosa MM, Carden HT, Jacks CC, Threadgill AY, Sidlovsky TC. Evidence to support treatment options for children with swallowing and feeding disorders: a systematic review. *J Pediatr Rehabil Med.* 2017;10(2):107–136. https://doi.org/10.3233/prm-170436
63. Gosa MM, Dodrill P, Robbins J. Frontline interventions: considerations for modifying fluids and foods for management of feeding and swallowing disorders across the life span. *Am J Speech Lang Pathol.* 2020;29(2s):934–944. https://doi.org/10.1044/2020_ajslp-19-00065
64. McCollough G, Pelletier C, Steele C. National dysphagia diet: what to swallow? *The ASHA Lead.* 2003;8(20). http://dx.doi.org/10.1044/leader.FTR3.08202003.16

65. Steele C. Mapping Bracco's Varibar® barium products to the IDDSI framework. Published 2017. Accessed October 11, 2023. https://iddsi.org/IDDSI/media/images/Publications/Mapping-Varibar-to-IDDSI-Framework.pdf
66. Dusick A. Investigation and management of dysphagia. *Semin Pediatr Neurol.* 2003;10(4):255–264. https://doi.org/10.1016/s1071-9091(03)00071-8
67. Fraker C, Fishbein M, Cox S, Walbert L. *Food Chaining: The Proven 6-Step Plan to Stop Picky Eating, Solve Feeding Problems, and Expand Your Child's Diet.* Marlowe & Company; 2007.

Test Your Knowledge Answers

1. The correct answer is **C**. Glucagon-like peptide 1 is one of the circulating peptides that is released from the GI tract in response to metabolism and visceral sensations produced after eating to decrease appetite. The sensory stimulus before eating prepares the body for the incoming meal. Ghrelin is released by the stomach when it is empty to stimulate appetite. Leptin comes from the adipose tissue, and an elevated level suppresses appetite.
2. The correct answer is **B**. During a swallow, there is physiological deglutition apnea that occurs to protect the airway. During a swallow, there are several protective muscular actions that occur to prevent items from getting where they do not belong. This includes the lift of the soft palate and uvula and closure of the epiglottis. Of course, the swallowed material must go somewhere, so the upper esophageal sphincter needs to open for the material to progress. Otherwise, it will remain in the airway and end up going somewhere undesired.
3. The correct answer is **A**. Mature chewing requires a rotary motion that results in the grinding of foods between the teeth. Suck-swallow-breathe cycles is the feeding pattern infants have while on breast or formula. Forward-backward patterning is the tongue motion that infants use for breast/nipple feedings. The up-down motion of the jaw is used for feeding soft, bite-size pieces of food and develops in late infancy as the child learns to manipulate foods in the mouth.

The authors wish to acknowledge the contributions to this chapter by Dr. Anna Dusick, who was a coauthor in the first edition. She later lost a battle with cancer but is not forgotten for her input.

2

Principles of Feeding and Gastrointestinal Motility

Molly Dienhart, MD; Jane Balint, MD; and Desale Yacob, MD

Learning Objectives

1. Describe the normal response of the stomach to nutrient intake.
2. Explain the different motor patterns of the small intestine in the fasting and fed states.
3. Explain the unique responses of the intestinal tract to different types of nutrients.
4. Develop management strategies for altered gastrointestinal motility.

Introduction

The gastrointestinal (GI) tract is a conduit that humans normally use to obtain their nutrition. The GI tract comprises an organized combination of mechanical and biochemical processes that turn food into our biologically needed nutrients. GI motility is necessary for the movement of food and nutrients from the stomach through the intestinal tract as well as for the breakdown and mixture of these nutrients with digestive enzymes, allowing for digestion and absorption. A basic understanding of these processes (as well as deviations from them) helps plan and manage nutrition support.

Background

The motor activity of the GI tract is regulated by the enteric nervous system (ENS), which consists of 2 nerve plexuses. The myenteric plexus (Auerbach's plexus) lies between the outer longitudinal muscle layer and the inner circular muscle layer. This plexus is key to the motility of the GI tract, including regulation of the normal motor patterns seen in the GI tract described in this chapter. The submucosal plexus (Meissner's plexus), found between the muscularis mucosa and the circular muscle layer, affects absorption, secretion, and blood flow. Although the ENS can act independently, it receives input from the parasympathetic nervous system (primarily the vagus nerve), the sympathetic nervous system, and sensory nerves in the intestine as well as from mast cells, paracrine signals, and endocrine signals. Additionally, the ENS involves multiple neurotransmitters for signaling, including acetylcholine, norepinephrine, serotonin, vasoactive intestinal peptide, nitric oxide, somatostatin, and tachykinins.[1–4]

Interstitial cells of Cajal (ICC), which are considered the pacemakers of the GI tract and mediate neurotransmission, are integral to the functioning of the GI tract. Two types of these cells exist: those around the myenteric plexus that generate and propagate electrical slow waves (pacemakers) and those between neural fibers and smooth muscle cells, providing communication between the two. As pacemakers, ICC help coordinate peristaltic movement of the GI tract.[5,6] Slow waves have variable frequencies in different parts of the GI tract. In the stomach, the slow-wave rhythm is 3 cycles per minute. In the proximal small bowel, the rhythm is 11 to 15 cycles per minute, decreasing to 7to 9 cycles per minute in the distal ileum. Slow waves do not generate contractions but dictate the frequency at which they can occur.[4,7]

Maturation of the ENS and hence that of intestinal motility is dependent on gestational age. Fasting motility, which is marked by cycles of phases of quiescence, irregular activity, and organized propagating contraction called migrating motor complex (MMC), serves as a marker of the health of the ENS and intestinal muscles. Berseth reported that MMC—the hallmark of normal and mature intestinal motility—is seen in term infants but rarely in preterm infants. Also, the motility index increases with gestational age. The

motility of preterm infants compared with that of term infants is therefore more immature and may contribute to feeding problems.[8]

Furthermore, neuronal development of the ENS is not complete at birth. Neurochemical maturation does not reach adult patterns until 1 month of postnatal life,[9] and the number and structure of cell bodies within the ganglia continue to change according to the age of the individual from the first day of life through age 15 years.[10]

Gastric Motility

The gastric fundus, which is the uppermost portion of the stomach, acts as a reservoir for ingested food. It lies above the antrum and body of the stomach, where food is ground into small particles before passage into the small intestine. Vagally mediated relaxation of the fundus occurs with swallowing at the onset of a feeding or meal. As food enters the stomach, the proximal stomach further relaxes to provide a reservoir for nutrients. This receptive relaxation and gastric accommodation allows for an initial increase in the volume of the stomach without an increase in pressure. However, the pressure will ultimately increase, leading to a tonic contraction that then pushes the gastric contents toward the antrum. At the same time, regular phasic contractions (3 cycles/min) start and mix and grind (triturate) the gastric contents. During the churning process, the food bolus is first pushed toward the antrum where some grinding takes place. Distention of the antrum results in fundic relaxation and in turn retropulsion of the contents back to the body of the stomach. Grinding is important for creating small particles <1 to 2 mm in size, which will pass into the duodenum through the pylorus. Mixing these particles with gastric acid and pepsin begins the chemical digestion of food. This initial phase of mixing and grinding is the lag phase in gastric emptying that occurs after ingestion of nutrients.[1,4,11–14]

Once the ingested nutrients are appropriately mixed and solid material is ground into small particles, antral contractions accompanied by pyloric relaxation allow small aliquots of this chyme to empty into the duodenum. This begins the second (or linear) gastric emptying phase. Gastric emptying

time varies depending on a variety of factors, but it is generally complete in 4 hours.[1,4,7,11,13,14]

The preterm infant has an immature pattern of GI motility, which affects both gastric emptying and small bowel motility, which in turn impacts feeding. Gastric emptying first occurs at 13 weeks of gestation with the duration of gastric slow waves increasing just before birth.[15] The normal electrical activity of the stomach, with a slow-wave frequency of 3 cycles per minute, does not develop until 32 weeks of gestation and does not become the dominant pattern until 35 weeks of gestation. This results in slower gastric emptying in preterm infants compared to term infants.[4,15,17] Additionally, extreme stress, such as the presence of systemic illness, which is not seen infrequently in preterm neonates, can delay gastric emptying.[18] Animal studies have demonstrated that antibiotics in the neonatal period can impact not only microbiota but also ENS and colonic motility.[19]

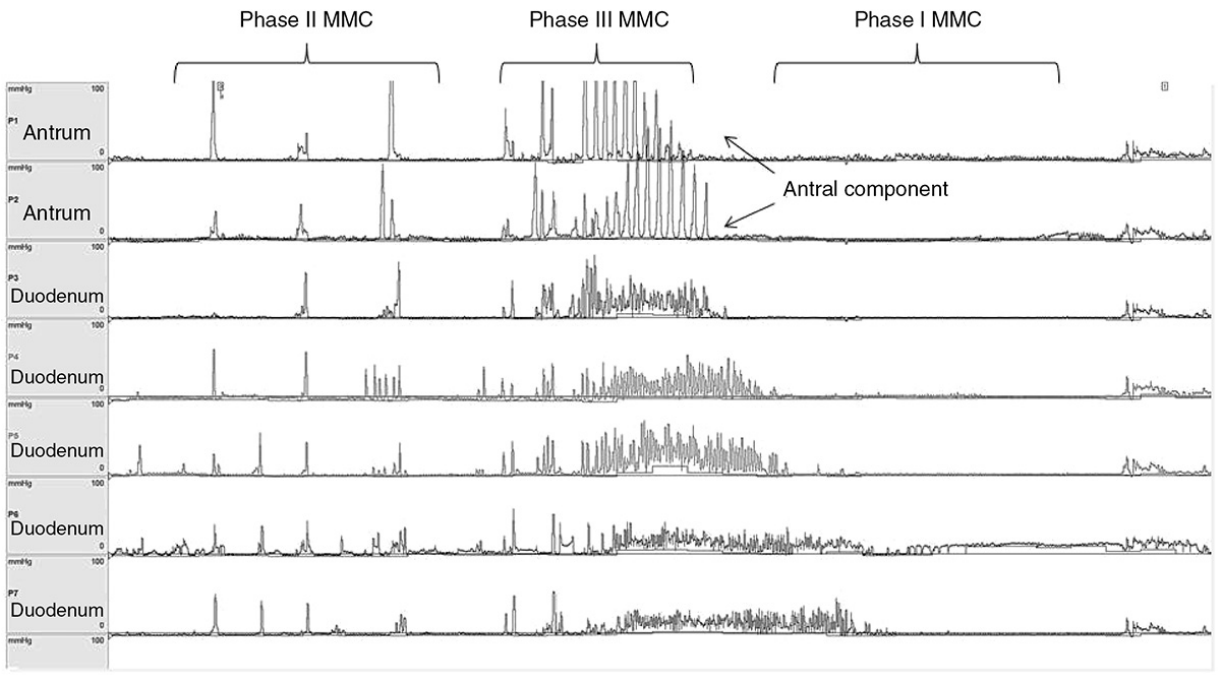
Small Bowel Motility

The motor activity of the small intestine serves many important functions, including mixing chyme with intestinal secretions for further digestion, enhancing contact between enteric contents and the mucosa for absorption, moving ingested contents distally, and clearing the intestinal tract by powerful contractions that propagate in an aboral direction.[20]

In the fasting state or interdigestive period, intestinal motility is marked by 3 distinct phases:

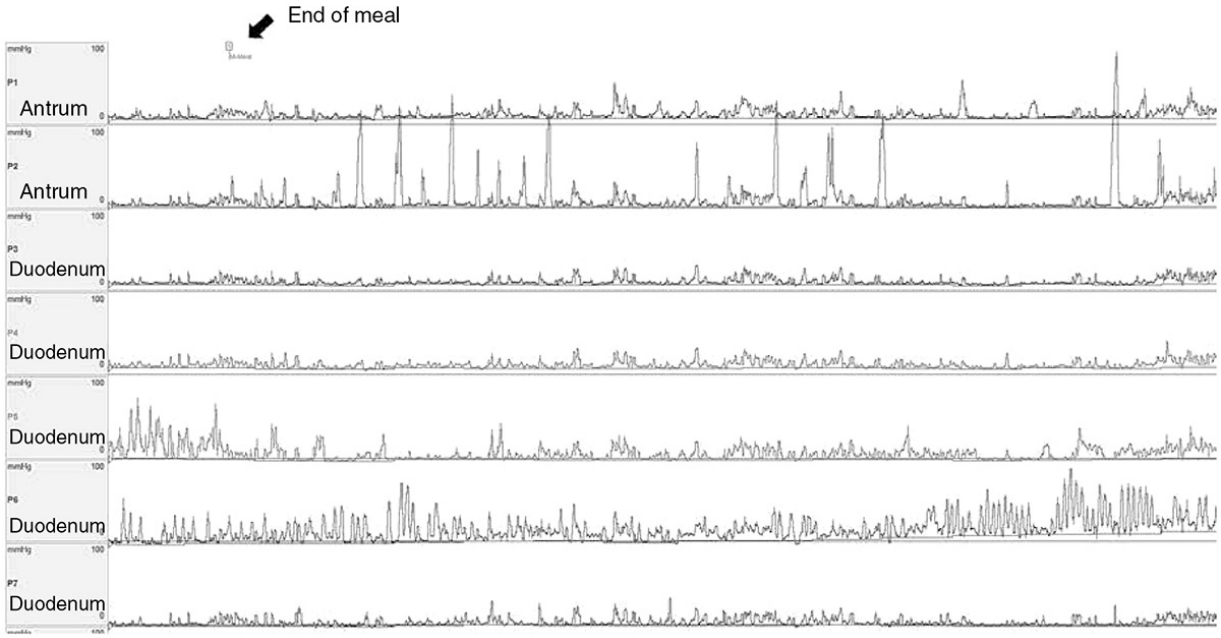
- Phase I is a quiescent phase.
- Phase II is characterized by intermittent and irregular contractions.
- Phase III, also known as MMC, is characterized by strong, propagating contractions that begin almost simultaneously in the stomach and duodenum and travel through the small bowel. The MMC provides the housekeeping function of intestinal motility, sweeping material through the small bowel. It occurs at irregular intervals, ranging from 18 to 145 minutes, with an average occurrence of every 80 minutes, and lasts from 2 to 14 minutes (see Figure 2-1).[1,4,20–22]

FIGURE 2-1. Normal Gastric and Small Bowel Motility During a Fasting State With All 3 Phases of MMC



In the fed state, the interdigestive motility including the MMC is suppressed, making room for the postprandial motor activity that facilitates the mixing and propulsion of nutritional contents. In general, random bursts of activity occur that primarily result in mixing (see Figure 2-2). The timing of this transition varies and lasts until phase III; the duration of the fed state is impacted by what is ingested, both its nutrient content and overall caloric content.[23] When a contraction occurs, intestinal contents move. If the contraction in a region of the small intestine occurs in a coordinated manner with the proximal and distal bowel, then the intestinal contents will be propelled downstream. If the contraction is not coordinated with the activity of adjacent areas, then the intestinal contents move both retrograde and antegrade in the intestine, resulting in mixing.[3,21]

FIGURE 2-2. Increased Antroduodenal Motility in the Postprandial Period



As noted previously, the preterm infant has not yet developed a normal pattern of intestinal motility. The fasting pattern of preterm infants is characterized by short bursts of activity, called clusters, that do not progress aborally as a mature phase III MMC does. The first motility patterns appear as spontaneous contractions that propagate both anally and orally and that are generated by the muscle cells themselves, not the ENS.[19] The nature of the clusters differs depending on the gestational age. The length of a cluster increases with gestational age of the infant: from <90 seconds at 27 to 28 weeks of gestation to 5–6 minutes at 36 weeks of gestation. At the same time, the frequency of the clusters decreases. Preterm infants do not exhibit MMCs before 32 weeks of gestation,[24] and true, propagating, cyclical MMCs with clearly defined phases develop between 37 and 40 weeks of gestation.[25] The fed pattern also differs in the preterm infant, with most demonstrating an abrupt cessation of intestinal contractions after a bolus feeding. Not surprisingly, intestinal transit is slower in the preterm infant. Some evidence exists from animal and clinical trials that early, small-volume feedings are safe and beneficial, thus, feeding preterm infants even small amounts can promote intestinal motility maturation.[16,26–28]

Effect of Intake on Motor Activity

Gastric emptying can be affected by a variety of characteristics of the ingested material as well as by the rapidity of transit through the GI tract. The time for gastric emptying can vary from 1 to 4 hours. The effect of nutrient composition on motor activity has been more clearly delineated for the stomach than the small bowel. Gastric emptying is not influenced by non-nutritive sucking but is impacted by caloric content as well as stress.[18] Also, in a comparison trial between intragastric versus intraduodenal continuous feeds over a 6-hour period, both fed and fasting state motilities were observed in the majority of the intragastric feeding group, whereas there was no generation of MMCs while the transpyloric feeding group remained in a fed state.[29]

Consistency and Temperature

Liquids empty from the stomach more quickly than solids, and clear liquids empty more rapidly than full liquids, with non-nutritive liquids emptying the fastest, leaving the stomach in about 20 minutes.[14,30] Viscosity also affects the speed of gastric emptying, with lower viscosity material emptying more rapidly. Thus, both soluble and insoluble fibers mixed with the feedings will slow emptying.[31,32] In addition to delaying gastric emptying, soluble fibers can prolong transit through the GI tract by prolonging the duration of the fed pattern of small bowel motor activity.[32] Meal temperature has also been shown to impact gastric emptying, with warmer meals emptying faster[33] and cold liquids leaving the stomach more slowly.[34]

Nutrient Content

The response to the type of nutrient ingested is complex. Both hormonal and neural responses to food occur to regulate motor activity of the stomach and small intestine. These are interrelated such that neural activity can affect the release of some GI hormones. Once chyme starts to pass through the pylorus, there is feedback via vagal afferents from receptors in the duodenum that regulate gastric emptying. These receptors include those that detect fat, amino acids, glucose, pH, and osmolarity.[35] A component of the

response is mediated by the release of gastrin, cholecystokinin, pancreatic polypeptide, glucagon-like peptide 1, and peptide YY.[4,36,37] Carbohydrates empty from the stomach more quickly than proteins, and fats empty the slowest.[4,38,39] Fats reaching the distal ileum inhibit both gastric emptying and small intestinal motility, a mechanism known as the ileal brake.[40] Complex carbohydrates that reach the distal small intestine can also stimulate the ileal brake.[1] In addition to the actual nutrient content, the pH will affect gastric emptying as well, with more acidic material emptying more slowly from the stomach.[41]

Caloric Density and Osmolarity

A higher caloric content of ingested food or liquid generally empties slower from the stomach in older children and adults.[31,42] This is less straightforward in infants. A study of infants ranging from 32 to 39 weeks gestational age demonstrated that altering the caloric density using different concentrations of infant formula below 20 kcal/oz (0 vs 6.5 kcal/oz; 6.5 vs 13 kcal/oz; and 13 vs 20 kcal/oz) impacted gastric emptying, with the higher caloric density emptying more slowly in each case.[43] Even with this slower emptying, higher calorie feedings resulted in more calories being emptied over comparable time periods. Other researchers[44–46] studying term (mean 36 wk gestation) and preterm (mean gestational age 31–34 wk) infants did not find differences in gastric emptying between formula and fortified human milk when the caloric density was increased above 20 kcal/oz. It has also been demonstrated, although somewhat inconclusively, that a meal with a higher calorie content will result in a longer fed pattern in the small bowel, leading to a longer transit time through the small intestine.[47,48]

Solutions that have a higher osmolarity will empty more slowly from the stomach than those that are lower in osmolarity.[37] In contrast, the small bowel motor response to chemically different liquid meals is similar to the length of the postprandial motor pattern as well as the contractile activity during the postprandial period.[46]

Although each of these factors individually can influence gastric emptying in older infants, children, and adults, the same is not always true

in preterm infants. In a study of infants at 25 to 30 weeks of gestation, separately altering osmolality, caloric density, or feeding volume did not change gastric emptying. However, when the feeding volume was increased at the same time the osmolality was decreased, gastric emptying was more rapid.[49] This further validates that across age groups, these factors can overlap because nutrient content is closely tied to caloric density (eg, a meal or formula that is higher in fat will likely be higher in calories).

Other Factors

There is some data to suggest that prebiotics may improve gastric motility potentially via increased motilin secretion, however, additional studies are needed.[50,51]

Altered Patterns of Motility and Potential Interventions

Disordered motility in any part of the GI tract can impact feeding tolerance.

Delayed Gastric Emptying

As noted earlier, slower gastric emptying occurs in preterm infants and may impair feeding advancement. Preterm infants who require tube feedings because of immature suck and swallow may benefit from a slower intermittent infusion for as long as 2 hours, rather than a 15-minute bolus, because slower infusion results in improved gastric emptying and a more mature duodenal motor pattern.[52,53] In older infants and children, delayed emptying may occur during or following infectious illnesses ranging from an acute viral illness to sepsis or other stress, secondary to marked constipation as negative feedback via the intestino-intestinal reflex loop. Patients in pediatric and neonatal intensive care units are at high risk for alterations in their normal gastrointestinal motility patterns, including gastric emptying. This results from decreased neuronal excitability signals, which can result from the insult itself (infection, trauma, surgery), inflammation, mechanical ventilation, and/or the need for pain or sedation

medications.[54–57] This delayed emptying results in fullness, bloating, decreased appetite, and emesis.[58]

Management strategies depend on the degree of the problem and how the child was being fed before onset. If the child was eating a regular diet, then smaller, more frequent meals that are lower in fat, fiber, and caloric density may empty better from the stomach.[59] Because liquids empty more readily than solids, increasing the liquid content of the meal may help. If the child is unable to tolerate any solids, a trial of liquid nutritional supplements is warranted. If the child was tube-fed prior to the onset of delayed gastric emptying, then adjusting the formula or delivery method may be necessary. Evaluate the osmolarity and caloric, fat, and fiber content of the formula and determine whether it should be changed because the higher each of these is, the slower emptying will be even under normal circumstances. Drip feedings (rather than bolus) may need to be considered.

Few pharmacologic options are currently available to improve gastric emptying. Erythromycin, which acts as a motilin receptor agonist, can accelerate gastric emptying.[60] Safe use of erythromycin in both preterm and term infants has been demonstrated; however, due to the lack of functional receptors, some debate exists regarding its effectiveness in infants <32 weeks gestation,[19,24,61] which is when motilin receptor-mediated MMCs have been shown to appear.[62] The impact of erythromycin on feeding intolerance in preterm infants thus remains inconclusive.[63,64] If the problem is severe enough, continuous transpyloric or jejunal feedings may be necessary, at least temporarily, while awaiting response to treatment of the underlying problem or resolution of the illness.

Other pharmacologic interventions for delayed gastric emptying include prucalopride and cyproheptadine, with the latter being more of a pro-gastric accommodation drug. Domperidone, cisapride, and metoclopramide have also been shown to have therapeutic benefits in patients with delayed gastric emptying, but they are not readily available or have limited use in the United States because of their extensive side effects.[65] Endoscopic and surgical interventions are also used to address delayed gastric emptying. These interventions include endoscopic pyloric botulinum toxin injection, gastric electrical stimulation, pyloric dilation, pyloroplasty, and pyloromyotomy.[65]

Dumping

Very rapid gastric emptying, or dumping, is relatively uncommon in pediatrics.[58] It can occur from surgery, particularly involving the pylorus, or from damage to the vagal nerve during fundoplication or cardiac surgery. Studies have shown that dumping can occur in up to 30% of patients following fundoplication; however, in many, the symptoms improve over time.[66,67] Symptoms include nausea, abdominal distention, cramping, diarrhea, and vasomotor changes associated with swings in glucose. Some of the management strategies are the opposite of those suggested for use in delayed emptying. Taking advantage of normal physiology by increasing the fat, protein, and fiber content of one's diet, including the addition of pectin and guar gum, can be helpful.[59] Rather than mixing liquids with the meal, they should be taken separately from solids. Some of the same strategies recommended for treating delayed gastric emptying may also be helpful with rapid emptying; for example, smaller, more frequent meals, as well as continuous drip or postpyloric feedings, may help.

Pharmacologic therapeutic options are limited. Acarbose, an α-glucosidase inhibitor, has been used to treat dumping syndrome because it delays the hydrolysis of carbohydrates, which in turn delays the absorption of glucose.[68,69] Octreotide, an analogue of somatostatin, can be beneficial because one of its specific actions is to delay gastric emptying.[70,71]

Slow Intestinal Transit

Slow intestinal transit may occur following surgery (postoperative ileus) or a viral infection or other systemic illness, as a side effect of certain drugs, or as part of a significant motility disorder, ranging from disruptions in normal feedback loops to extreme circumstances of chronic intestinal pseudoobstruction. In addition to delayed gastric emptying, as previously noted, patients requiring intensive care and respiratory support have multiple factors that negatively impact GI motility. Opioids and sedatives, although impor-tant factors in care, have been shown to decrease intestinal transit and secretion of water and electrolytes into the GI tract. Alterations in the MMCs, resting tone, and peristalsis all contribute to the disruption of overall propulsion through the small bowel.[54,56,57] No clear evidence or

consensus opinion exists to support recommendations of nutrition interventions that may be beneficial in these circumstances.[54–57]

Currently, few drugs are available to help promote motility of the small bowel. Erythromycin has some augmenting effect on phase III MMCs in the small bowel.[72,73] Some data also indicate that amoxicillin-clavulanate may promote small bowel motility.[74] It has been shown that amoxicillin-clavulanate, when given preprandially, induces duodenal phase III MMCs within 10 minutes of enteral administration.[75] In more severe cases, octreotide may be beneficial. This somatostatin analogue has various effects on the GI tract, including induction of phase III MMC when given in small doses subcutaneously.[76]

Rapid Intestinal Transit

Rapid intestinal transit may occur following a systemic illness or surgery on the GI tract and can result in malabsorption of nutrients and diarrhea. Feeding strategies will be discussed in detail in later chapters on GI disease and intestinal failure. One approach that may be beneficial, regardless of the feeding selected or delivery route, is the addition of soluble fiber (eg, pectin, guar gum) because it will prolong intestinal transit time.[77]

Various drugs can also be used to slow transit through the small bowel. Loperamide, a peripherally acting opioid analogue, inhibits both small bowel and colonic motility and has been shown to decrease stool frequency and urgency.[73] Anticholinergic agents, such as hyoscyamine, can also help to slow intestinal transit.

Conclusion

Although the impact of gastric and intestinal motility on feeding is important, there are many other factors to consider, which will be discussed in subsequent chapters. Having a basic understanding of the principles discussed in this chapter will provide a framework for considering which interventions might be appropriate for individual patients.

Test Your Knowledge Questions

1. Which of the following does not slow gastric emptying?
   A. Soluble fibers
   B. Fats
   C. Liquids
   D. Protein
2. Which one of the following strategies is not effective in rapid and delayed gastric emptying?
   A. Small frequent feeds
   B. Giving liquids with meals to increase the fluid content of the meal
   C. Continuous drip feeds
   D. Postpyloric feeds
3. Which of the following is true for preterm infants?
   A. Bolus feeds will promote normal small bowel motor activity.
   B. Transit through the small bowel is shorter than in the older infant.
   C. Gastric emptying is more rapid than in the older infant.
   D. Feeding can promote the development of intestinal motility.

References

1. Camilleri M. Integrated upper gastrointestinal response to food intake. *Gastroenterology*. 2006;131:640–658. https://doi.org/10.1053/j.gastro.2006.03.023
2. Costa M, Brookes SJH, Hennig GW. Anatomy and physiology of the enteric nervous system. *Gut*. 2000;47(suppl IV):iv15–iv19. https://doi.org/10.1136/gut.47.suppl_4.iv15
3. Leger G. Basic physiology of motility, absorption and secretion. In: Langnas AN, Goulet O, Quigley EMM, Tappenden KA, eds. *Intestinal Failure: Diagnosis, Management and Transplantation*. Blackwell Publishing; 2008:20–32. https://doi.org/10.1002/9781405195805.ch3
4. Saps M, Di Lorenzo C. Gastric motility: normal motility and development of the gastric neuroenteric system. In: Kleinman RE, Sanderson IR, Goulet O, Sherman PM, Mieli-Vergani G, Shneider BL, eds. *Walker's Pediatric Gastrointestinal Disease.* Vol 1. 5th ed. BC Decker, Inc; 2008:187–193.

5. Rolle U, Piaseczna-Piotrowska A, Puri P. Interstitial cells of Cajal in the normal gut and in intestinal motility disorders of childhood. *Pediatr Surg Int*. 2007;23:1139–1152. https://doi.org/10.1007/s00383-007-2022-7
6. Sanders KM, Koh SD, Ward SM. Interstitial cells of Cajal as pacemakers in the gastrointestinal tract. *Annu Rev Physiol*. 2006;68:307–343. https://doi.org/10.1146/annurev.physiol.68.040504.094718
7. Altaf MA, Sood MR. The nervous system and gastrointestinal function. *Dev Disabil Res Rev.* 2008;14:87–95. https://doi.org/10.1002/ddrr.15
8. Berseth, CL. Gestational evolution of small intestine motility in preterm and term infants. *J Pediatr.* 1989;115(4):646–651. https://doi.org/10.1016/s0022-3476(89)80302-6
9. Faure C, Thapar N, Di Lorenzo C. Introduction to gut motility and sensitivity. In: Faure C, Thapar N, Di Lorenzo C., eds. *Pediatric Neurogastroenterology.* Springer, Cham; 2022:3–9. https://doi.org/10.1007/978-3-031-15229-0_1
10. Wester T, O'Briain DS, Puri P. Notable postnatal alterations in the myenteric plexus of normal human bowel. *Gut.* 1999;44:666–674. https://doi.org/10.1136/gut.44.5.666
11. Cuomo R, Sarnelli G. Food intake and gastrointestinal motility. A complex interplay. *Nutr Metab Cardiovasc Dis*. 2004;14:173–179. https://doi.org/10.1016/s0939-4753(04)80001-2
12. Hennig GW, Brookes SJH, Costa M. Excitatory and inhibitory motor reflexes in the isolated guinea-pig stomach. *J Physiol*. 1997;501:197–212. https://doi.org/10.1111/j.1469-7793.1997.197bo.x
13. Lacy BE, Koch KL, Crowell MD. The stomach: normal function and clinical disorders. Manometry. In: Schuster MM, Crowell MD, Koch KL, eds. *Schuster Atlas of Gastrointestinal Motility in Health and Disease*. 2nd ed. BC Decker, Inc; 2002:135–150.
14. Siegel JA, Urbain J-L, Adler LP, et al. Biphasic nature of gastric emptying. *Gut*. 1988;29:85–89. https://doi.org/10.1136/gut.29.1.85
15. Sase M, Miwa I, Sumie M, et al. Gastric emptying cycles in the human fetus. *Am J Obstet Gynecol.* 2005;193(3 Pt 2):1000–1004. https://doi.org/10.1016/j.ajog.2005.05.044

16. Berseth CL. Assessment in intestinal motility as a guide in the feeding management of the newborn. *Clin Perinatol*. 1999;26:1007–1015. https://doi.org/10.1016/S0095-5108(18)30032-0
17. Riezzo G, Indrio F, Montagna O, et al. Gastric electrical activity and gastric emptying in term and preterm newborns. *Neurogastroenterol Motil*. 2000;12:223–229. https://doi.org/10.1046/j.1365-2982.2000.00203.x
18. Berseth CL. Motor function in the stomach and small intestine in the neonate. *NeoReviews.* 2006;7:e28–33. https://doi.org/10.1542/neo.7-1-e28
19. Kellow JE. Small intestine: normal function and clinical disorders. Manometry. In: Schuster MM, Crowell MD, Koch KL, eds. *Schuster Atlas of Gastrointestinal Motility in Health and Disease*. 2nd ed. BC Decker, Inc; 2002:219–236.
20. Boccia G, Staiano A. Intestinal motility: normal motility and development of the intestinal neuroenteric system. In: Kleinman RE, Sanderson IR, Goulet O, Sherman PM, Mieli-Vergani G, Shneider BL, eds. *Walker's Pediatric Gastrointestinal Disease.* Vol. 1. 5th ed. BC Decker, Inc; 2008:665–674.
21. Scott SM, Knowles CH, Wang D, et al. The nocturnal jejunal migrating motor complex: defining normal ranges by study of 51 healthy adult volunteers and meta-analysis. *Neurogastroenterol Motil*. 2006;18:927–935. https://doi.org/10.1111/j.1365-2982.2006.00824.x
22. Foong JPP, Becket EA, Young HM, Jadcherla SR, Bornstein JC. Development of gut motility. In: Faure C, Thapar N, Di Lorenzo C., eds.) *Pediatric Neurogastroenterology.* Springer, Cham; 2022:21–41. https://doi.org/10.1007/978-3-031-15229-0_3.
23. Rybak A, Seliakellis E, Thapar N, Borrelli, O. Antroduodenal manometry. In: Faure C, Thapar N, Di Lorenzo C., eds. *Pediatric Neurogastroenterology.* Springer, Cham; 2022: 131–144. https://doi.org/10.1007/978-3-031-15229-0_3
24. Jadcherla SR, Klee G, Berseth CL. Regulation of migrating motor complexes by motilin and pancreatic polypeptide in human infants. *Pediatr Res.* 1997;42(3):365–369. https://doi.org/10.1203/00006450-199709000-00018

25. Bisset WM, Watt JB, Rivers RP, Milla PJ. Ontogeny of fasting small intestinal motor activity in the human infant. *Gut.* 1988;29(4):483–488. https://doi.org/10.1136/gut.29.4.483
26. Berseth CL. Effect of early feeding on maturation of the preterm infant's small intestine. *J Pediatr*. 1992;120:947–953. https://doi.org/10.1016/s0022-3476(05)81969-9
27. Commare CE, Tappenden KA. Development of the infant intestine: implications for nutrition support. *Nutr Clin Pract*. 2007;22:159–173. https://doi.org/10.1177/0115426507022002159
28. McClure RJ, Newell SJ. Randomised controlled trial of trophic feeding and gut motility. *Arch Dis Child Fetal Neonatal Ed*. 1999;80:F54–F58. https://doi.org/10.1136%2Ffn.80.1.f54
29. Ledeboer M, Masclee AAM, Coenraad M, et al. Antroduodenal motility and small bowel transit during continuous intraduodenal or intragastric administration of enteral nutrition. *Eur J Clin Invest.* 1999;29:615–623. https://doi.org/10.1046/j.1365-2362.1999.00507.x
30. Collins PJ, Houghton LA, Read NW, et al. Role of the proximal and distal stomach in a mixed solid and liquid meal emptying. *Gut*. 1991;32:615–619. https://doi.org/10.1136/gut.32.6.615
31. Marciani L, Gowland PA, Spiller RC, et al. Effect of meal viscosity and nutrients on satiety, intragastric dilution, and emptying assessed by MRI. *Am J Physiol Gastrointest Liver Physiol*. 2001;280:G1227–G1233. https://doi.org/10.1152/ajpgi.2001.280.6.g1227
32. Schönfeld J, Evans DF, Wingate DL. Effect of viscous fiber (guar) on postprandial motor activity in human small bowel. *Dig Dis Sci.* 1997;42:1613–1617. https://doi.org/10.1023/a:1018888726646
33. Mishima Y, Amano Y, Takahashi Y, et al. Gastric emptying of liquid and solid meals at various temperatures. *J Gastroenterol.* 2009;44(5):412–418. https://doi.org/10.1007/s00535-009-0022-1
34. Sun WM, Houghton LA, Read NW, Grundy DG, Johnson AG. Effect of meal temperature on gastric emptying of liquids in man. *Gut.* 1988;29(3):302–305. https://doi.org/10.1136/gut.29.3.302
35. Schwartz GJ, Moran TH. Duodenal nutrient exposure elicits nutrient-specific gut motility and vagal afferent signals in rat. *Am J Physiol Regul Integr Comp Physiol*. 1998;274:R1236-R1242. https://doi.org/10.1152/ajpregu.1998.274.5.r1236

36. MacIntosh CG, Andrews JM, Jones KL, et al. Effects of age on concentrations of plasma cholecystokinin, glucagon-like peptide 1, and peptide YY and their relation to appetite and pyloric motility. *Am J Clin Nutr*. 1999;69:999–1006. https://doi.org/10.1093/ajcn/69.5.999
37. Feinle C, O'Donovan D, Doran S, et al. Effects of fat digestion on appetite, APD motility, and gut hormones in response to duodenal fat infusions in humans. *Am J Physiol Gastrointest Liver Physiol*. 2003;284:G798–G807. https://doi.org/10.1152/ajpgi.00512.2002
38. Houghton LA, Mangnall YF, Read NW. Effect of incorporating fat into a liquid test meal on the relation between intragastric distribution and gastric emptying in human volunteers. *Gut*. 1990;31:1226–1229. https://doi.org/10.1136/gut.31.11.1226
39. Paraskevopoulos JA, Houghton LA, Eyre-Brooke I, Johnson AG, Read NW. Effect of composition of gastric contents on resistance to emptying of liquids from stomach in humans. *Dig Dis Sci*. 1988;33:914–918. https://doi.org/10.1007/bf01535984
40. Ohtani N, Sasaki I, Naito H, Shibata C, Matsuno S. Mediators for fat-induced ileal brake are different between stomach and proximal small intestine in conscious dogs. *J Gastrointest Surg*. 2001;5:377–382. https://doi.org/10.1016/s1091-255x(01)80065-2
41. Chaw CS, Yazaki E, Evans DF. The effect of pH change on the gastric emptying of liquids measured by electrical impedance tomography and pH-sensitive radiotelemetry capsule. *Int J Pharm.* 2001;227:167–175. https://doi.org/10.1016/s0378-5173(01)00795-5
42. Boulby P, Moore R, Gowland P, Spiller RC. Fat delays emptying but increases forward and backward antral flow as assessed by flow-sensitive magnetic resonance imaging. *Neurogastroenterol Motil*. 1999;11:27–36. https://doi.org/10.1046/j.1365-2982.1999.00133.x
43. Siegel M, Lebenthal E, Krantz B. Effect of caloric density on gastric emptying in premature infants. *J Pediatr.* 1984;104(1):118–122. https://doi.org/10.1016/s0022-3476(84)80607-1
44. Siegel M, Lebenthal E, Topper W, Krantz B, Li PK. Gastric emptying in prematures of isocaloric feedings with differing osmolalities. *Pediatr Res.* 1982;16:141–147. https://doi.org/10.1203/00006450-198202000-00013

45. McClure RJ, Newell SJ. Effect of fortifying breastmilk on gastric emptying. *Arch Dis Child.* 1996;74:60–62. https://doi.org/10.1136%2Ffn.74.1.f60
46. Gathwala G, Shaw C, Shaw P, Yadav S, Sen J. Human milk fortification and gastric emptying in the preterm neonate. *Int J Clin Pract.* 2008;62(7):1039–1043. https://doi.org/10.1111/j.1742-1241.2006.01201.x
47. Schönfeld J, Evans DF, Wingate DL. Daytime and nighttime motor activity of the small bowel after solid meals of different caloric value in humans. *Gut.* 1997;40:614–618. https://doi.org/10.1136/gut.40.5.614
48. Schönfeld JV, Evans DF, Renzing K, Castillo FD, Wingate DL. Human small bowel motor activity in response to liquid meals of different caloric value and different chemical composition. *Dig Dis Sciences.* 1998;43(2):265–269. https://doi.org/10.1023/a:1018885717947
49. Ramirez A, Wong WW, Shulman RJ. Factors regulating gastric emptying in preterm infants. *J Pediatr*. 2006;149:475–479. https://doi.org/10.1016/j.jpeds.2006.05.028
50. Indrio F, Riezzo G, Raimondi F, et al. Prebiotics Improve Gastric Motility and Gastric Electrical Activity in Preterm Newborns. *J Pediatr Gastroenterol Nutr.* 2009;49(2):258–261. https://doi.org/10.1097/mpg.0b013e3181926aec
51. Dasopoulou M, Briana DD, Boutsikou T, et al. Motilin and gastrin secretion and lipid profile in preterm neonates following prebiotics supplementation: a double-blind randomized controlled study. *J Parenter Enteral Nutr*. 2015 Mar;39(3):359–68. https://doi.org/10.1177/0148607113510182
52. Baker JH, Berseth CL. Duodenal motor responses in preterm infants fed with formula with varying concentrations and rates of infusion. *Pediatr Res*. 1997;42:618–622. https://doi.org/10.1203/00006450-199711000-00012
53. De Ville K, Knapp E, Al-Tawil Y, Berseth CL. Slow infusion feedings enhance duodenal motor responses and gastric emptying in preterm infants. *Am J Clin Nutr*. 1998;68:103–108.
54. Yan Y, Chen Y, Zhang X. The effect of opioids on gastrointestinal function in the ICU. *Critical Care.* 2021;25:370. https://doi.org/10.1186/s13054-021-03793-1

55. Martinez E, Douglas K, Nurko S, Mehta N. Gastric dysmotility in critically ill children: pathophysiology, diagnosis and management. *Pediatr Crit Care Med.* 2015;16(9):828–836. https://doi.org/10.1097/pcc.0000000000000493
56. Simons S, Anand KJS. Pain control: opioid dosing, population kinetics and side-effects. *Seminars in Fetal & Neonatal Medicine.* 2006;11:260–7. https://doi.org/10.1016/j.siny.2006.02.008
57. Patel D, Callaway J, Vaezi M. Opioid-induced foregut dysfunction. *Am J Gastroenterology.* 2019;114:1716–1725. https://doi.org/10.14309/ajg.0000000000000354
58. Di Lorenzo C, Ciamarra P. Pediatric gastrointestinal motility. In: Schuster MM, Crowell MD, Koch KL, eds. *Schuster Atlas of Gastrointestinal Motility in Health and Disease*. 2nd ed. BC Decker, Inc; 2002:411–428.
59. Karamanolis G, Tack J. Nutrition and motility disorders. *Best Pract Res Clin Gastroenterol*. 2006;20:485–505. https://doi.org/10.1016/j.bpg.2006.01.005
60. Karamanolis G, Tack J. Promotility medications—now and in the future. *Dig Dis*. 2006;24:297–307. https://doi.org/10.1159/000092883
61. Ng PC. Use of oral erythromycin for the treatment of gastrointestinal dysmotility in preterm infants. *Neonatology.* 2009;95:97–104. https://doi.org/10.1159/000153093
62. Jadcherla SR, Berseth, CL. Effect of erythromycin on gastroduodenal contractile activity in developing neonates. *J Pediatr Gastroenterol Nutr.* 2002;34:16–22. https://doi.org/10.1097/00005176-200201000-00005
63. El Hennaway AA, Sparks JW, Armentrout, et al. Erythromycin fails to improve feeding outcome in feeding-intolerant preterm infants. *J Pediatr Gastroenterol Nutr.* 2003;37:281–6. https://doi.org/10.1097/00005176-200309000-00015
64. Ng YY, Su PH, Chen JY, et al. Efficacy of intermediate-dose oral erythromycin on very low birthweight infants with feeding intolerance. *Pediatr Neonatol.* 2012;53(1):34–40. https://doi.org/10.1016/j.pedneo.2011.11.007
65. Kovacic K, Elfar W, Rosen J, et al. Update on pediatric gastroparesis: A review of published literature and recommendations for future research.

Neurogastroenterol Motil. 2020. Mar;32(3):e13780. https://doi.org/10.1111/nmo.13780
66. Yamoto M, Fukumoto K, Takahashi T, et al. Risk factors for dumping syndrome after fundoplication for gastroesophageal reflux in children. *Pediatr Surg Int.* 2021;37(2):183–189. https://doi.org/10.1007/s00383-020-04783-0
67. Samuk I, Afriate R, Horne T, et al. Dumping syndrome following Nissen fundoplication, diagnosis and treatment. *J Pediatr Gastroenterol Nutr.* 1996;23(3):235–40. https://doi.org/10.1097/00005176-199610000-00006
68. Ng DD, Ferry RJ, Kelly A, et al. Acarbose treatment of postprandial hypoglycemia in children after Nissen fundoplication. *J Pediatr*. 2001;139:877–879. https://doi.org/10.1067/mpd.2001.119169
69. Zung A, Zadik Z. Acarbose treatment of infant dumping syndrome: extensive study of glucose dynamics and long-term follow-up. *J Pediatr Endocrinol Metab.* 2003;16:905–915. https://doi.org/10.1515/jpem.2003.16.6.907
70. Lamers CB, Bijlstra AM, Harris AG. Octreotide, a long-acting somatostatin analog, in the management of post-operative dumping syndrome. An update. *Dig Dis Sci*. 1993;38:359–364. https://doi.org/10.1007/bf01307556
71. Scarpignato C. The place of octreotide in the medical management of the dumping syndrome. *Digestion*. 1996;57(suppl 1):114–118. https://doi.org/10.1159/000201413
72. Costalos C, Gounaris A, Varhalama E, et al. Erythromycin as a prokinetic agent in preterm infants. *J Pediatr Gastroenterol Nutr.* 2002;34(1):23–25. https://doi.org/10.1097/00005176-200201000-00006
73. Maheshwari A, Sood MR. Drugs acting on the gut: Prokinetics, antispasmodics, laxatives. In: Faure C, Thapar N, Di Lorenzo C, eds. *Pediatric Neurogastroenterology.* Springer, Cham; 2022:555–571. https://doi.org/10.1007/978-3-031-15229-0_43
74. Caron F, Ducrotte P, Lerebours E, et al. Effects of amoxicillin-clavulanate combination on the motility of the small intestine in human beings. *Antimicrob Agents Chemother*. 1991;35:1085–1088. https://doi.org/10.1128/aac.35.6.1085

75. Gomez R, Fernandez S, Aspirot A, et al. Effect of amoxicillin/clavulanate on gastrointestinal motility in children. *J Pediatr Gastroenterol Nutr.* 2012;54(6):780–784. https://doi.org/10.1097/mpg.0b013e31824204e4
76. Di Lorenzo C, Lucanto C, Flores AF, Idries S, Hyman PE. Effect of octreotide on gastrointestinal motility in children with functional gastrointestinal symptoms. *J Pediatr Gastroenterol Nutr*. 1998;27:508–512. https://doi.org/10.1097/00005176-199811000-00002
77. Finkel Y, Brown G, Smith HL, et al. The effects of a pectin-supplemented elemental diet in a boy with short bowel syndrome. *Acta Paediatr Scand*. 1990;79:983–986. https://doi.org/10.1111/j.1651-2227.1990.tb11368.x

Test Your Knowledge Answers

1. The correct answer is **C**. Liquids empty from the stomach faster than solids; feedings higher in fiber, fat, and protein will empty more slowly.
2. The correct answer is **B**. Giving liquids with a meal increases gastric emptying, which is counterproductive in dumping syndrome.
3. The correct answer is **D**. Even small amounts of enteral feeding in preterm infants will encourage maturation of intestinal motility and bolus feeds will cause a cessation of contractions in the proximal small bowel. Both gastric emptying and intestinal transit are slower in preterm infants.

3

Carbohydrates

Suzanna L. Attia, MD, MScPH

Learning Objectives

1. Describe the basic structure and classification of carbohydrates.
2. Explain the primary steps of carbohydrate digestion and absorption.
3. Know the defects that lead to and consequences of carbohydrate malabsorption.

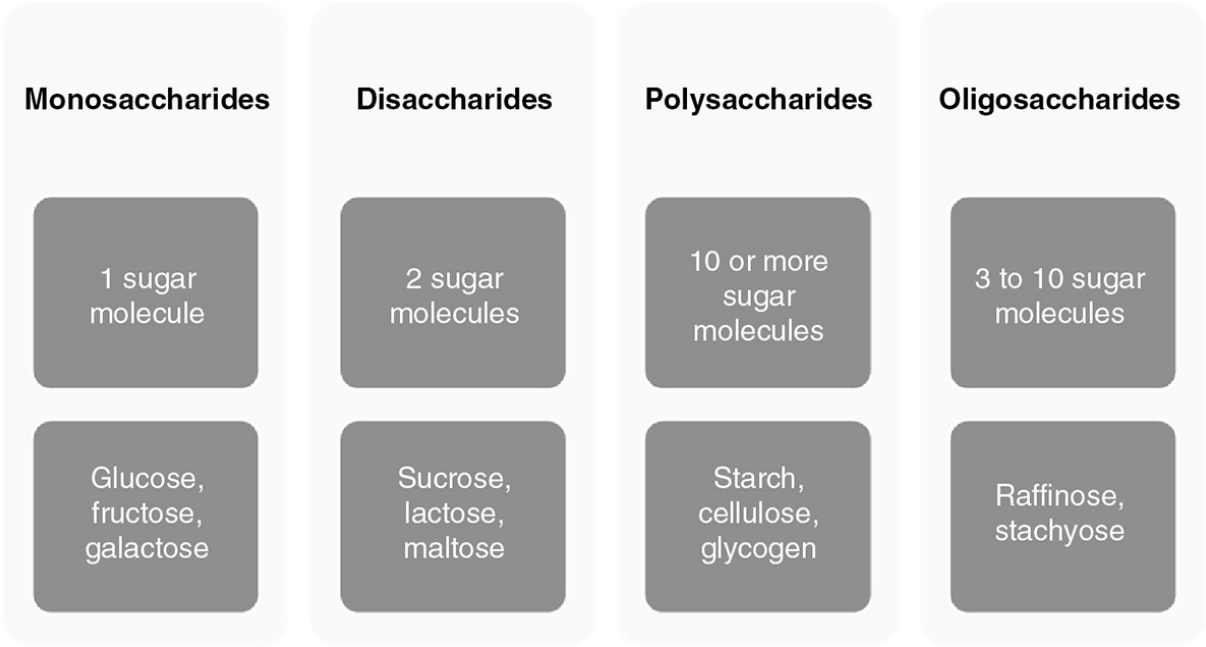
Introduction

Carbohydrates form a significant portion of the human diet. They provide 4 kcal/g and typically supply 50% of the body's total energy requirement. Infant formula composition standards suggest that 36% to 56% of calories should come from carbohydrates, and as the child gets older, dietary reference intake guidelines suggest that carbohydrates should comprise 45% to 60% of calories.[1,2]

Human metabolic processes are finely tuned to regulate carbohydrate levels in the bloodstream, adapting to a variety of circumstances. This adaptability is evident when considering the efficacy of ketogenic diets (low in carbohydrates, high in fats) for treating intractable epilepsy. This metabolic shift from carbohydrate-based energy to primarily fat-based energy demonstrates the feasibility of a "carbohydrate-free" diet.

Dietary carbohydrates are categorized by their physical structure. The simplest carbohydrates are 6-carbon chain molecules of sugar called *monosaccharides* (also known as simple sugars); these include glucose, fructose, and galactose. Two monosaccharides connected form a *disaccharide*; an example is lactose (comprised of single molecules of glucose and galactose). Three to 10 sugars stacked in length form *oligosaccharides* and longer-chain sugars are referred to as *polysaccharides* (see Figure 3-1). Both oligosaccharides and polysaccharides can be called starches. Starches are abundant in normal diets and are found in many foods, such as rice, corn, and tapioca.

FIGURE 3-1. Classification of Carbohydrates



Fiber refers to starches that resist digestion. Insoluble fiber (eg, wheat bran) does not dissolve in water, and soluble fiber (eg, psyllium husk, nuts and seeds, oat bran) does. While sugars and starches offer direct caloric value, fiber serves numerous crucial functions. It nurtures beneficial intestinal bacteria as prebiotics, transforms into short-chain fatty acids through bacterial fermentation, increases intestinal transit time, and softens or bulks up stool (softening, bulking, and enhancing intestinal transit). The

term *complex carbohydrates* refers to multiple sugars in complex chains and can be distinguished from *simple sugars* such as glucose, fructose, and galactose.

Complex carbohydrates consist of many glucose monomers joined by 1–4 linkages, and each one has a unique spatial arrangement. Starch is in the α configuration, while the fiber cellulose is in the β configuration.[3] Amylose, typically the simplest starch consumed early in life, is a linear polymer of glucose molecules linked by α-1,4 glycosidic bonds.[3] Amylopectin, a plant starch that is the major form of starch in the diet, is structurally similar to amylose, but α-1,6 branch points occur at every 20 to 30 glucose units.[3]

Exclusively breastfed infants receive carbohydrates primarily from lactose in human milk, complemented by fructose, other monosaccharides, and oligosaccharides. Lactose naturally breaks down into glucose and galactose during digestion. In addition to their nutritional value, carbohydrates—specifically human milk oligosaccharides (HMO)—play a role in promoting the growth of healthy bacteria in the intestine and reducing the ability of pathogens to infect the growing infant.[4] This has prompted formula companies to add and advertise HMOs in their infant products.

In contrast to breastfed infants, formula-fed infants are typically exposed to a distinct array of carbohydrates, many of which consist of corn syrup solids and glucose polymers. Over time, the human diet should expand with an increasing variety of carbohydrates, preferably with a parallel increase of dietary fiber.

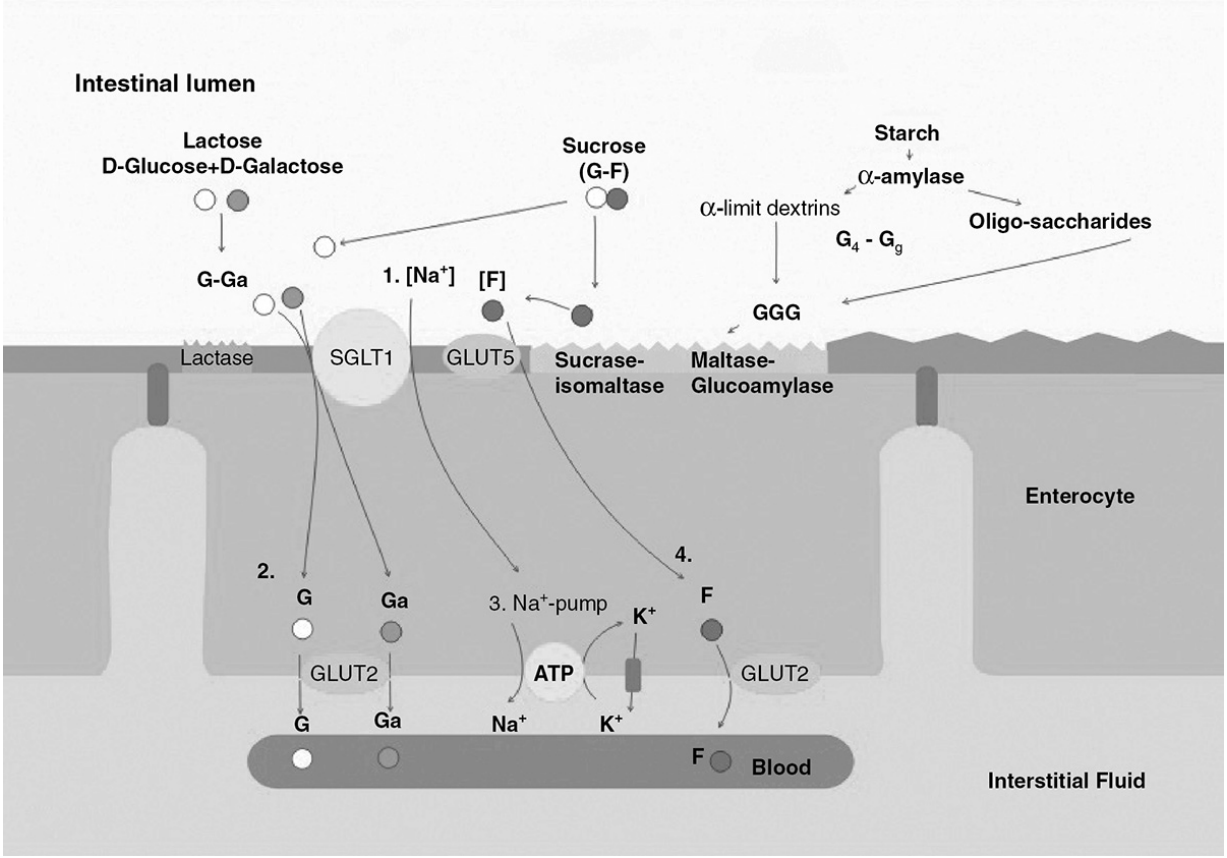
Digestion

Starch and Sucrose

Starch digestion begins in the mouth with salivary amylases and continues in the small intestine with pancreatic amylases. Amylase hydrolyzes starches at the internal α-1,4 bonds (see Figure 3-2). Because it does not cleave bonds located next to α-1,6 bonds or at the reducing end of the starch molecule, amylase breaks down amylose and amylopectin into maltotriose, maltose, and α-limit dextrins (a short-chain amylopectin that retains its 1–6 linkage; see Figure 3-2).[5] In older children and adults, sufficient

intraluminal α-amylase activity exists to digest 10 times more starch than is typically consumed daily.[6]

FIGURE 3-2. Digestion and Absorption of Dietary Carbohydrates



Adapted with permission from Paulev P-E, Zubieta-Calleja G. In: Gastrointestinal function and disorders. *Textbook in Medical Physiology and Pathophysiology Essentials and Clinical Problems*. 2nd ed. Chapter 22. http://www.zuniv.net/physiology/book/chapter22.html

Amylase secreted by the salivary glands is present in preterm infants. Although salivary amylase is inactivated at a pH <4, it tends to remain active in the stomachs of newborns because of poor acidification.[7] Pancreatic amylase activity is initially present at low levels in preterm and term infants and then increases at 4 to 6 months of age before finally reaching adult activity levels by 1 to 2 years of age.[8] Further digestion of

the disaccharides and oligosaccharides occurs at the intestine's brush border (enterocyte surface) via maltase-glucoamylase and sucrase-isomaltase.

Maltase-glucoamylase is in the brush border of the small intestine and is most active in the ileum. It cleaves α-1,4 bonds of nonbranching glucose polymers (ie, amylose) and nonreducing ends of polysaccharides (see Figure 3-2). Short chains (ie, <10 glucose units) are more readily digested by glucoamylase than longer chains.[9]

Glucoamylase activity is detectable early in gestation, and by 28 weeks of gestation, is comparable to that at term.[10,11] Infants <1 year have glucoamylase activity similar to that of children and adults.[11,12] In preterm and term infants, glucoamylase is the primary enzyme for complex carbohydrate digestion because pancreatic amylase activity is low.[13] In adults, glucoamylase activity increases steadily throughout the small intestine, with greatest activity near the ileocecal valve.[12]

Sucrase-isomaltase, a disaccharidase also found in the brush border, has a high degree of activity in the proximal small intestine. Sucrase-isomaltase hydrolyzes 75% to 80% of maltase, almost all dietary isomaltose, and 100% of sucrose. Sucrase-isomaltase is cleaved by pancreatic proteases into 2 enzymes, sucrase and isomaltase.[3,5] Sucrase hydrolyzes sucrose into the monosaccharides glucose and fructose (see Figure 3-2). Isomaltase cleaves the α-1,6 glycosidic bonds of amylopectin (see Figure 3-2). By the beginning of the third trimester, sucrase-isomaltase activity is comparable to that of adults.[14] This activity remains high throughout life. Congenital sucrase-isomaltase deficiency is a relatively rare (1/5000) autosomal recessive disorder in which patients lack sucrase and have variable isomaltase activity.[15]

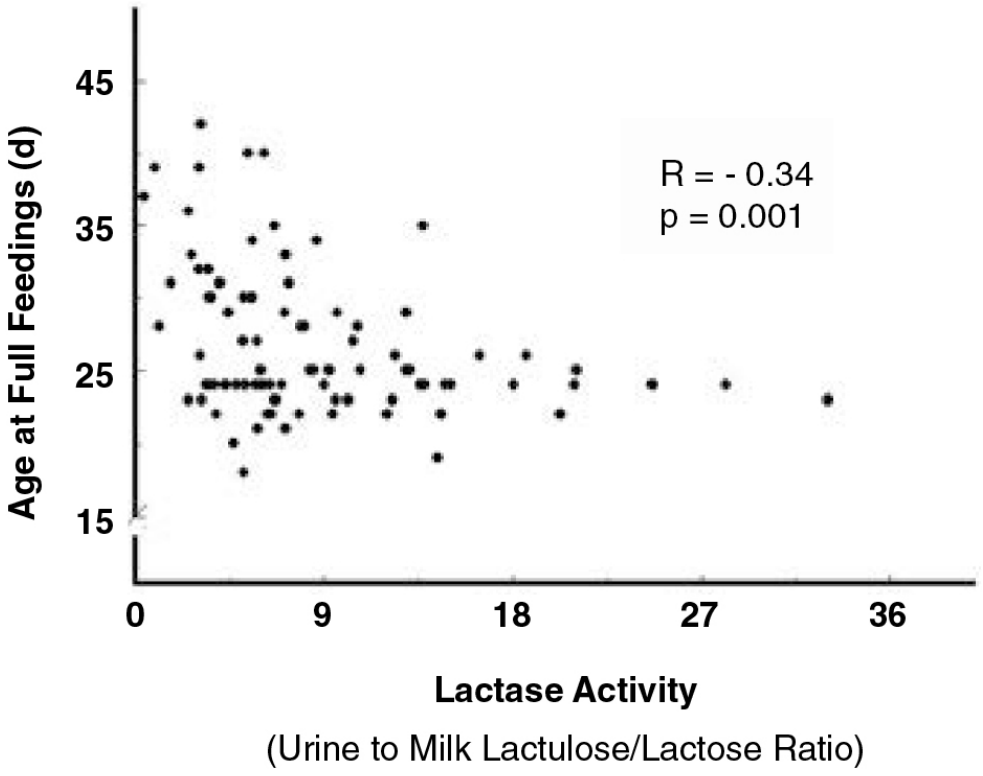
Lactose

Lactase is the enzyme responsible for digesting lactose, which is the primary carbohydrate in human milk and most infant formulas. Lactase hydrolyzes the disaccharide lactose into monosaccharides glucose and galactose (see Figure 3-2).[3,5] Like maltase-glucoamylase and sucrase-isomaltase, lactase is located along the brush border of the enterocytes lining the villi of the small intestine. Because the optimum pH for lactase

activity is 6.0, its activity is highest in the jejunum and decreases toward the ileum.[12] This gradient is established by 11 weeks of gestation.[10] During gestation, lactase activity increases until birth, with the greatest increase occurring during the third trimester. At the beginning of the third trimester, lactase activity is approximately 25% of that at term.[14,16]

In most individuals, lactase activity begins to decline with advancing age.[17] This genetically predetermined process, also known as primary lactase deficiency or primary hypolactasia, commonly begins between 3 and 5 years of age and continues into adulthood.[18] The prevalence of hypolactasia varies across ethnic populations as follows: 90% Asian, 80% Black, 53% Hispanic, and 15% to 25% non-Hispanic White.[18] The role of variable digestive capacity for lactose in the development of illness among neonates is of uncertain significance. Studies conducted in preterm pigs suggest that incomplete digestion of carbohydrates may be linked to the pathogenesis of necrotizing enterocolitis.[19] Additionally, the time until full feeding tolerance is inversely related to lactase activity (see Figure 3-3).[16,20]

FIGURE 3-3. Lactase Development With Age and Type of Feeding



Lactase activity increases with age, but the increase is greater in the early fed group compared to the standard group ($p < 0.01$). Lactase activity in the early fed group is greater than that in the standard group at 10 and 28 days of age ($p = 0.004$) but not at 50 days of age ($p > 0.5$). Reprinted with permission from Elsevier from Schulman et al.[14]

Among preterm infants who are receiving formula, the substitution of a combination of lactose and glucose polymers for lactose alone resulted in less feeding intolerance.[21] However, early enteral feeding in preterm infants increases lactase activity (see Figure 3-3).[16] Moreover, human milk feeding promotes the development of lactase activity in preterm infants.[16] For instance, preterm infants fed human milk demonstrate greater lactase activity than those fed formula containing a combination of lactose and glucose polymers.[16] These observations further support the importance of human milk feeding.[22]

Congenital lactase deficiency is an autosomal recessive disorder characterized by a complete absence of lactase expression.[23] The incidence

is unknown, but the disorder is too rare to be reportable. Symptoms manifest at birth with the introduction of lactose in the diet. This newborn, genetic-type hypolactasia stands in stark contrast to secondary lactase deficiency, which results as a consequence of mucosal injury to the small intestine. Secondary lactase deficiency occurs most commonly following acute infectious gastroenteritis and generally resolves with the resolution of the acute illness.[24] However, infants with a prolonged diarrheal illness resulting in severe dehydration may show clinical signs of lactose intolerance and temporarily benefit from a lactose-free formula until their symptoms resolve.[24,25]

Absorption

Dietary carbohydrates are absorbed in the form of glucose, galactose, and fructose.[25] Two categories of transporters, glucose transporters (GLUTs) and sodium-glucose cotransporters (SGLT1), mediate absorption of glucose from the intestinal lumen into the interstitial space (see Figure 3-2).[26,27] Active transport of glucose and galactose is present by 12 weeks of gestation and increases through gestation.[28,29] SGLT1 transports glucose along the sodium gradient maintained by the sodium-potassium ATPase pump located at the basolateral surface of the enterocyte (see Figure 3-2).[26,27] SGLT1 is a high-affinity active transporter of glucose and galactose located at the intestinal villus brush border with binding sites for one glucose (or galactose) molecule and two sodium molecules. Once all sites are occupied, glucose and sodium are translocated across the enterocyte's apical membrane and are released into the enterocyte.[26,27] This sodium-linked transport of glucose accentuates the osmotic absorption of water and accounts for the increased efficacy of oral rehydration solutions when electrolytes and glucose are present in concentrations that facilitate their uptake.

Glucose-galactose malabsorption is a rare autosomal recessive disorder that results in watery diarrhea soon after birth.[34] Approximately 300 cases have been reported to date. Treatment entails substituting dietary glucose and galactose with fructose. Fructose is still absorbed effectively in this

disorder because it is transported into enterocytes via GLUT5 along its concentration gradient in a sodium-independent fashion (see Figure 3-2).[26] GLUT2 has also been identified at the brush border (luminal surface), with evidence suggesting that ingestion of a carbohydrate load stimulates SGLT1, resulting in the recruitment of GLUT2 receptors to the apical membrane of enterocytes.[31,32]

Short-Chain Fatty Acids

Up to 5% to 20% of ingested starches resist digestion in the small intestine.[33] Upon reaching the colon, colonic bacterial fermentation of this resistant starch results in the production of short-chain fatty acids (SCFAs).[34] SCFAs are produced by the fermentative modification of the carbon backbone structure of carbohydrates escaping digestion in the small bowel. The soluble components of fiber are fermented into SCFAs, while the insoluble components resist fermentation and contribute to fecal bulk.[26]

The total volume of SCFAs generated depends on colonic microbial characteristics, the amount of resistant starch ingested, and gut transit time.[35,36] Despite the variability of these factors in a healthy gastrointestinal tract, the ratio of the SCFAs produced is fairly constant (acetate, propionate, and butyrate; 60:20:20, respectively).[35] This ratio is similar in both the proximal and distal colon, reflecting a relatively uniform absorptive capacity of the mucosa throughout the colon. The absorption of SCFAs by the colon is very efficient; only 5% to 10% of SCFAs produced are excreted in feces.[35] SCFAs play an essential role in maintaining gut health with their important effects on colonic luminal pH, intracellular pH, cell volume, and ion transport as well as moderating effects on enterocyte proliferation, differentiation, and gene expression.[35]

Maldigestion and Malabsorption of Carbohydrates

Disorders of carbohydrate digestion and absorption are categorized in several ways (see Exhibit 3-1). The following disorders are considered

according to their pathogenesis:[36]

- Impairment of intrinsic digestive processes (usually congenital); examples include sucrase-isomaltase deficiency and glucose-galactose malabsorption
- Malabsorption due to an associated disease state (may be acquired or heritable); examples include viral diarrhea, environmental enteropathy, celiac disease, and cystic fibrosis
- Reduction of the gut's absorptive surface (usually acquired); examples include short bowel syndrome

EXHIBIT 3-1. Selected Disorders Associated with Carbohydrate Malabsorption

Congenital

- Sucrase-isomaltase deficiency
- Glucose-galactose malabsorption
- Congenital lactase deficiency
- Congenital microvillus atrophy
- Tufting enteropathy

Heritable

- Adult-type hypolactasia
- Cystic fibrosis
- Schwachman-Diamond syndrome
- Celiac disease

Acquired

- Postviral enteritis
- Environmental enteropathy
- Short bowel syndrome
- Autoimmune enteropathy

In all these disorders, the volume of diarrhea is roughly proportional to the amount of ingested carbohydrate that is malabsorbed. The unabsorbed carbohydrate in the small intestine causes an increased osmotic gradient, which draws more water into the lumen and increases the volume of intestinal contents. This leads to increased peristalsis and decreased transit

time, which further impairs digestion and absorption of carbohydrates. Upon reaching the colon, fermentation of undigested carbohydrate results in an increased concentration of SCFAs, reducing the intestinal pH below 5.5. This increased acidity disrupts sodium absorption, leading to further increases of luminal water.[5] Once the rate of delivery of carbohydrates into the colon exceeds the fermentative capacity, the increased carbohydrate load in the colon (as in the small intestine) results in the worsening of the osmotic diarrhea.[5]

Carbohydrate malabsorption can be detected by testing stool pH, testing for stool-reducing substances, and/or conducting a hydrogen breath test. A stool pH <5.5 indicates excessive SCFA production in the stool, whereas the presence of stool-reducing substances indicates malabsorption of sugars from the small intestine (except for intact sucrose) Fermentation of carbohydrates in the colon also produces hydrogen gas, a portion of which is absorbed into the systemic circulation and excreted in breath.[37] This forms the basis of the breath hydrogen test to detect carbohydrate malabsorption in the small intestine.[37] Malabsorption of carbohydrates ranges from mild to severe depending on the cause. Similarly, treatment will vary depending on the entity causing malabsorption and may include special diets and formulas (eg, gluten-free diet for patients with celiac disease) or enzyme supplements (eg, sucrase for sucrase-isomaltase deficiency). In the future, gene therapy may become a viable therapeutic option for certain congenital enzyme defects.

Metabolism

In the general economy of the body's metabolism, glucose is the common currency and is used by nearly all cells in the body. Upon feeding after birth, dietary carbohydrates provide glucose in the blood for uptake by cells throughout the body. Glucose that is not immediately utilized is stored in the form of glycogen (a storage carbohydrate).[3] Insulin is responsible for glycogenesis (glycogen synthesis), while glucagon affects glycogenolysis (glycogen degradation).

Conclusion

Carbohydrates thus comprise an essential macronutrient in infancy and a key macronutrient thereafter. Carbohydrates mediate diverse functions in the body beyond their main function of providing energy.

Case Study and Test Your Knowledge Questions

A baby girl is born at a gestational age of 27 weeks to a first-time mother. The child weighs 1431 g, and despite significant respiratory distress at birth, is stabilized shortly thereafter with mechanical ventilator support. Following transfer to the neonatal intensive care unit at a regional children's hospital, an orogastric tube is placed and trophic feedings of expressed breast milk are started.

1. As enteral feedings are advanced, the supply of maternal milk is inadequate to meet nutritional requirements, thus the infant receives formula. Which of the carbohydrates in the formula is a polysaccharide?
   A. Lactose
   B. Sucrose
   C. Maltose
   D. Amylose
2. When fed human milk, which of the following types of enzymes is least important?
   A. Disaccharidases
   B. Lipases
   C. Amylases
   D. Proteases
3. The carbohydrate in human milk is hydrolyzed to which of the following by the action of lactase?
   A. Glucose and glucose
   B. Galactose and glucose
   C. Glucose and fructose
   D. Galactose and fructose

4. At the time of discharge from the hospital (39 wk gestational age), which of the following enzymes will have exhibited the greatest increase in activity from the time of admission?
   A. Glucoamylase
   B. Lactase
   C. Sucrase
   D. Salivary amylase
5. Because of gastroesophageal reflux, rice cereal is added to the infant's feeding, resulting in more frequent and watery stools. The stool pH is 4.5, suggesting which of the following?
   A. Production of increased SCFAs
   B. Increased osmotic drag
   C. Increased colonic fermentation
   D. All of the above

References

1. Infant Formula Guidance Documents & Regulatory Information. U.S Food & Drug Administration. Updated December 13, 2023. Accessed February 12, 2024. https://www.fda.gov/food/guidance-documents-regulatory-information-topic-food-and-dietary-supplements/infant-formula-guidance-documents-regulatory-information
2. U.S. Food & Drug Administration. CFR - Code of Federal Regulations Title 21. Accessed February 12, 2024. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=107.100
3. Kleinman RE. Micronutrients and macronutrients. In: Kleinman RE, ed. *Pediatric Nutrition Handbook.* 6th ed. American Academy of Pediatrics; 2009:343–356.
4. Bode L, Jantscher-Krenn E. Structure-function relationships of human milk oligosaccharides. *Adv Nutr*. 2012;3(3):383S-91S. https://doi.org/10.3945/an.111.001404
5. Schmitz J. Maldigestion and malabsorption. In: Walker WA, Goulet O, Kleinman RE, Sherman PM, Shneider BL, Sanderson IR, eds. *Pediatric Gastrointestinal Disease.* 4th ed. B.C. Decker Inc; 2004:8–9.

6. Fogel MR, Gray GM. Starch hydrolysis in man: an intraluminal process not requiring membrane digestion. *J Appl Physiol.* 1973;35:263–267. https://doi.org/10.1152/jappl.1973.35.2.263
7. Hodge C, Lebenthal E, Lee PC, Topper W. Amylase in the saliva and in the gastric aspirates of premature infants: its potential role in glucose polymer hydrolysis. *Pediatr Res.* 1983;17:998–1001. https://doi.org/10.1203/00006450-198312000-00014
8. McClean P, Weaver LT. Ontogeny of human pancreatic exocrine function. *Arch Dis Child.* 1993;68:62–65. https://doi.org/10.1136/adc.68.1_spec_no.62
9. Eggermont E. The hydrolysis of the naturally occurring alpha-glucosides by the human intestinal mucosa. *Eur J Biochem.* 1969;9:483–487. https://doi.org/10.1111/j.1432-1033.1969.tb00634.x
10. Raul F, Lacroix B, Aprahamian M. Longitudinal distribution of brush border hydrolases and morphological maturation in the intestine of the preterm infant. *Early Hum Dev.* 1986;13:225–234. https://doi.org/10.1016/0378-3782(86)90010-1
11. Lee PC, Werlin S, Trost B, Struve M. Glucoamylase activity in infants and children: normal values and relationship to symptoms and histological findings. *J Pediatr Gastroenterol Nutr.* 2004;39:161–165. https://doi.org/10.1097/00005176-200408000-00007
12. Triadou N, Bataille J, Schmitz J. Longitudinal study of the human intestinal brush border membrane proteins: distribution of the main disaccharidases and peptidases. *Gastroenterology.* 1983;85:1326–1332. https://doi.org/10.1016/S0016-5085(83)80014-6
13. Shulman RJ, Kerzner B, Sloan HR, et al. Absorption and oxidation of glucose polymers of different lengths in young infants. *Pediatr Res.* 1986;20:740–743. https://doi.org/10.1203/00006450-198608000-00008
14. Mobassaleh M, Montgomery RK, Biller JA, Grand RJ. Development of carbohydrate absorption in the fetus and neonate. *Pediatrics.* 1985;75:160–166. https://doi.org/10.1542/peds.75.1.160
15. Naim HY, Heine M, Zimmer KP. Congenital sucraseisomaltase deficiency: heterogeneity of inheritance, trafficking, and function of an intestinal enzyme complex. *J Pediatr Gastroenterol Nutr.* 2012;55(suppl 2):S13–S20. https://doi.org/10.1097/01.mpg.0000421402.57633.4b

16. Shulman RJ, Schanler RJ, Lau C, Heitkemper M, Ou CN, Smith EO. Early feeding, feeding tolerance, and lactase activity in preterm infants. *J Pediatr.* 1998;133:645–649. https://doi.org/10.1016/s0022-3476(98)70105-2
17. Lomer MC, Parkes GC, Sanderson JD. Review article: lactose intolerance in clinical practice—myths and realities. *Aliment Pharmacol Ther.* 2008;27:93–103. https://doi.org/10.1111/j.1365-2036.2007.03557.x
18. Sahi T. Genetics and epidemiology of adult-type hypolactasia. *Scand J Gastroenterol Suppl.* 1994;202:7–20. https://doi.org/10.3109/00365529409091740
19. Thymann T, Møller HK, Stoll B, et al. Carbohydrate maldigestion induces necrotizing enterocolitis in preterm pigs. *Am J Physiol Gastrointest Liver Physiol.* 2009;297:G1115-G1125. https://doi.org/10.1152/ajpgi.00261.2009
20. Shulman RJ, Ou CN, Smith EO. Evaluation of potential factors predicting attainment of full gavage feedings in preterm infants. *Neonatology.* 2011;99:38–44. https://doi.org/10.1159/000302020
21. Griffin MP, Hansen JW. Can the elimination of lactose from formula improve feeding tolerance in premature infants? *J Pediatr.* 1999;135:587–592. https://doi.org/10.1016/s0022-3476(99)70057-0
22. Kim JH, Froh EB. What nurses need to know regarding nutritional and immunobiological properties of human milk. *J Obstet Gynecol Neonatal Nurs.* 2012;41(1):122–137. https://doi.org/10.1111/j.1552-6909.2011.01314.
23. Torniainen S, Freddara R, Routi T, et al. Four novel mutations in the lactase gene (LCT) underlying congenital lactase deficiency (CLD). *BMC Gastroenterol.* 2009;9:8. https://doi.org/10.1186/1471-230X-9-8
24. Brown KH. Dietary management of acute diarrheal disease: contemporary scientific issues. *J Nutr.* 1994;124:1455S-1460S. https://doi.org/10.1093/jn/124.suppl_8.1455s
25. Caballero B, Solomons NW. Lactose-reduced formulas for the treatment of persistent diarrhea. *Pediatrics.* 1990;86:645–646. https://doi.org/10.1542/peds.86.4.645
26. Karasov WH, Douglas AE. Comparative digestive physiology. *Compr Physiol.* 2013;3:741–783. https://doi.org/10.1002/cphy.c110054

27. Wright EM, Hirayama BA, Loo DF. Active sugar transport in health and disease. *J Intern Med.* 2007;261:32–43. https://doi.org/10.1111/j.1365-2796.2006.01746.x
28. Levin RJ, Koldovský O, Hosková J, Jirsová V, Uher J. Electrical activity across human foetal small intestine associated with absorption processes. *Gut.* 1968;9:206–213. https://doi.org/10.1136/gut.9.2.206
29. Rouwet EV, Heineman E, Buurman WA, Terriet G, Ramsay G, Blanco CE. Intestinal permeability and carrier-mediated monosaccharide absorption in preterm neonates during the early postnatal period. *Pediatr Res.* 2002;51:64–70. https://doi.org/10.1203/00006450-200201000-00012
30. Wright EM, Turk E, Martin MG. Molecular basis for glucose-galactose malabsorption. *Cell Biochem Biophys.* 2002;36:115–121. https://doi.org/10.1385/cbb:36:2-3.115
31. Kellett GL, Brot-Laroche E. Apical GLUT2: a major pathway of intestinal sugar absorption. *Diabetes.* 2005;54:3056–3062. https://doi.org/10.2337/diabetes.54.10.3056
32. Roder PV, Geillinger KE, Zietek TS, Thorens B, Koepsell H, Daniel H. The role of SGLT1 and GLUT2 in intestinal glucose transport and sensing. *PLoS One.* 2014;9:e89977. https://doi.org/10.1371/journal.pone.0089977
33. Cummings JH, Stephen AM. Carbohydrate terminology and classification. *Eur J Clin Nutr.* 2007;61(suppl 1):S5–S18. https://doi.org/10.1038/sj.ejcn.1602936
34. Cummings JH, Macfarlane GT. Role of intestinal bacteria in nutrient metabolism. *JPEN J Parenter Enteral Nutr.* 1997;21:357–365. https://doi.org/10.1177/0148607197021006357
35. Wong JM, de Souza R, Kendall CW, Emam A, Jenkins DJ. Colonic health: fermentation and short chain fatty acids. *J Clin Gastroenterol.* 2006;40:235–243. https://doi.org/10.1097/00004836-200603000-00015
36. Montalto M, Santoro L, D'Onofrio F, et al. Classification of malabsorption syndromes. *Dig Dis*. 2008;26:104–111. https://doi.org/10.1159/000116767
37. Simren M, Stotzer PO. Use and abuse of hydrogen breath tests. *Gut.* 2006;55:297–303. https://doi.org/10.1136/gut.2005.075127

Test Your Knowledge Answers

1. The correct answer is **D**. Lactose, sucrose, and maltose are disaccharides. Amylose is a polysaccharide consisting of multiple glucose units.
2. The correct answer is **C**. The breakdown of sugars, especially lactose, lipids, and proteins is required to nourish the infant. Amylases would be used to break down complex starches; human milk does have HMOs and complex carbohydrates, but these are not digested by humans and are not necessary for infant nutrition.
3. The correct answer is **B**. It is hydrolyzed to galactose and glucose.
4. The correct answer is **B**. Lactase activity at the start of the third trimester is <25% of that at term.
5. The correct answer is **D**. Low amylase activity could result in the malabsorption of the rice cereal, which is a starch, with a resultant increase in osmotic drag from the poorly absorbed carbohydrate and the passage of the malabsorbed carbohydrate into the colon where it is fermented to SCFAs.

Thaddaeus May, MD; Robert Shulman, MD; and Seema Mehta, MD contributed to previous editions of this text.

4

Fats

Peggy R. Borum, PhD

Learning Objectives

1. List the different types of fatty acids.
2. Contrast the different fatty acid oxidation pathways.
3. Relate different pathological conditions to altered fat metabolism.

Introduction

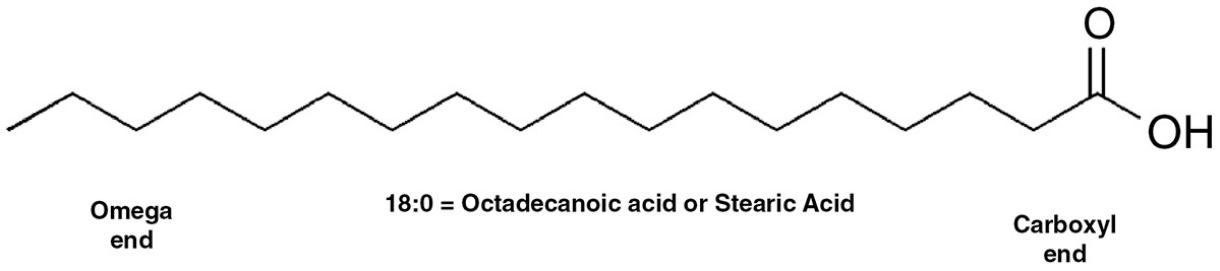
The body depends on 3 macronutrients to fuel physiological processes: carbohydrates, protein, and fat (lipids). The overgeneralization that fat is bad (and we should subsequently limit intake of it) remains popular among the general population. An effective diet adjusts amounts of different lipids according to type, rather than indiscriminately reducing them all. Understanding the diversity of lipids in their chemical structures, oxidation pathways, and metabolic processes is key to optimizing nutrition support. Familiarity with lipid characteristics leads to better patient outcomes, specifically prevention and management of health conditions related to lipid metabolism.

Different Types of Fat

Although various lipid types have uniformly poor solubility in water, their structures—and thus, their functions in the body—are diverse. The building blocks of lipids are fatty acids. Fatty acids are calorically dense because their hydrocarbons are highly reduced. They provide more metabolic energy per gram than any other dietary macronutrient. This density benefits patients who have limited stomach capacity, fluid restrictions, and/or increased caloric needs (eg, growth or critical illness).

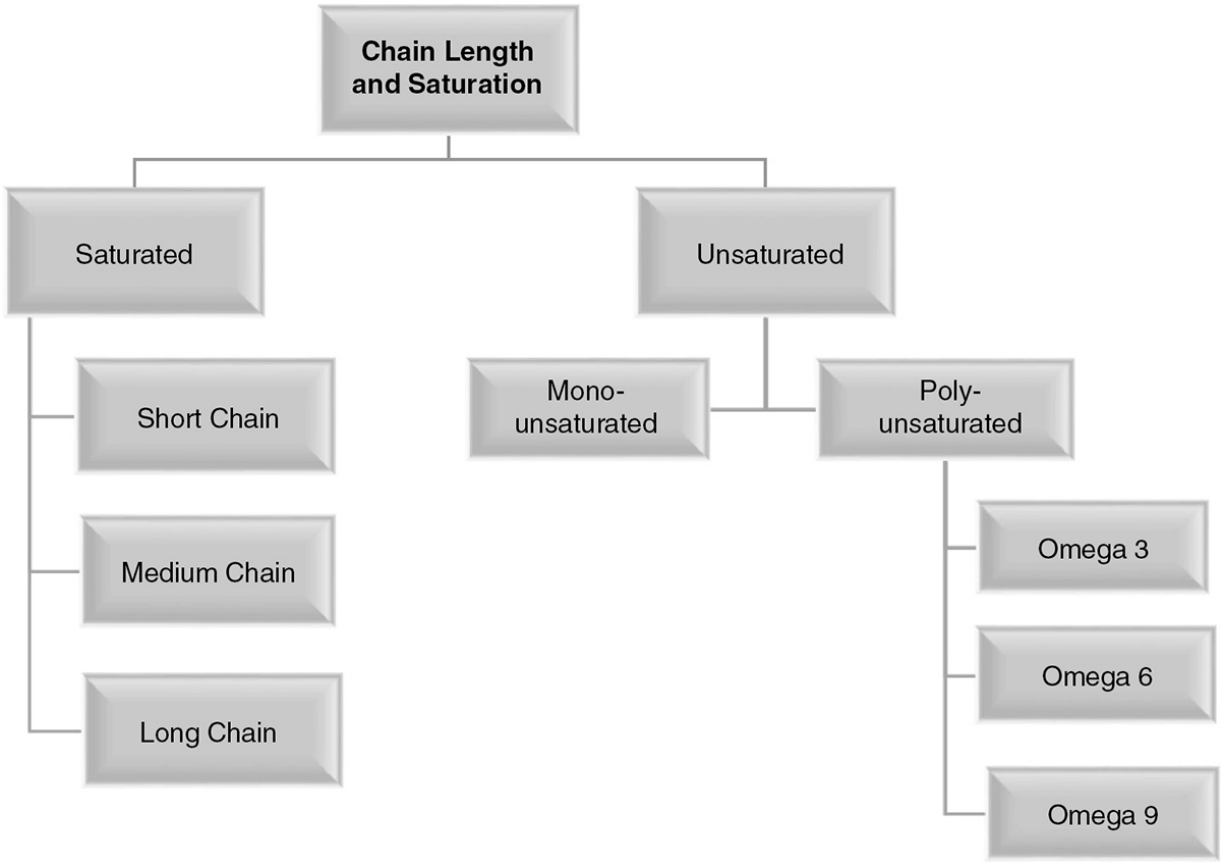
A typical fatty acid is a chain of 4 to 24 hydrocarbons with a carboxylic acid group (COOH) at one end (see Figure 4-1). The degree of saturation of a fatty acid is determined by how many double bonds it contains: saturated contains no double bonds, monounsaturated contains 1 double bond, and polyunsaturated contains 2 or more double bonds. Although often unbranched, fatty acid chains may include hydroxyl groups, methyl groups, and rings.[1] Fatty acids can also be described by chain length (see Figure 4-2), however, no consensus currently exists on this axis of classification. Most definitions describe short chains as a string of 2 to 6 carbons, while a medium chain has 8 to 12, and a long chain has 14 or more. These lengths contribute to the physical characteristics of the food and the metabolism of the fat once it enters the body.

FIGURE 4-1. 18-Carbon Steric Acid



The structure of typical fatty acids is a carboxylic acid with hydrocarbon chains ranging from 4 to 24 carbons.

FIGURE 4-2. Classification of Fatty Acids Based on Degree of Chain Saturation and Chain Length



Fats with longer, less saturated chains (eg, butter, lard) will have higher melting points and be solid at room temperature (see Figure 4-1). Shorter chains with more double bonds (more unsaturated) will have a lower melting point, making them liquid at room temperature. For example, coconut oil is liquid at room temperature because it is a medium-chain (8–12 carbon) triglyceride oil containing a significant amount of saturated fatty acids. Although olive oil is a long-chain fatty acid, it is also liquid at room temperature because it contains a higher percentage of monounsaturated fatty acid chains (ie, oleic acid) with one double bond.[1] When 3 fatty acid chains are joined by a glycerol backbone, this creates a fatty acid compound called a triglyceride. The body stores energy mainly in the form of triglycerides.

Membrane fluidity or viscosity is important in the function of many cell types and is greatly influenced by the degree of saturation of the fatty acids in the membrane phospholipids.[1] A 3-dimensional view of saturated fatty acids reveals that the hydrocarbon chains are straight and thus can be packed very tightly in membrane phospholipids. Most physiological unsaturated fatty acids have *cis* double bonds (ie, chains on the same side of the double bond). Every cis double bond puts a "kink" or bend in the hydrocarbon chain. However, fatty acids with *trans* double bonds (ie, chains on the opposite side of the double bond) are straight hydrocarbons and can be packed very tightly in membranes, reducing membrane fluidity. Phospholipids containing cis unsaturated fatty acids cannot be packed as tightly, resulting in a membrane with increased fluidity.

In the food industry, trans fatty acids are made from unsaturated fatty acids to change the consistency of the fat product as well as make it less liquid-like at room temperature. Shelf life is increased by reducing the number of double bonds that make the fat product susceptible to rancidity. An increased concentration of polyunsaturated fatty acids in the membrane increases membrane susceptibility to oxidation and peroxidation. Because vitamin E is a major antioxidant in the membrane, an increase in dietary polyunsaturated fatty acids should always be accompanied by a careful evaluation of adequate vitamin E intake. Because the fatty acid composition of the membrane reflects the fatty acid composition of the diet, careful attention to the type of fatty acids in the diet is warranted.[2] Optimizing the dietary fatty acid profile can alter the membrane structure provided to the body, which can alter cell signaling associated with clinical symptomatology.

Essential Fatty Acids

Two methods are used to number the carbons of a fatty acid. In the field of chemistry, the numbering usually begins with the carboxylic acid carbon. In the field of nutrition, the numbering usually begins with the methyl carbon, or ω carbon, which is at the opposite end of the molecule from the carboxylic acid (see Figure 4-1). Using the ω system of numbering, an ω-3 fatty acid has its first double bond between C3 and C4 from the ω carbon,

an ω-6 fatty acid has its first double bond between C6 and C7 from the ω carbon, and an ω-9 fatty acid has its first double bond between C9 and C10 from the ω carbon. Humans cannot synthesize ω-3 or ω-6 fatty acids, but many physiological processes are dependent on these fatty acids and their myriad products. Therefore, ω-3 and ω-6 fatty acids are required in the human diet and are termed "essential fatty acids."[1]

The shortest chain ω-6 fatty acid is linoleic acid (LA). Humans can convert LA to arachidonic acid (ARA). The shortest chain ω-3 fatty acid is α-linolenic acid (αLA). Humans can convert αLA to eicosapentaenoic acid (EPA) and convert EPA very slowly to docosahexaenoic acid (DHA). The same enzyme pool is used to metabolize LA and αLA to their respective longer-chain metabolites. The more prevalent fatty acid is preferentially metabolized. Thus, with a diet high in the ω-6 fatty acid LA, LA will be preferentially metabolized over the ω-3 fatty acid αLA. ARA (20-carbon polyunsaturated ω-6) and EPA (20-carbon polyunsaturated ω-3) are released from membranes and further metabolized to a cascade of eicosanoids. Although it is not quite so simple, eicosanoids from ω-6 fatty acids are generally considered proinflammatory and those from ω-3 fatty acids are considered weakly anti-inflammatory. The docosanoid products of DHA also have anti-inflammatory actions.[3]

The fatty acid composition of the diet influences the composition of the cell membranes, which influences the availability of appropriate substrate to make either proinflammatory or anti-inflammatory fatty acid products. Three methods are available to diagnose essential fatty acid deficiency. Traditionally, low intake of ω-3 and ω-6 fatty acids is associated with an increase in an ω-9 fatty acid known as Mead acid in plasma and has been used to diagnose essential fatty acid deficiency. A more recent method uses red blood cells and measures 2 additional parameters.[4] The emerging field of investigation known as lipidomics measures all small molecular weight lipids in a sample and will likely provide the nutrition community with improved methods for specific essential fatty acid evaluation.

With the industrialization of Western society, dietary intake of essential fatty acids has changed, reflecting the trend away from grains to more processed foods high in fat. Intake of LA relative to αLA has increased significantly. Currently, the ratio of LA to αLA in the diet is 14:1 in contrast

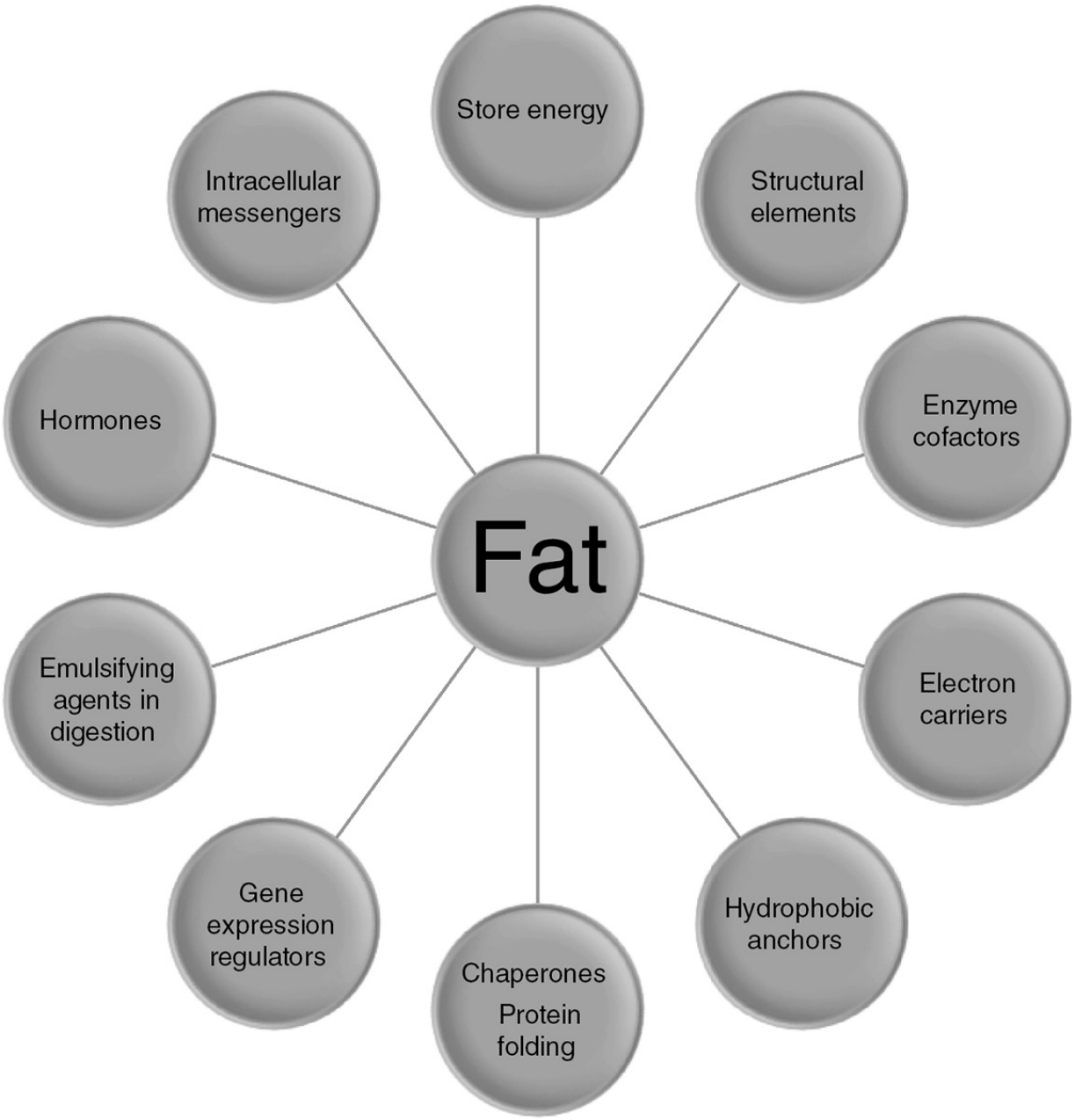
to the 2:1 or 1:1 ratio that is usually recommended.[2] Interestingly, the change in dietary fat intake follows a similar temporal pattern to the increase in inflammatory bowel disease incidence in the pediatric population.[5]

Different Functions of Adipose Tissue

Adipose tissue is not simply a place for the body to store fat. Adipose tissue is a complex organ with many different cell types containing receptors sensitive to inflammatory signals. Thus, changing the size of adipose tissue has far-reaching effects. When stimulated by signals accompanying changes in physiology, adipose tissue releases more than 20 diverse molecules known as adipokines, which have a wide range of metabolic effects during both health and disease. Fat deposits in subcutaneous, intramuscular, and intrathoracic depots can differ in fatty acid composition, adipokine secretion, and storage capacity. Macrophage content of adipose tissue can increase from the usual range of 5% to 10% to 60% during obesity and secrete an increasing amount of inflammatory cytokines. Taken together, obesity can have a striking effect not only on the size but also on the metabolism of the body.[2]

Storage of a metabolic fuel source and structural elements of membranes are the most generally recognized functions of fats. However, numerous other functions of fat are now recognized, as shown in Figure 4-3. Adipose tissue maintains a balance between clearance of plasma triglycerides and release of fatty acids. Excess dietary energy cannot be excreted. Diets with excess calories are frequently high in fat because dietary fat is highly palatable and calorically dense. Excess dietary energy from any of the macronutrients is converted to fatty acids and stored as triglycerides in adipocytes. Therefore, surplus dietary calories will increase adipose depots.

FIGURE 4-3. Critical Functions of Fat



Importance of Dietary Fat in Infants

The percentage of total fetal body weight that is adipose tissue increases dramatically during human gestation. Fetal white adipose tissue increases at a rate of about 67 mg/d during the last trimester. The brain also grows very rapidly during the last trimester and requires a large amount of DHA for the

synthesis of myelin. At birth, the human brain is about 50% of its adult size and continues to grow rapidly until reaching near-adult size at about 2 years of age. Thus, the extremely preterm infant born at 24 or 25 weeks of gestation requires a large amount of essential fatty acids, ω-3 fatty acids in particular, to achieve the type of growth usually experienced by a fetus in utero during the same period postconception.[6,7]

Fatty acids and eicosanoids can also change the abundance of transcription factors, which regulate gene expression. Regulation of gene expression by nutrients is critically important in preterm neonates. Regulation of gene expression by ω-3 fatty acids involves multiple complex processes including regulation of the transcription factors sterol regulatory element-binding proteins and peroxisome proliferator-activated receptors that modulate many critical steps in metabolism.[8,9]

The 2 most abundant long-chain polyunsaturated fatty acids in the brain are DHA and ARA. DHA is concentrated in the prefrontal cortex and some retinal cells.[10] Inadequate intake of ω-3 fatty acids not only results in decreased brain DHA but also increased brain ω-6 fatty acid concentration.[11,12] Worldwide, the various commercial enteral products differ in their supply of ω-3 fatty acids, particularly DHA. However, none of them provide the amount of essential fatty acids that would accumulate in the fetal brain during the last trimester of gestation without additional supplementation. Thus, the current diet provided to these infants appears to be deficient in DHA. Preterm infants fed increased amounts of DHA have improved visual acuity and mental development.[13,14]

A multicenter prospective, randomized, double-blind placebo-controlled trial in Italy compared 580 healthy term neonates receiving 20 mg of liquid DHA to 580 healthy term infants receiving a placebo with a focus on developmental milestones.[15] The infants receiving DHA were able to sit without support 1 week earlier than the placebo group, but there was no difference in crawling, standing, or walking without assistance. It is unclear how these data from healthy term neonates relate to preterm neonates. For parenterally fed infants, the challenge to provide adequate DHA and ARA is even greater with the currently available intravenous lipid emulsions approved for use in this population.[16]

Digestion and Absorption

Because dietary lipids are hydrophobic, they must be hydrolyzed and emulsified to very small micelles before they can be absorbed by the intestine. Lingual and gastric lipases hydrolyze triglycerides to diglycerides and free fatty acids. After activation by colipase, pancreatic lipase hydrolyzes dietary fat to 2-monoglycerides, which are poor substrates for continued hydrolysis.[17] Gastric lipolysis is incomplete in adults, being responsible for 30% or less of dietary fat lipolysis.[18] Because neonates have limited expression of pancreatic enzymes needed for fat digestion in the intestine, gastric lipolysis has been thought to have a more important role in neonates.[19] Supplementation of infant formula with medium-chain triglycerides has been reported to have conflicting effects on intragastric lipolysis in infants (no effect vs decreased lipolysis).[20] This finding may be related to differences in the medium-chain triglyceride concentration of the formulas studied.[21]

The pH increases as the acidic stomach contents move to the intestine. The free fatty acid products of gastric lipase are ionized and become oriented to the outside of the oil droplets, which surrounds the oil droplets with a charge and stabilizes the emulsion. Some of the free fatty acids dissociate from the droplet and interact with the intestinal epithelium. These fatty acids are potent stimuli for cholecystokinin release. Cholecystokinin stimulates an increase in pancreatic enzymes; relaxes the sphincter of Oddi, which allows the pancreatic juice to flow into the intestinal lumen; and contracts the gallbladder to provide a bolus of concentrated bile. The bile contains bile salts, which are needed to form micelles (spheres of lipids that form in aqueous environments).[18] The micelles created by the bile salts have an important role in solubilizing the products of luminal lipolysis and facilitating their transfer to the absorptive epithelium.

Fatty acids and monoglycerides have enough solubility in the luminal contents that they can diffuse to the brush border and be absorbed.[17] The micelles transport the digested fat products through the aqueous intestinal lumen, making close contact with the brush border of the mucosal cells. Bile salts continue to the ileum, where they are absorbed into the enterohepatic circulation.[17]

Phospholipase A_2 from the pancreas cleaves the fatty acid in the 2-position of dietary phospholipids. Pancreatic juice also contains cholesterol esterase, which hydrolyzes cholesterol esters; esters of vitamins A, D, and E; and all 3 fatty acids in triglycerides.[18] Human milk lipase, produced by the mammary glands of lactating females, is very similar to cholesterol esterase. Human milk lipase also has broad specificity and may "predigest" the lipid components of the milk, thus increasing the efficiency of their uptake.[18,20]

Role of Mucosal Cells During Enteral Nutrition

The intestinal epithelium is the site for some very important metabolic steps. The absorbed 2-monoglycerides are reacylated to triglycerides. Several 1-monoglycerides in the emulsion are absorbed and hydrolyzed to fatty acids and glycerol. The glycerol released within the intestinal epithelium is reutilized for triglyceride synthesis. Long-chain fatty acids are esterified to triglycerides, secreted into the lymphatics as chylomicrons, and enter the blood via the thoracic duct. Free short-chain and medium-chain fatty acids are absorbed into the hepatic portal vein.[17]

Metabolism During Normal Physiology

Dietary fat can enter a diverse set of metabolic pathways that are intricately controlled and coordinated to meet the needs of the body. The cell can either oxidize fatty acids for immediate metabolic energy or synthesize fatty acids from other dietary components and store them for later use.

Synthesis of Fatty Acids

Excess calories in the form of protein, carbohydrate, or fat cannot be eliminated from the body once ingested or administered and must be stored in the form of fatty acids and glycogen. Six cytosolic enzymes plus an acyl carrier protein are needed for fatty acid synthesis from acetyl-CoA. In the first step, malonyl-CoA is formed from acetyl-CoA, which has been shuttled out of the mitochondria. This reaction, forming malonyl-CoA, is the regulatory step for fatty acid synthesis. The sequence of subsequent reactions is (1) condensation, (2) reduction, (3) dehydration, and (4)

reduction again. Both reduction reactions use nicotinamide adenine dinucleotide phosphate (NADPH) as the electron donor. The sequence of reactions adds 2 carbons at a time and is repeated until a chain length of about 16 carbons is made and then released from the acyl carrier protein.[1]

As discussed in the "Essential Fatty Acids" section, humans cannot synthesize LA or αLA. Although humans have the necessary enzymes to make EPA from αLA and DHA from EPA, the capacity to do so is very low.[28] Only about 5% of αLA can be converted to EPA and <0.5% of αLA can be converted to DHA. The capacity to convert LA to ARA is also low. Thus, although only LA and αLA are termed essential fatty acids, the administration of only LA or αLA often has only a negligible effect on plasma ARA, EPA, and DHA.[28,29] Additional ARA, EPA, and DHA may be required depending on the overall health of the patient. The optimal ratio of preformed EPA and DHA has not been established, but ratios of 1:2 to 2:1 are expected to be effective.[30]

β-Oxidation of Long-Chain Fatty Acids in Mitochondria

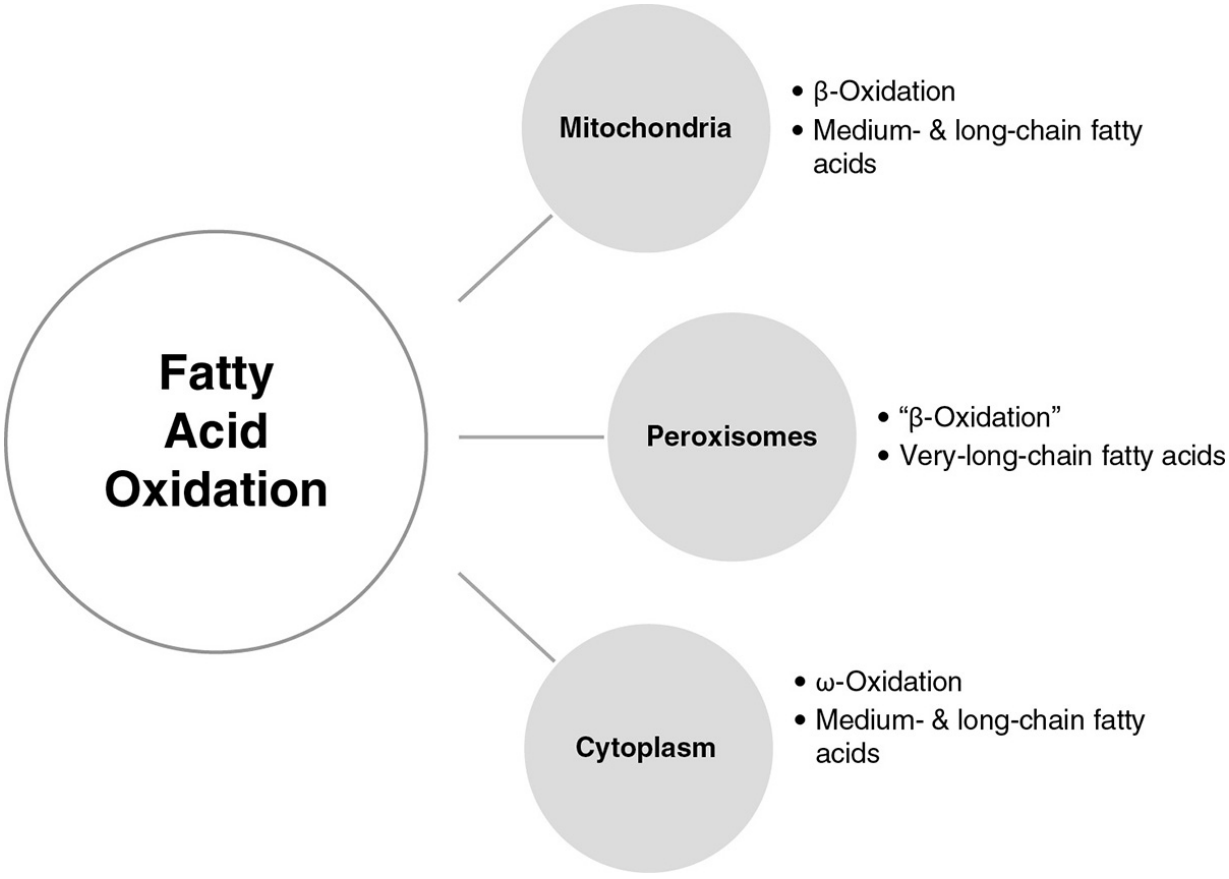
Hormone-sensitive lipase mobilizes triglycerides from adipose tissue when needed. Lipoprotein lipase in the capillary endothelium releases free fatty acids, which are delivered to tissues by chylomicrons. The fatty acids are carried in the blood bound to albumin and are delivered to the tissues to use for fuel. When fatty acids are used for fuel, they are activated to the fatty acyl-CoA at the outer mitochondrial membrane. Fatty acyl-CoA is the correct high-energy state for β-oxidation, but the enzymes for β-oxidation are located within the mitochondrial matrix (see Figure 4-3), and the fatty acyl-CoA cannot cross the inner membrane of the mitochondria to reach these enzymes. To use long-chain fatty acids for metabolic energy, fatty acyl-CoA is converted to fatty acylcarnitine via carnitine palmitoyltransferase 1, transported across the inner mitochondrial membrane via carnitine acylcarnitine translocase in exchange for free carnitine, and reconverted to fatty acyl-CoA in the matrix of the mitochondria via carnitine palmitoyltransferase 2. This results in the high-energy fatty acyl-CoA being in the same location as the metabolic machinery for β-oxidation. Fatty acid oxidation and fatty acid synthesis do not occur at the same time because malonyl-CoA (an early intermediate in

fatty acid synthesis) inhibits carnitine palmitoyltransferase1 and thus prevents the fatty acyl-CoA from reaching the site of β-oxidation.[1,31]

β-Oxidation of Medium-Chain Fatty Acids in Mitochondria

In liver cells, medium-chain fatty acids are transported into mitochondria (see Figure 4-4) as free fatty acids and then activated to medium-chain fatty acyl-CoA. Therefore, oxidation of medium-chain fatty acids is carnitine-independent in the liver. However, other tissues activate medium-chain fatty acids to medium-chain fatty acyl-CoA on the cytoplasmic side of the inner mitochondrial membrane and require the carnitine shuttle for β-oxidation.[32,33] For example, if dietary medium-chain fatty acids are provided in quantities expected to comprise a fuel substrate for skeletal muscle, carnitine will be required for their oxidation.

FIGURE 4-4. Oxidation of Medium-Chain, Long-Chain, and Very-Long-Chain Fatty Acids in Mitochondria



Mitochondrial β-Oxidation

In mitochondria, 4 repeating reactions (dehydrogenation requiring flavin adenine dinucleotide, hydration, dehydrogenation requiring nicotinamide adenine dinucleotide, and cleavage requiring coenzyme A [CoA]) produce a fatty acyl-CoA shortened by 2 carbons and acetyl-CoA. The shortened fatty acyl-CoA reenters the sequence, and the acetyl-CoA is oxidized to carbon dioxide in the citric acid cycle. The citric acid cycle coupled with the oxidative phosphorylation pathway yields metabolic energy as adenosine triphosphate (ATP). Oxidation of unsaturated fatty acids requires 2 additional enzymes in the mitochondria to deal with the double bonds.[1]

Peroxisome β-Oxidation

Peroxisomes are subcellular organelles in the cytoplasm that carry out β-oxidation in 4 repeating steps that are similar to those in the mitochondria. The difference is that the first reaction transfers electrons directly to oxygen, producing hydrogen peroxide. Peroxisomes oxidize very-long-chain fatty acids (see Figure 4-4) and branched fatty acids. Fatty acids enter the peroxisome before they are esterified to fatty acyl-CoA, so the carnitine shuttle is not needed to deliver the fatty acids to the peroxisomes. The very-long-chain fatty acids are shortened by 2 carbons during each reaction sequence, producing the shortened fatty acyl-CoA and acetyl CoA. When the fatty acyl-CoA is a medium-chain fatty acyl-CoA, the oxidation sequence stops. Acetyl-CoA and the medium-chain fatty acyl-CoA must be transported out of the peroxisome via a carnitine shuttle. The medium-chain fatty acylcarnitine is transported into mitochondria to complete the oxidation to acetyl-CoA.[1]

ω-Oxidation of Fatty Acids

ω-Oxidation of fatty acids occurs in the endoplasmic reticulum in the cytoplasm (see Figure 4-4). The ω carbon is first converted to an alcohol by a cytochrome P450 mixed function oxidase, which requires both oxygen and NADPH. Alcohol dehydrogenase and aldehyde dehydrogenase convert the alcohol to a carboxylic acid on the ω carbon. Thus, the fatty acid is converted to a dicarboxylic acid, which can be esterified to carnitine and transported to the mitochondrial matrix. There it can enter the β-oxidation

pathway to be shortened at both ends of the molecule at the same time. ω-Oxidation of fatty acids is normally a minor pathway. Dysfunctional β-oxidation in the mitochondria will increase ω-oxidation.[34]

Long-Chain Fatty Acids as Substrates for Cascades

In addition to providing substrates to make important cell structures and substrates to produce metabolic fuel, fatty acids are often used in signaling pathways. The 2 essential fatty acids and their elongated metabolites are the beginning of 2 enormous cascades controlling many aspects of physiology.[3] If the dietary supply of either essential fatty acid is inadequate or if the dietary ratio of the 2 essential fatty acids is inappropriate, one would expect pathophysiology.

Fat as Fuel for Preterm Infants

Early introduction of lipid emulsions to preterm neonates has not been shown to increase complications,[35] but it also has not been shown to improve short-term growth or prevent morbidity and mortality.[36] An emulsion with a mixture of medium-chain and long-chain fatty acids appears to be superior to an emulsion containing only long-chain fatty acids in terms of incorporation of essential fatty acids and long-chain polyunsaturated fatty acids into circulating lipids.[37] Adequate energy intake during the first days of life is associated with improved brain function. A recent study of 148 extremely low birth weight survivors showed that every 42 kJ/kg/d (10 kcal/kg/d) provided during the first postnatal week was associated with a 4.6-point increase in the Mental Development Index.[38]

Fat Content in PN in Pediatrics

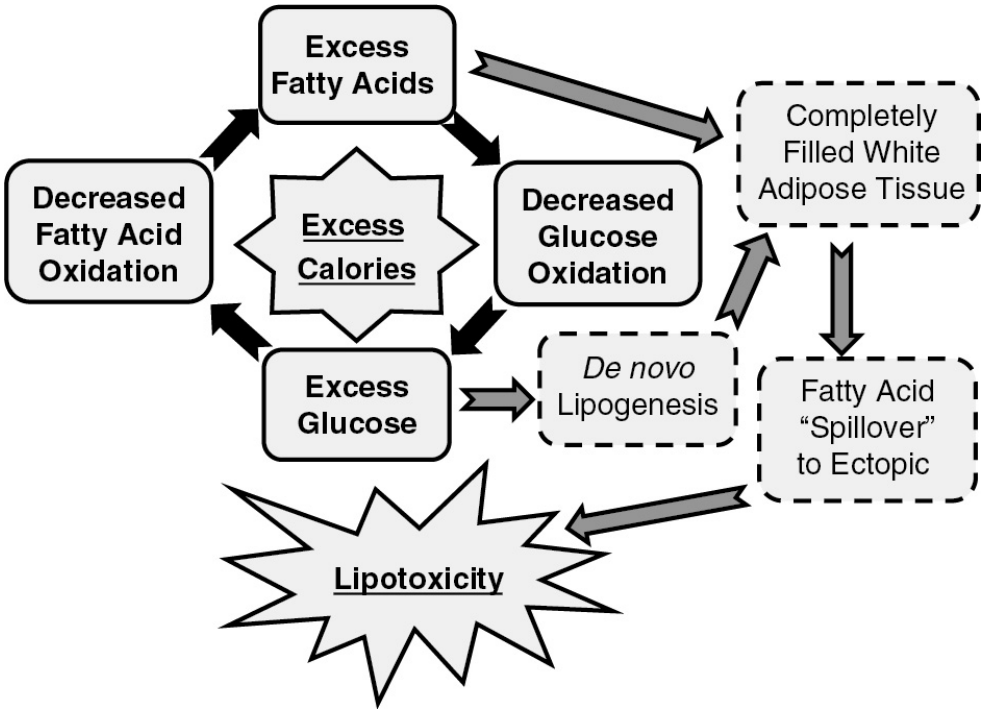
As previously discussed, ω-3 fatty acids (including EPA and DHA), sometimes called fish oils, have several important functions in the body during both health and disease. In a 2009 study by Diamond et al. 12 children with pediatric short bowel syndrome who developed PN-associated liver disease received parenteral ω-3 fatty acids while awaiting liver

transplant.[39] They showed restoration of liver function to the point that 9 of the children were no longer considered for liver transplant. The remaining 3 children received a liver transplant with no complications attributable to the ω-3 emulsion. In another study, 18 infants who developed cholestasis while receiving a parenteral emulsion high in ω-6 fatty acids were switched to an emulsion high in ω-3 fatty acids and were compared to 21 historical controls who had similar symptoms and had been maintained on the ω-6 fatty acid emulsion. Patients receiving the ω-3 fatty acids experienced a reversal of cholestasis 6.8 times faster when the data were adjusted for baseline bilirubin concentration, gestational age, and diagnosis of necrotizing enterocolitis. The ω-3 fatty acid cohort had 2 deaths and no liver transplants, and the historical control cohort had 7 deaths and 2 liver transplants. Parenteral lipid emulsions containing fish oil as the component were approved by the Food and Drug Administration (FDA) in July 2018 and are approved for use in pediatrics.[41]

To Esterify or to Oxidize—That Is the Cell's Question

The ability to synthesize or oxidize fatty acids allows the cell to store excess calories as fat and to mobilize the stored fatty acids for metabolic fuel, which is a lifesaving adaptation during times of starvation. When products of digested macronutrients enter the cell during normal physiological situations, the cell responds to metabolic signals indicating the metabolic fuel status of the cell. It either uses the fuel substrates to produce needed metabolic energy or stores the fuel substrate as fatty acids in triglycerides. However, if excess calories are chronically delivered to the cell, the ability of adipose tissue to serve as a "sink" and protect nonadipose tissues from fatty acid "spillover" appears to become saturated. As diagrammed in Figure 4-5, the result is lipid overload, or lipotoxicity, which overwhelms the abilities of both the endoplasmic reticulum and mitochondria to maintain cellular homeostasis and results in the systemic release of both free fatty acids and inflammatory cytokines.

FIGURE 4-5. Schematic of the Steps Leading to Lipotoxicity



Accumulation of fatty acids in skeletal muscle, heart, liver, and pancreas is likely the underlying factor in the development of insulin resistance, cardiomyopathy, liver steatosis, and type 2 diabetes. During normal physiological conditions, the use of fatty acids for energy and the use of glucose for energy are intricately coordinated. Likewise, during chronic intake of excess calories, excess lipids inhibit glucose use, and hyperglycemia interferes with fatty-acid catabolism, resulting in a state that some have termed glucolipotoxicity.[42] Intake of excess carbohydrates increases cellular malonyl-CoA concentrations, which inhibits carnitine palmitoyltransferase 1 activity, impairing β-oxidation of fatty acids. Insulin resistance is associated with excess calorie intake and high saturated fat intake. Substituting saturated fat with unsaturated fat seems to improve insulin sensitivity.[43]

Metabolism of dietary fat is altered in patients with overweight. For example, patients with overweight and a fatty liver have a higher postprandial triglyceride response and an increased production of large very low-density lipoproteins after a fat load compared to control subjects.[44]

When providing nutrition support, it is important to not only provide appropriate calories for the specific patient but also carefully evaluate how the patient's current metabolic status may impact the body's metabolism of the nutritional fat substrate provided.

Test Your Knowledge Questions

1. Which of the following is an optimal nutrition-support prescription for a patient receiving home PN to maintain good health and prevent overweight?
   A. Restricts fat to an absolute minimum, while providing a generous amount of glucose
   B. Provides adequate calories including a fatty-acid blend with appropriate chain length; chain saturation; and ratios of LA, αLA, ARA, EPA, and DHA
   C. Provides 80% of the calories recommended for oral intake
   D. Provides all fat calories as essential fatty acids LA and αLA
2. The cellular site(s) for fatty-acid oxidation in the body include(s) which of the following?
   A. Mitochondria
   B. Peroxisomes
   C. Cytoplasm
   D. Mitochondria, peroxisomes, and cytoplasm
3. A critically ill 24-week neonate in the neonatal intensive care unit requires which dietary essential fatty acids?
   A. LA and αLA
   B. αLA and DHA
   C. LA and ARA
   D. LA, αLA, ARA, and DHA

References

1. Nelson DL, Cox MM. *Lehniger Principles of Biochemistry*. 6th ed. W.H. Freeman and Company; 2013.

2. Innis SM. Dietary lipids in early development: relevance to obesity, immune and inflammatory disorders. *Curr Opin Endocrinol Diabetes Obes.* 2007;14(5):359–364. https://doi.org/10.1097/med.0b013e3282be90b9
3. Maskrey BH, Megson IL, Rossi AG, Whitfield PD. Emerging importance of omega-3 fatty acids in the innate immune response: molecular mechanisms and lipidomic strategies for their analysis. *Mol Nutr Food Res*. 2013;57(8):1390–400. https://doi.org/10.1002/mnfr.201200723
4. Fokkema MR, Smit EN, Martini IA, Woltil HA, Boersma ER, Muskiet FAJ. Assessment of essential fatty acid and omega 3-fatty acid status by measurement of erythrocyte 20:3ω9 (Mead acid), 22:5ω6/20:4ω6 and 22:5ω6/22:6ω3. *Prostaglandins Leukot Essent Fatty Acids.* 2002;67(5):345–356. https://doi.org/10.1054/plef.2002.0440
5. Innis SM, Jacobson K. Dietary lipids in early development and intestinal inflammatory disease. *Nutr Rev.* 2007;65(12 Pt 2):S188–S193. https://doi.org/10.1111/j.1753-4887.2007.tb00361.x
6. Marszalek JR, Lodish HF. Docosahexaenoic acid, fatty acid-interacting proteins, and neuronal function: breastmilk and fish are good for you. *Annu Rev Cell Dev Biol.* 2005;21:633–657. https://doi.org/10.1146/annurev.cellbio.21.122303.120624
7. Heird WC, Lapillonne A. The role of essential fatty acids in development. *Annu Rev Nutr.* 2005;25:549–571. https://doi.org/10.1146/annurev.nutr.24.012003.132254
8. Deckelbaum RJ, Worgall TS, Seo T. n-3 fatty acids and gene expression. *Am J Clin Nutr.* 2006;83(6):1520S-1525S. https://doi.org/10.1093/ajcn/83.6.1520s
9. Georgiadi A, Kersten S. Mechanisms of gene regulation by fatty acids. *Adv Nutr*. 2012;3(2):127–134. https://doi.org/10.3945/an.111.001602
10. Agostoni C. Role of long-chain polyunsaturated fatty acids in the first year of life. *J Pediatr Gastroenterol Nutr.* 2008;47(suppl 2):S41–S44. https://doi.org/10.1097/01.mpg.0000338811.52062.b2
11. Innis SM. Dietary omega 3 fatty acids and the developing brain. *Brain Res.* 2008;1237:35–43. https://doi.org/10.1016/j.brainres.2008.08.078
12. Novak EM, Dyer RA, Innis SM. High dietary omega-6 fatty acids contribute to reduced docosahexaenoic acid in the developing brain and

inhibit secondary neurite growth. *Brain Res.* 2008;1237:136–145. https://doi.org/10.1016/j.brainres.2008.07.107
13. Hay WW Jr. Strategies for feeding the preterm infant. *Neonatology.* 2008;94(4):245–254. https://doi.org/10.1159/000151643
14. Innis SM. Omega-3 Fatty acids and neural development to 2 years of age: do we know enough for dietary recommendations? *J Pediatr Gastroenterol Nutr.* 2009;48(suppl 1):S16–S24. https://doi.org/10.1097/mpg.0b013e31819773cf
15. Agostoni C, Zuccotti GV, Radaelli G, et al. Docosahexaenoic acid supplementation and time at achievement of gross motor milestones in healthy infants: a randomized, prospective, double-blind, placebo-controlled trial. *Am J Clin Nutr.* 2009;89(1):64–70. https://doi.org/10.3945/ajcn.2008.26590
16. Vanek VW, Seidner DL, Allen P, et al; Novel Nutrient Task Force, Intravenous Fat Emulsions Workgroup; American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. A.S.P.E.N. position paper: clinical role for alternative intravenous fat emulsions. *Nutr Clin Pract.* 2012;27(2):150–192. https://doi.org/10.1177/0884533612439896
17. Bender DA, Mayes PA. Nutrition, digestion, and absorption. In: Murray RK, Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil PA, eds. *Harper's Illustrated Biochemistry*. 29th ed. McGraw-Hill; 2012. 18 Barrett KE. Lipid assimilation. In: Barrett KE, ed. *Gastrointestinal Physiology*. McGraw-Hill; 2006.
19. Hamosh M. Digestion in the newborn. *Clin Perinatol.* 1996;23(2):191–209. https://doi.org/10.1016/S0095-5108(18)30238-0
20. Hernell O, Blackberg L. Human milk bile salt-stimulated lipase: functional and molecular aspects. *J Pediatr.* 1994;125(5 Pt 2):S56–S61. https://doi.org/10.1016/s0022-3476(06)80737-7
21. Hamosh M, Bitman J, Liao TH, et al. Gastric lipolysis and fat absorption in preterm infants: effect of medium-chain triglyceride or long-chain triglyceride-containing formulas. *Pediatrics*. 1989;83(1):86–92. https://doi.org/10.1542/peds.83.1.86
22. Peterson LW, Artis D. Intestinal epithelial cells: regulators of barrier function and immune homeostasis. *Nat Rev Immunol.* 2014;14(3):141–153. https://doi.org/10.1038/nri3608

23. Johansson ME, Sjovall H, Hansson GC. The gastrointestinal mucus system in health and disease. *Nat Rev Gastroenterol Hepatol*. 2013;10(6):352–361. https://doi.org/10.1038/nrgastro.2013.35
24. Ursell LK, Metcalf JL, Parfrey LW, Knight R. Defining the human microbiome. *Nutr Rev.* 2012;70(suppl 1):S38–S44. https://doi.org/10.1111/j.1753-4887.2012.00493.x
25. Fujimura KE, Slusher NA, Cabana MD, Lynch SV. Role of the gut microbiota in defining human health. *Expert Rev Anti Infect Ther.* 2010;8(4):435–454. https://doi.org/10.1586/eri.10.14
26. Mehta NM, Corkins MR, Lyman B, et al; American Society for Parenteral and Enteral Nutrition Board of Directors. Defining pediatric malnutrition: a paradigm shift toward etiology-related definitions. *JPEN J Parenter Enteral Nutr.* 2013;37(4):460–481. https://doi.org/10.1177/0148607113479972
27. Alverdy J, Gilbert J, DeFazio JR, et al. Proceedings of the 2014 A.S.P.E.N. Research workshop: the interface between nutrition and the gut microbiome: implications and applications for human health. *JPEN J Parenter Enteral Nutr.* 2014;38(2):167–178. https://doi.org/10.1177/0148607113517904
28. Russo GL. Dietary n-6 and n-3 polyunsaturated fatty acids: from biochemistry to clinical implications in cardiovascular prevention. *Biochem Pharmacol.* 2009;77(6):937–946. https://doi.org/10.1016/j.bcp.2008.10.020
29. Plourde M, Cunnane SC. Extremely limited synthesis of long chain polyunsaturates in adults: implications for their dietary essentiality and use as supplements. *Appl Physiol Nutr Metab.* 2007;32(4):619–634. https://doi.org/10.1139/h07-034
30. Harris WS, Mozaffarian D, Lefevre M, et al. Towards establishing dietary reference intakes for eicosapentaenoic and docosahexaenoic acids. *J Nutr.* 2009;139(4):804S-819S. https://doi.org/10.3945/jn.108.101329
31. Rasmussen BB, Wolfe RR. Regulation of fatty acid oxidation in skeletal muscle. *Annu Rev Nutr.* 1999;19:463–484. https://doi.org/10.1146/annurev.nutr.19.1.463
32. Groot PHE, Hulsmann WC. The activation and oxidation of octanoate and palmitate by rat skeletal muscle mitochondria. *Biochim Biophys*

Acta. 1973;316:124–135. https://doi.org/10.1016/0005-2760(73)90002-7
33. Rössle C, Carpentier YA, Richelle M, et al. Medium-chain triglycerides induce alterations in carnitine metabolism. *Am J Physiol Endocrinol Metab.* 1990;258:E944–E947. https://doi.org/10.1152/ajpendo.1990.258.6.e944
34. Miura Y. The biological significance of ω-oxidation of fatty acids. Accessed March 27, 2024. https://www.jstage.jst.go.jp/article/pjab/89/8/89_PJA8908B-01/_pdf/-char/en
35. Drenckpohl D, McConnell C, Gaffney S, Niehaus M, Macwan KS. Randomized trial of very low birth weight infants receiving higher rates of infusion of intravenous fat emulsions during the first week of life. *Pediatrics.* 2008;122(4):743–751. https://doi.org/10.1542/peds.2007-2282
36. Simmer K, Rao SC. Early introduction of lipids to parenterally-fed preterm infants. *Cochrane Database Syst Rev.* 2005;(2):CD005256. https://doi.org/10.1002/14651858.cd005256
37. Krohn K, Koletzko B. Parenteral lipid emulsions in paediatrics. *Curr Opin Clin Nutr Metab Care.* 2006;9(3):319–323. https://doi.org/10.1097/01.mco.0000222118.76536.ad
38. Stephens BE, Walden RV, Gargus RA, et al. First-week protein and energy intakes are associated with 18-month developmental outcomes in extremely low birth weight infants. *Pediatrics.* 2009;123(5):1337–1343. https://doi.org/10.1542/peds.2008-0211
39. Diamond IR, Sterescu A, Pencharz PB, Kim JH, Wales PW. Changing the paradigm: omegaven for the treatment of liver failure in pediatric short bowel syndrome. *J Pediatr Gastroenterol Nutr.* 2009;48(2):209–215. https://doi.org/10.1097/mpg.0b013e318182c8f6
40. Gura KM, Lee S, Valim C, et al. Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease. *Pediatrics.* 2008;121(3):e678–e686. https://doi.org/10.1542/peds.2007-2248
41. Omegaven. Prescribing information. Fresenius Kabi; 2018. Accessed May 3, 2023.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/210589s001lbl.pdf
42. Brenna JT, Salem N Jr, Sinclair AJ, Cunnane SC; International Society for the Study of Fatty Acids and Lipids, ISSFAL. alpha-Linolenic acid supplementation and conversion to n-3 long-chain polyunsaturated fatty acids in humans. *Prostaglandins Leukot Essent Fatty Acids.* 2009;80(2–3):85–91. https://doi.org/10.1016/j.plefa.2009.01.004
43. Riserus U. Fatty acids and insulin sensitivity. *Curr Opin Clin Nutr Metab Care.* 2008;11(2):100–105. https://doi.org/10.1097/mco.0b013e3282f52708
44. Assy N, Nassar F, Nasser G, Grosovski M. Olive oil consumption and non-alcoholic fatty liver disease. *World J Gastroenterol.* 2009;15(15):1809–1815. https://doi.org/10.3748/wjg.15.1809

Test Your Knowledge Answers

1. The correct answer is **B**. Overweight and obesity are the result of excess calories rather than simply too much fat. The ideal nutrition support will provide customized caloric intake to meet the patient's needs as well as appropriate ratios of preformed LA, αLA, ARA, EPA, and DHA that cannot be made in adequate amounts by the patient.
2. The correct answer is **D**. Medium-chain and long-chain fatty acids are oxidized in mitochondria. Very long-chain fatty acids are oxidized in peroxisomes and mitochondria. Although it is normally a minor pathway, ω-oxidation in the endoplasmic reticulum of the cytoplasm becomes important if mitochondrial dysfunction occurs.
3. The correct answer is **D**. The neonate cannot synthesize LA or αLA. Although the enzymes are present to convert LA to ARA and αLA to EPA and DHA, the capacity to do so is not adequate to meet the needs of the neonate.

5

Protein Digestion, Absorption, and Metabolism

Oscar R. Herrera, PharmD, and Richard A. Helms, PharmD

Learning Objectives

1. Explain how protein metabolism and physiology are profoundly affected by the ontogeny of the gastrointestinal tract.
2. Review the roles of the liver and kidney in amino acid metabolism.
3. Understand the functions of amino acids and proteins, protein requirements for different ages, and protein energy ratios during growth.
4. Discuss protein turnover, assessment of plasma amino acids, and nitrogen balance.

Introduction

An extraordinary range of knowledge exists related to protein in human nutrition. This chapter focuses on the pediatric population and will specifically address the rapid development of neonates and infants. The basics of protein in adult nutrition are reviewed in *The ASPEN Adult Nutrition Support Core Curriculum*.[1] Ontogenic events relating to protein metabolism and physiology render young infants very differently than older

children and adults. In this chapter, we will review aspects of digestion, absorption, and metabolism of protein, focusing on these differences.

Ontogeny of the Gastrointestinal Tract vin Relation to Protein

The gastrointestinal (GI) tract has been described as the largest endocrine organ. It produces numerous regulatory gut peptides that are involved in GI tract development, growth, absorption, secretion, and gut motility. They function in classic endocrine, autocrine, paracrine, and neurocrine pathways.[2,3] Selected GI regulatory peptides involved with the ontogeny of the GI tract as it relates to proteins are outlined in Table 5-1. These peptides are all present in the fetus by the end of the first trimester, but adult levels may not be present until term.[4] The peptides that function as hormones are released in response to feeding. The release of some of these hormones is limited in newborns compared to adults.[4,5] Even though both pepsin and gastric lipase are located at the same site (ie, in the chief cells of the gastric mucosa), the enzymes have different developmental patterns.[6] Pepsin activity and output are much lower in infants than adults.[7,8] In contrast, gastric lipase activity and output are equal in infants and adults.[7,8]

TABLE 5-1. Gastrointestinal Regulatory Peptides

Regulatory Peptide	Sources	Mechanisms	Actions
Epidermal growth factor	Salivary glands; Brunner's glands; Paneth cells	Hormone; paracrine	• Stimulates mucosal proliferation and differentiation • Regulates gastrointestinal secretion • Has cytoprotective/ulcer-healing effects
Insulin-like growth factor	Gastrointestinal tract; liver	Hormone; autocrine paracrine	Stimulates crypt cell proliferation and enterocyte differentiation; promotes intestinal adaptation
Glucagon-like peptides	Ileum; colon	Hormone	Stimulates gut mucosal growth and regulates gut motility
Neurotensin	Ileum; central nervous system	Hormone; neurocrine	Inhibits gastric emptying and acid secretion
Vasoactive intestinal polypeptide	All tissues	Neurocrine	Promotes secretomotor, vasodilatation, and smooth muscle relaxation
Pancreatic polypeptide	Pancreas	Hormone	Inhibits pancreatic enzyme secretion and gallbladder contraction
Motilin	Proximal small intestine	Hormone	Stimulates gastrointestinal motility
Peptide YY	Gastrointestinal tract; central nervous system	Hormone; paracrine; neurocrine	Inhibits gastric acid secretion and gut motility

Reprinted with permission from Lippincott Williams & Wilkins from Gilger.[2]

The ontogeny of the brush border amino-oligopeptidases as well as the dipeptide and amino-acid transport systems parallel that of the carbohydrate enzymes. Amino-oligopeptidases are first detected immunohistochemically by 10 to 16 weeks gestation, and their activity progressively increases during development. By 28 to 30 weeks gestation, enzyme levels are

approximately one-half of the values found in term infants. Proteolytic activity increases rapidly after birth in preterm and full-term infants.[9]

Protein Digestion

Initial protein digestion occurs in the stomach, where proteins are exposed to hydrochloric acid (HCl) and pepsin. Gastric acid produces an acidic environment in the stomach and denatures protein.[10,11] Although protein digestive activity within the GI tract has been identified as early as 16 weeks gestation, gastric acid secretion is relatively low, and consequently, less protein denaturation occurs in both preterm and term infants. There is relatively minimal functional protein digestion in the stomach in the first few weeks of life. It is not until about 2 years of age that adult levels of gastric acid secretion are reached.[9]

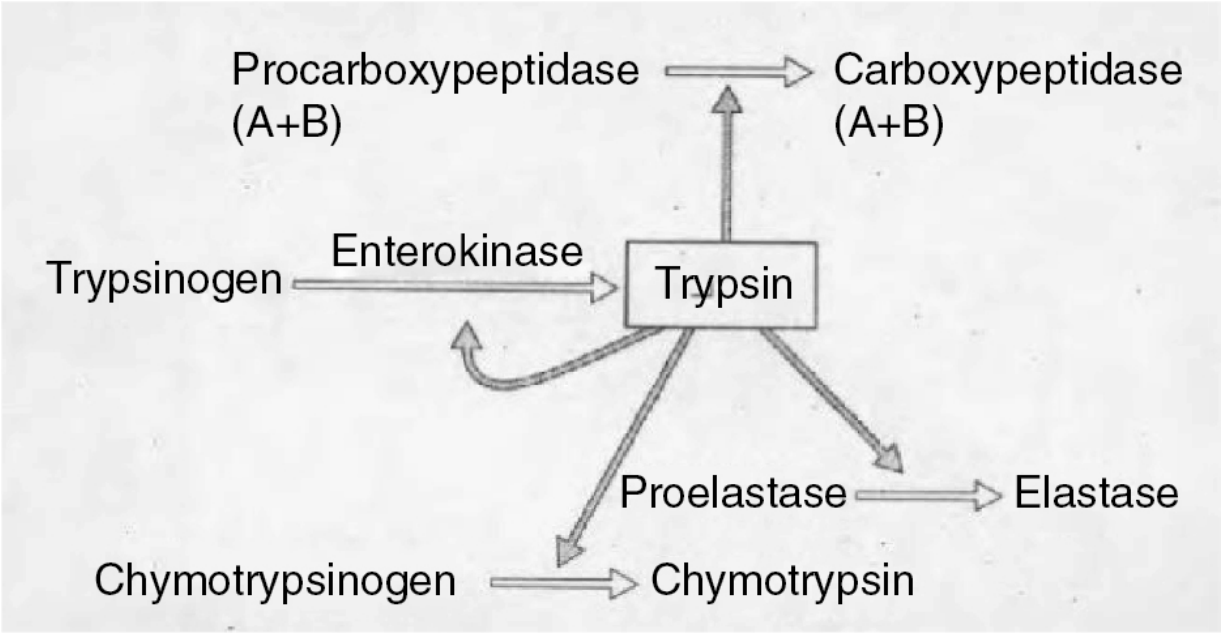
Gastrin stimulates both gastric acid and pepsin production and secretion, which initiates protein digestion in the stomach.[10] Chief cells secrete proenzymes (pepsinogen 1 and 2) into the stomach, which undergo autoactivation to form pepsins in the acidic milieu.[12] This acidic environment is critical for pepsin function, as evidenced by its inactivity in the duodenum, where the pH is neutral.[13] These pepsins function as endopeptidases; they hydrolyze internal bonds of the polypeptides to primarily form shorter polypeptides, oligopeptides, and some free amino acids.[9,11]

The protein denaturation within the stomach does not appear to be critical because patients with a more neutral gastric pH do not have impaired protein digestion. However, the amino acids that are produced from protein digestion in the stomach do assist in releasing cholecystokinin (CCK) or pancreozymin.[12] CCK has a role in protein digestion, helping to release pancreatic digestive enzymes, stimulate gallbladder contraction, and relax the sphincter of Oddi.[11,12] CCK is released by the I cells located in the epithelium of the small intestine (mostly in the duodenum and jejunum). In contrast, the hormone secretin promotes pancreatic secretion of bicarbonate-rich fluid to help establish a favorable pH.[10]

The pancreatic digestive enzymes are secreted in their inactive proenzyme form, similar to the secretion of pepsin as pepsinogen in the stomach. The pancreas secretes both endopeptidases (trypsinogen, chymotrypsinogen, and proelastase) and exopeptidases (procarboxypeptidase A and B) into the proximal small intestine.[11] The activated endopeptidases and exopeptidases hydrolyze the proteins at peptide bonds within the polypeptide chains to form oligopeptides and at the carboxyl terminal to form single amino acids, respectively.[9–11]

Bile acids and trypsinogen together cause the release of enterokinase, a brush border enzyme, which converts trypsinogen into its active form, trypsin. Trypsin then converts the remaining pancreatic peptidases into their respective active forms (chymotrypsin, elastase, and carboxypeptidase A and B) and assists in forming more trypsin from trypsinogen (see Figure 5-1).[9,10,13] Overall, the products of luminal protein digestion are about 70% oligopeptides and 30% free amino acids.[9]

FIGURE 5-1. Pancreatic Enzyme Activation



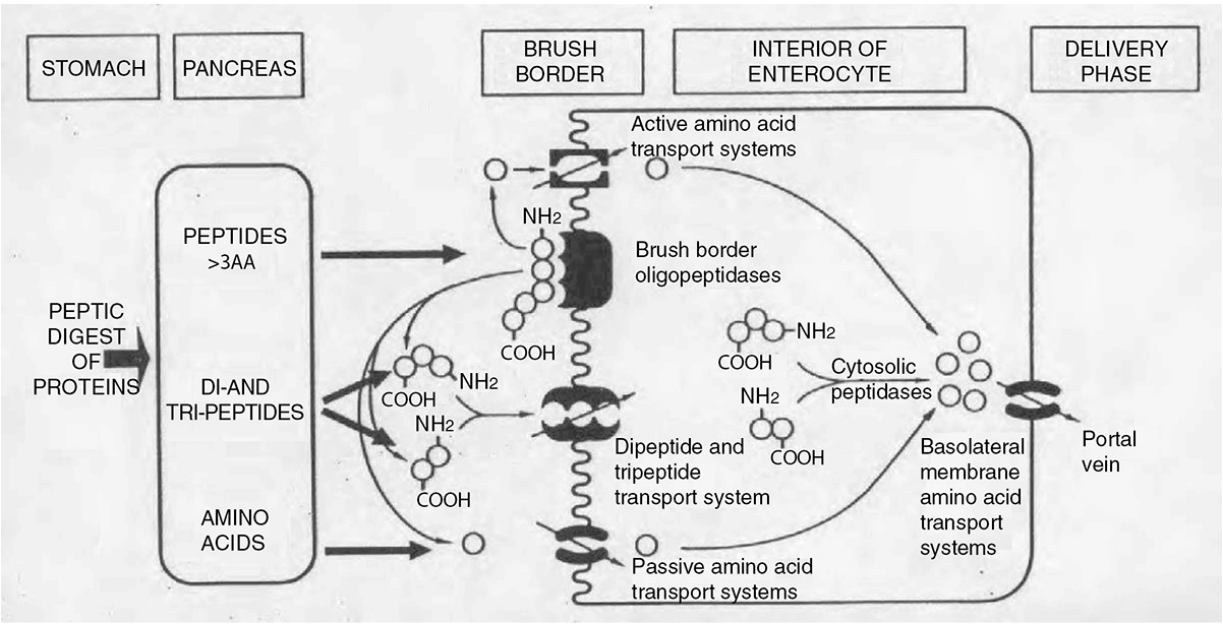
Reprinted with permission from Elsevier from Wahbeh and Green.[10]

Enterokinase and trypsin have been detected at 26 weeks and 28 weeks gestation, respectively. Enterokinase levels at the time of birth are about 10% of adult levels except in those rare infants with congenital enterokinase deficiency.[9,14] Trypsin activity in duodenal juice of preterm infants is slightly less than in full-term infants, but it does increase in response to food as in full-term infants. Infants have decreased trypsin activity in duodenal fluid compared with older children.[15] Trypsin activity has been demonstrated to increase over the first 4 months of life, possibly resulting from the infants' increased enteral protein intake.[9] However, the significance of these differences is unclear, given that protein digestion and absorption are fairly efficient even in preterm infants. Full-term infants digest and absorb about 80% to 85% of luminal proteins, while estimates for adults range from 95% to 98%.[9,11]

Protein Absorption

Normal protein absorption involves luminal processing, absorption into the intestinal mucosa, and transport into the circulation.[12] The brush border of enterocytes has different types of peptidases, including oligopeptidases, that further hydrolyze the partially digested proteins into amino acids, dipeptides, and tripeptides (see Figure 5-2).[9,10,12,16] Oligopeptidases have been detected as early as 10−16 weeks gestation, and they increase to nearly half of full-term levels by 28−30 weeks gestation.[9]

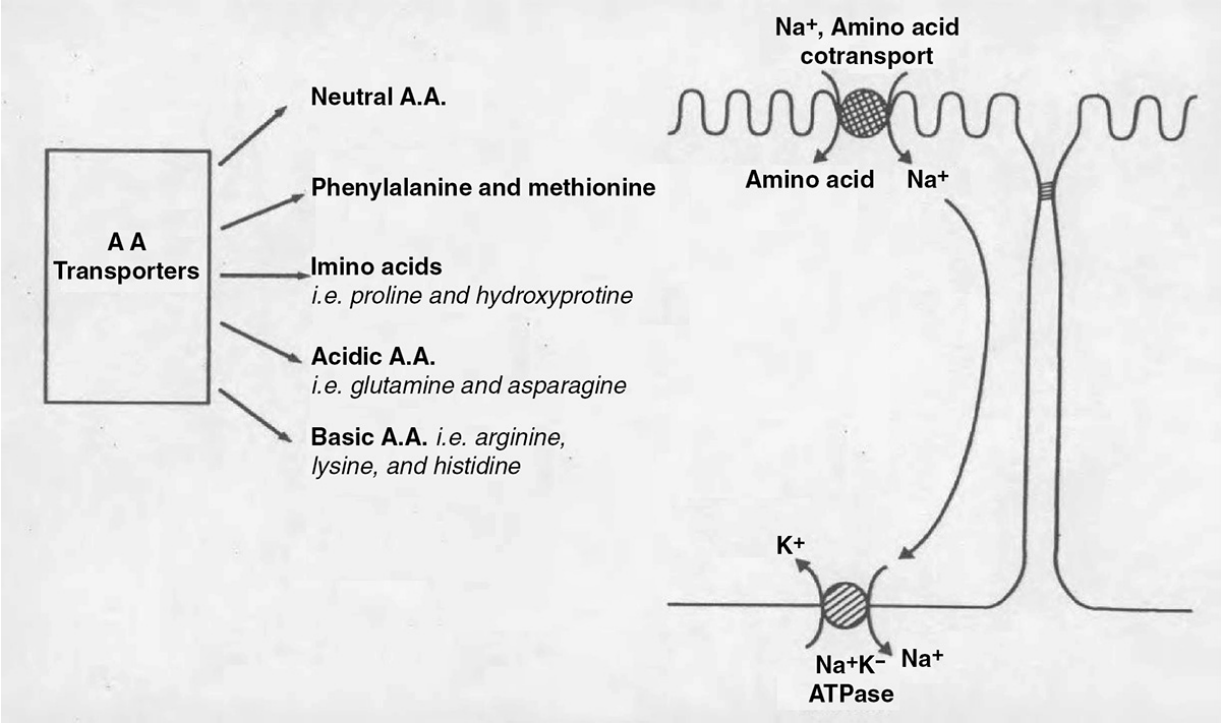
FIGURE 5-2. Pancreatic Enzyme Activation



Abbreviation: AA, amino acid. Reprinted with permission from Elsevier from Roy, Silverman, and Alagille.[16]

Absorption into the enterocyte involves both sodium-dependent and sodium-independent transport systems.[9] The sodium-dependent amino acid transporters are driven by a low intracellular sodium concentration and negative intracellular potential resulting from the sodium-potassium-adenosine triphosphatase (Na+−K+ ATPase) pump.[12] Many different transporters exist, including ones for neutral, acidic, and basic amino acids with narrow substrate specificity and for dipeptides and tripeptides with a broad substrate specificity (see Figure 5-3).[9,10,12,16]

FIGURE 5-3. The Transport of Amino Acids



Abbreviation: AA, amino acid. Reprinted with permission from Elsevier from Roy, Silverman, and Alagille.[16]

Once the amino acids are transported into the cytoplasm, they undergo additional processing by cytoplasmic peptidases, mostly dipeptidases and tripeptidases, which convert the dipeptides and tripeptides into free amino acids.[10,12,13] Although most of these amino acids are transported into the bloodstream, approximately 10%, particularly glutamine and glutamic acid, are used directly by the enterocyte.[10,13] Luminal protein sources are more readily used than systemic protein, especially in apical villous cells. Animals receiving parenteral nutrition (PN) without enteral feeds develop mucosal atrophy.[10]

Some of the sodium-independent amino acid transporters are located on the basolateral surface of the enterocyte and function to transport amino acids into the portal vein.[9] Although a significant majority of protein that enters the portal circulation is in the form of free amino acids, small

amounts of dipeptides and tripeptides enter the bloodstream intact through normal transport systems.[10]

Studies have shown that an infant's intestine may have a higher capacity for absorption of macromolecules than the adult intestine.[17] Thus, among susceptible infants (eg, infants who sustain severe postinfectious villous injury and extensive injury from necrotizing enterocolitis), the early introduction of specific foods of increased antigenic potential may increase their risk of protein sensitization.[18,19]

Given the broad substrate specificity for dipeptidase and tripeptidase at the brush border, it is not surprising that clinically significant deficiencies resulting from specific amino acid transport abnormalities are uncommon. Two of the more well-known inherited defects of protein absorption include Hartnup syndrome and cystinuria. In Hartnup syndrome, neutral amino acid transport is defective, and patients present with pellagra-like skin eruptions. In cystinuria (see Chapter 22, "Renal Disease"), a defect in cystine reabsorption results in excessive cystine in the urine and subsequent renal stone formation. In contrast, acquired defects of protein absorption, including exocrine pancreatic insufficiency and transient brush border enzyme deficiency from gastroenteritis, are more common.[8]

Digestion and Absorption of Whey and Casein

The major proteins in milk are whey and casein. The protein content of unmodified cow's milk is approximately 18% whey and 82% casein. When this unheated casein-predominant substance enters the acidic environment of the stomach, it forms a relatively hard curd composed of casein and minerals that can be difficult to digest. In contrast, human milk protein is approximately 60% to 70% whey and 30% to 40% casein.[20,21] Human milk forms a very small, soft curd in acid. Some infant formula manufacturers have developed whey-predominant formulas by combining equal amounts of demineralized whey protein and skim milk protein to yield a formula with 60% whey and 40% casein.

Important differences exist between whey and casein. Whey results in a faster gastric emptying time and is more easily digested overall. In contrast, casein is less soluble and has a slower rate of digestion, which results in an extended release of amino acids into circulation. In human studies, casein-predominant formulas result in lower zinc bioavailability than whey-predominant formulas, presumably because of less casein digestion.[22]

Other types of human whey proteins include secretory IgA and lactoferrin.[21] Secretory IgA attaches to the lining of the GI tract and prevents potential pathogenic microorganisms from adhering.[9] Lactoferrin is an iron-binding protein that limits the ability of bacteria to thrive in the intestines. Because this protein is biochemically similar to transferrin, it may have a significant role in iron absorption. However, in vivo studies have not definitively established this role.[23] Also, some evidence suggests that lactoferrin has a role in stimulating intestinal mucosa growth.[24] These 2 proteins found in human milk, secretory IgA and lactoferrin, and the main protease inhibitors, α1-antitrypsin and α1-antichymotrypsin, are not well digested in early infancy.[24,25] In fact, approximately 10% of intact milk proteins are found in infant stools before 1 month of age, decreasing to about 3% at 4 months of age.[24]

In vitro studies suggest that α1-antitrypsin resists proteolysis by pepsin and pancreatic enzymes.[24,26] Alpha 1-antitrypsin has been found in considerable quantities in both human milk and in the stool of infants fed human milk; therefore, it should not be used to ascertain enteric protein loss in breastfed infants.[26] Later in life, alpha 1-antitrypsin monitoring may be useful if a mucosal disorder is suspected in the child (eg, Crohn's or celiac diseases).[27]

Overall, infant formulas traditionally contain more protein than human milk because of concern that proteins in infant formulas are less digestible. Despite this concern in reduced breakdown, it has been observed that formula-fed infants have higher blood urea nitrogen (BUN) levels because of higher protein exposure. These infant formulas also have a higher proportion of whey, which should increase their digestibility. Additionally, it is important to note that heat treatment of milk proteins does affect their digestibility. It has been observed that the protein digestibility of powdered

formulas is greater compared to identical ready-to-feed forms. The heat treatment for powdered formulas is less intense than liquid formulas, with a lower maximum temperature and shorter duration. Protein digestibility is increased with less intense heat treatment.[24]

Amino Acids

Literally hundreds of amino acids exist in nature, but only 20 are considered relevant in human nutrition. Lafayette B. Mendel (1872–1935) was the first to demonstrate that some amino acids cannot be synthesized in rats and subsequently defined them as essential amino acids required in their diet. In an amazing series of experiments completed in the 1940s and 1950s, William C. Rose (1887–1985, who completed his training under Mendel), and co-investigators determined the amino acid requirements of normal adults.[28] These experiments revealed the following 8 amino acids that resulted in negative nitrogen balance when excluded from the diet (see Table 5-2):

- Isoleucine
- Leucine
- Lysine
- Methionine
- Phenylalanine
- Threonine
- Tryptophan
- Valine

TABLE 5-2. Essential, Nonessential, and Conditionally Essential Amino Acids in Human Nutrition

Amino acid	Essential	Nonessential	Conditionally Essential
Alanine		X	
Arginine[a,b]		X	
Asparagine		X	
Aspartic acid		X	
Cyst(e)ine[c]			X
Glutamic acid		X	
Glutamine		X	
Glycine[a,b]		X	
Histidine[d]	X		
Isoleucine	X		
Leucine	X		
Lysine	X		
Methionine	X		
Phenylalanine	X		
Proline[b]		X	
Serine[a,b]		X	
Taurine			X
Threonine	X		
Tryptophan	X		
Tyrosine			X
Valine	X		

[a] Glycine and serine carbon skeletons can be readily synthesized by neonates and infants, but the transamination rate is low.

[b] Laidlaw-Kopple classification as acquired indispensable (see Table 5-3).

[c] Cyst(e)ine is the sum of cysteine and cystine.

[d] Not initially identified by Rose as being an essential amino acid.[27]

Upon resumption of these amino acids in adequate amounts, the negative nitrogen balance was completely reversed. Other amino acids can be withheld without appreciable effect on nitrogen balance. Studies have confirmed these findings in infants and school-age children.

Amino acids can exist in 2 isomeric forms. The L-amino acids are utilized in humans and most animals. The stereoselectivity is related to enzymes that only recognize and utilize the L isomer. Amino acids do exist as D isomers, but only D-methionine can be converted to L-methionine by some animals (and not by humans). For the remainder of this chapter, we will not identify amino acids as the L isomer; it should be assumed that we are discussing the L isomer.

Conditionally Essential Amino Acids

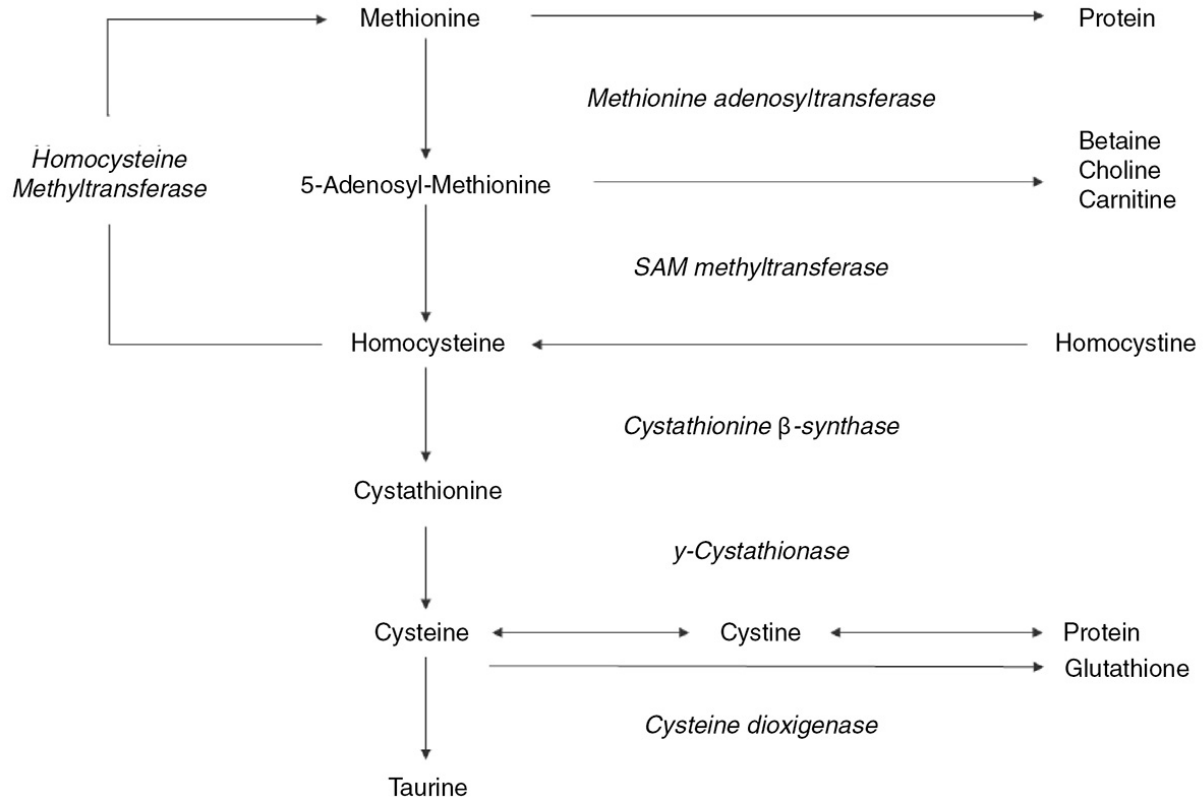
Investigations following Rose's extraordinary work generated questions as to whether other amino acids may be required in the diet under certain conditions of immaturity, metabolic imbalance, organ failure, disease, and highly defined diets such as PN. Histidine, for example, is now considered essential in the human diet.[29] Histidine stores are particularly high in hemoglobin and in carnosine (found in large quantities in muscle).[30,31] It is widely accepted that histidine is the ninth essential amino acid in humans (see Table 5-2). Snyderman et al established histidine intake requirements in infants of 24 mg/kg/d, which is generally less than other essential amino acids.[32] In studies by Heird et al. the histidine requirements in neonates and infants who were receiving PN were greater than those demonstrated by these earlier studies and higher than predicted from older child and adult requirements (adjusted by kilogram of body weight).[33,34] The *Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients* states that histidine is a conditionally essential amino acid for neonates and infants up to 6 months of age.[35]

Sulfur amino acid requirements of infants and children have been an area of intense research. The sulfur amino acids include methionine, cysteine, and taurine. Cysteine contains a free sulfhydryl group, and it is oxidized with another cysteine moiety to form the dimer cystine. After cysteine is incorporated into newly synthesized protein, the formation of cystine dimers aids in proper protein folding and stability. Cysteine is

metabolized from methionine and can replace 50% to 80% of methionine intake. Because it can reduce the required intake of an essential amino acid, Jackson has classified it as a conditionally essential amino acid.[36] Snyderman defined intakes of cysteine in infants at 85 mg/kg/d, similar to many of the essential amino acids.[37] Pohlandt discovered that the dietary requirement for cysteine continues into infancy, perhaps to 5 months of age.[38]

Most of the metabolic machinery for the metabolism of methionine and cysteine resides in liver parenchymal tissue near the portal circulation. The transsulfuration pathway for methionine metabolism is a complex series of enzymatic steps leading to cysteine and taurine production (see Figure 5-4). Many investigators have shown that multiple enzymes in this pathway have lower or no activity in the fetal liver or in the livers of infants of various gestational ages who died from non–liver-related causes.[39,40] λ-Cystathionase and cystathionine β-synthase were absent or had less than half the activity of older children or adults. Zlotkin and Anderson[41] demonstrated that λ-cystathionase in the liver of preterm and full-term infants did not reach adult activity until 6 to 9 months postnatal age. This may be the reason that human milk is relatively rich in cysteine content. This renders cysteine conditionally essential in neonates and infants.

FIGURE 5-4. Transsulfuration Pathway in the Metabolism of Methionine



Conflicting data on the essentiality of cysteine in neonates have been reported. In 2001, Lyons et al showed that pediatric septic patients receiving limited and variable protein intakes had higher plasma fluxes as well as increased oxidation rates for cysteine after a tracer (L-[1-^{13}C] cysteine) infusion compared to healthy controls.[42] In addition, septic patients were found to have lower whole-blood concentrations and lower absolute as well as fractional synthesis rates of glutathione.

More recently, Courtney-Martin et al observed no difference in glutathione concentrations and synthesis rates (absolute or fractional) in neonates who received cysteine supplementation (10 mg/kg/d) to their PN, in which the daily sulfur amino acid requirement was provided as methionine, compared to those who did not receive cysteine.[43] The difference may be from two factors: (1) concurrent clinical conditions and (2) provision of total sulfur amino acids. Sepsis can create enormous stress in preterm neonates and depletes essential amino acid stores despite

adequate parenteral protein provision. In more clinically stable infants, as long as an adequate amount of sulfur amino acid substrate is provided, additional cysteine supplementation may not be required.

As Shew et al demonstrated, very low birth weight (VLBW) neonates have the enzymatic ability to synthesize cysteine by transsulfuration pathways.[44] Whether that production is sufficient to maintain appropriate levels of taurine and glutathione during disease or for further use in the body remains to be seen. These differences will need to be further addressed to establish a true essentiality of cysteine in vulnerable infants.

Cysteine is gradually oxidized to the dimer cystine in aqueous solution at neutral pH. Therefore, for PN solutions that contain it, cysteine is added at the time of preparation. The commonly used intravenous additive is provided as the cysteine hydrochloride salt. Helms et al have studied the pediatric daily requirement for cysteine[45,46] and found that a dose of 77.4 mg/kg/d, close to that of Snyderman,[37] appears to be required for ideal nitrogen retention, nitrogen balance, and growth in infants on PN. Acidosis problems occasionally occur in VLBW infants and require acetate to be substituted for chloride in PN solutions. For every 160 mg of cysteine HCl that is infused as part of PN, 1 mmol of HCl is given to the patient. For preterm infants and neonates, the prescriber should consider substituting 1 mmol of acetate for 1 mmol of additional chloride given as part of cysteine HCl.

Taurine is one of the most abundant free “amino” acids in humans. It is not incorporated into protein because no aminoacyl tRNA synthetase recognizing taurine has been identified. Taurine is a sulfonic acid (rare in nature) and does not contain a carboxyl group like other amino acids. It has a host of important biological functions:

- Neurotransmitter
- Bile acid conjugation
- Brain and central nervous system development
- Osmoregulation
- Immunoregulation
- Antioxidant
- Retinal physiology
- Platelet function

- Mitochondrial function

It is essential in the feline diet and its absence results in retinal degeneration and blindness. In children on home PN with no added taurine, degenerative changes in electroretinograms were observed.[47] Cysteine sulfinic acid decarboxylase is key to the production of taurine from cysteine (see Figure 5-4). The enzyme has much lower overall activity in humans than in rats and cats, but its activity is even lower in human fetal liver.[48] Taurine is found in high concentrations in human milk compared to cow's milk.[49] Formulas made from cow's milk protein require taurine supplementation, and taurine deficiency may occur with synthetic formulas not containing taurine. In neonates and preterm infants, taurine continues to be renally wasted even in the presence of low serum taurine.[50]

Taurine is added to crystalline amino acid formulas designed for infants. Helms et al described plasma amino acid concentrations in preterm infants and long-term home PN patients receiving a pediatric-designed amino acid formula as part of their PN. [46,51] These investigators found that concentrations of sulfur amino acids in infants remain within age-related norms with the use of one of the commercially available formulas with L-cysteine HCl supplementation. Interestingly, even older children on home PN required cysteine supplementation to normalize plasma taurine concentrations.[51]

Tyrosine is exclusively metabolized from phenylalanine. Tyrosine, like cysteine for methionine, can reduce the dietary requirement for phenylalanine. Snyderman found that preterm infants have a dietary need for tyrosine of approximately 50 mg/kg/d.[37] Classic phenylketonuria (PKU), the absence of the enzyme phenylalanine hydroxylase, results in extreme elevations in phenylalanine concentration and a requirement for tyrosine in the diet. PKU can lead to brain damage and possibly death if untreated. Tyrosine may be conditionally essential in patients with liver disease and is the precursor for the neurotransmitter dopamine.

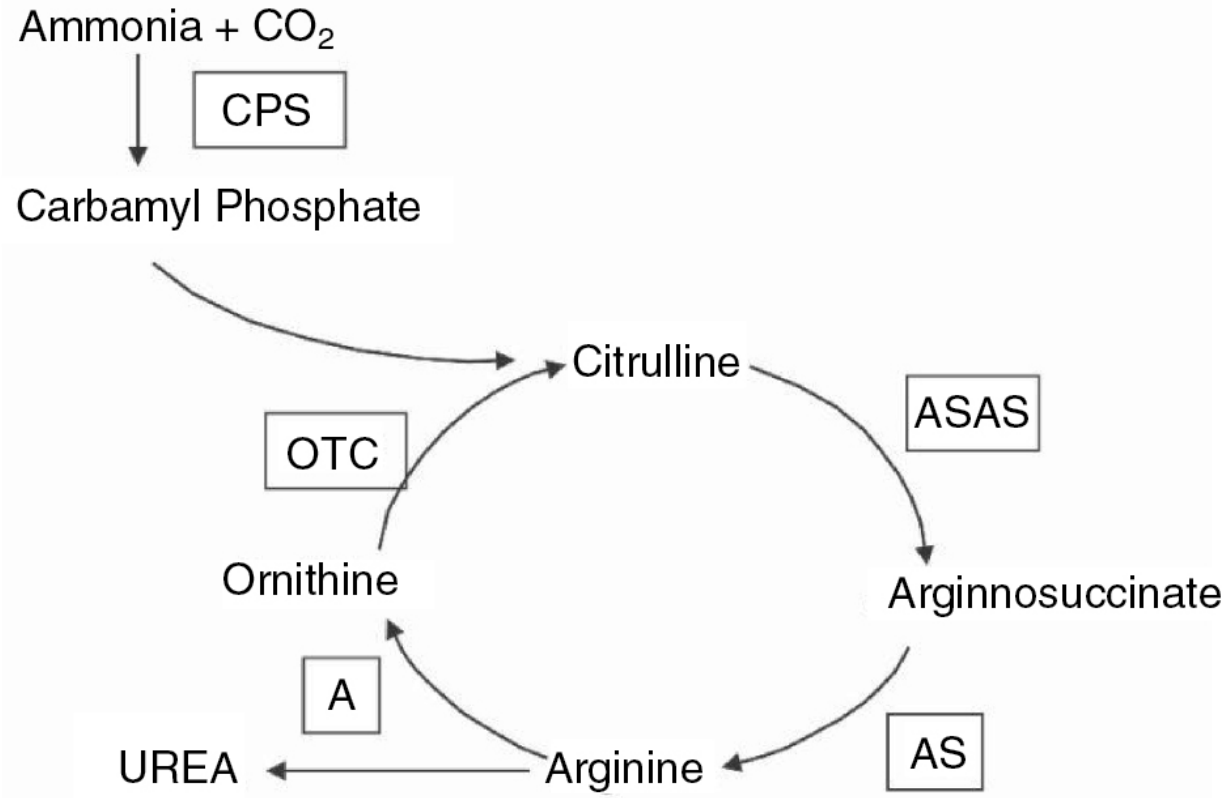
Tyrosine content in parenteral amino acid solutions is restricted because of poor solubility. Christensen et al found that N-acetyl-tyrosine (NAT), an aqueously soluble form of tyrosine with good stability in solution, was a reasonable intravenous source of tyrosine in older infants. [52] However,

clearance and nonrenal clearance were significantly decreased in younger infants of lower postconceptional age, suggesting that NAT may not be the ideal tyrosine source in VLBW neonates. This investigative group was unable to normalize plasma tyrosine concentrations in most infants at a dose of approximately 50 mg/kg/d. Van Goudoever et al were able to normalize plasma tyrosine levels with a NAT intake of 162 mg/kg/d.[53]

Amino Acids of the Urea Cycle

The amino acids of the urea cycle are considered nonessential (see Figure 5-5). Snyderman et al found no evidence that arginine is essential in preterm infants.[54] However, early amino acid solutions with relatively lower concentrations of arginine resulted in hyperammonemia in infants receiving these formulas as part of PN.[55] Higher concentrations of arginine reversed the finding of hyperammonemia.[56] Acute renal failure patients given large doses of protein with little supplemental arginine also present with hyperammonemia, which can be reversed with arginine supplementation.[57]

FIGURE 5-5. Urea Cycle With Enzymes and Substrates



Abbreviations: A, arginase; AS, argininosuccinase; ASAS, argininosuccinic acid synthetase; CPS, carbamyl phosphate synthetase; OTC, ornithine transcarbamylase.

Another intermediate of the urea cycle, citrulline, has entered the clinical research arena. Most of the citrulline produced in the liver is consumed in the next step of the cycle; however, enterocytes also synthesize citrulline and have been shown to contribute most of the circulating plasma citrulline.[58] This particular property has gathered the interest of investigators for citrulline as a GI biomarker, which will be discussed in a later section. Other intermediates can become deficient because of abnormal enzymatic activity, leading to urea cycle disorders. Treatment for these conditions generally involves the supplementation of low-dose essential amino acids and arginine.

Useful Classification of Amino Acids for the Clinician

Laidlaw and Kopple[59] offer an alternative approach to the Jacksonian[36] classification of essential and nonessential amino acids. These 5 classifications enable clinicians to better understand amino acid requirements in the diet or a particular disease state (see Table 5-3).

TABLE 5-3. Modification of Amino Acid Classification in Humans

Classification	Description	Example
1. Totally indispensable	No metabolic precursor or product can be substituted	Lysine and threonine
2. Carbon-skeleton indispensable	Ketoacid analogue or hydroxyacid analogue can be substituted	Histidine, isoleucine, leucine, methionine, phenylalanine, tryptophan, and valine
3. Conditionally indispensable	Reduce requirement for indispensable and become indispensable in the absence of precursor in diet	Tyrosine, cysteine, and taurine; possibly ornithine and citrulline
4. Acquired indispensable	Become indispensable in states of metabolic disorders, immaturity, and severe stress	Cysteine, taurine, tyrosine, arginine, citrulline, glycine, serine, and proline
5. Dispensable	—	Alanine, glutamate, and aspartate

Data from Windmueller and Spaeth.[58]

Roles of the Liver and Kidney in Amino Acid Metabolism

The liver is important in the synthesis of transport and other constituent and functional proteins, metabolism of amino acids, gluconeogenesis, and urea formation.[60,61] Major plasma proteins derived from the liver, such as albumin, transthyretin (TTR; also known as prealbumin for its migration pattern during electrophoresis), and retinol-binding protein (RBP) are present at early stages of development. Most liver-derived plasma proteins

are at lower concentrations in preterm infants. Lipoprotein concentrations rise rapidly after birth in response to high dietary fat intake, while albumin and TTR increase toward adult values in the first few months through the first year of life. Acute phase proteins, such as C-reactive protein (CRP), appear to be inducible even in prematurity and are used to monitor inflammatory response to infection or metabolic stress. Reduction in visceral protein occurs in preterm infants, and response to protein and energy intake can be assessed through monitoring changes in serum concentrations of albumin, TTR, and RBP.[62]

The production of glutathione in the liver is essential; however, other tissues can produce it. Glutathione is an important sulfhydryl-reducing agent that protects cells from oxygen-free radicals.[63] It is synthesized from glutamate, cysteine, and glycine, and cysteine is the rate-limiting substrate in production. Glutathione production depends on two distinct steps in cysteine production via the transsulfuration pathway (principally in the liver) or from dietary intake. The tripeptide also appears to be important in the transport of amino acids and the synthesis of leukotrienes via the enzyme γ-glutamyl transpeptidase.[64,65]

The metabolism of amino acids is an important function of the liver. Several enzymes and enzyme systems, such as the transsulfuration pathway and phenylalanine hydroxylase, both predominantly located in the liver, are responsible for metabolizing the essential amino acids methionine and phenylalanine, respectively. Enzyme activity is reduced in prematurity and early infancy, rendering the products of these enzyme systems as conditionally essential amino acids.

Approximately one-third of amino acids entering the liver from portal blood are used for protein synthesis.[66] The remainder may be used in energy production, or gluconeogenesis, with perhaps only a third of dietary amino acids entering the peripheral blood. This explains why plasma amino acids do not fluctuate substantially in the postprandial period.

Branched-chain amino acids (ie, leucine, isoleucine, and valine) are released at higher relative concentrations from the liver in the postprandial period[67] and are involved in hepatic protein and albumin synthesis, which has been shown recently to be attenuated by exosomes found in human milk.[68] Branched-chain amino acids are preferentially metabolized in the

periphery because they, as well as arginine, stimulate insulin release and muscle protein synthesis.[69] All stimulation is reversed in the postabsorptive period. As insulin concentrations fall, the muscle provides the principal gluconeogenic substrate (alanine) to the liver for glucose production in the fasting period.

In parenterally fed neonates and infants, Heird et al found that the branched-chain amino acid needs of infants increased despite their relatively lower muscle mass. [33,34] This would suggest that the shuttling of amino acids between the periphery and the small infant liver is higher than in adults. Increased requirement of amino acids and energy for synthesis may be the likely explanation.

The urea cycle is the principal mechanism for nitrogen disposal (see Figure 5-5). The catabolism of proteins and their component amino acids results in ammonia production. The liver will hydrolyze arginine to form urea and ornithine under the enzymatic control of arginase. Urea is then delivered to the kidney for excretion. In neonates and infants, the quantity of amino acids that enter urea production is small, presumably because of the substantial need for amino acids for growth; therefore, BUN will be low.[70]

The kidney, when healthy, plays a minor role in amino acid and protein metabolism. Ninety percent of dietary protein nitrogen is incorporated into new tissue, and therefore, it never requires formation of urea in the liver and excretion by the kidney. In preterm infants and neonates, excretion of nitrogen is limited for the first months of life. Tubular reabsorption of amino acids is reduced in preterm infants and neonates and may explain increased amino acid needs in these patients compared to older children or adults.[71,72]

Functions of Amino Acids and Proteins

Protein has multiple functions: It is essential for cell structure, maturation, remodeling, and growth. Besides being utilized for energy, amino acids and proteins serve as essential precursors for many biological processes.[73]

When protein is consumed, it is broken down to amino acids in the GI tract, which can then enter cells or continue to circulate in plasma. Once in

the cell, amino acids can be combined by peptide linkages to form small peptides (such as glutathione), they can be substrates for protein synthesis, or they can function as individual amino acids in the urea cycle. Specific amino acids can act as substrates, regulators, transporters, and precursors to neurotransmitters and hormones.[74]

In the cell, protein can be utilized for energy, or it can be stored. Proteins are continuously being broken down. The carbon chain of the amino acids can be utilized for energy, and free amino acids can be released back into the plasma to maintain plasma amino acid concentrations.[73]

After synthesis within the cell, many proteins are released into the plasma. The 3 major types of plasma proteins are albumin, globulin, and fibrinogen. Albumin's role is to maintain osmotic pressure in the plasma. Globulins are involved in enzymatic activity in the plasma and play a vital role in natural and acquired immunity. Fibrinogen is essential for coagulation, both in blood clotting and repair of blood vessels.[73] For specific examples of the functions of amino acids and protein, refer to Table 5-4.

TABLE 5-4. Functions of Amino Acids and Protein

	Function	Example
Amino acids	Substrates for protein synthesis Regulators of protein turnover Regulators of enzyme activity (allosteric) Precursor of signal transducer Methylation reactions Neurotransmitters Ion fluxes Precursor of physiologic molecules Nitrogen transport Oxidation and reduction Precursor of conditionally indispensable amino acids Gluconeogenic substrate and fuel	Amino acids with a codon Leucine, arginine Arginine and NAG synthetase, Phe and PAH activation Arginine and nitric oxide Methionine Tryptophan (serotonin), glutamate, glycine, GABA Taurine, glutamate Arginine (creatinine), glutamine Alanine, glutamine Cystine, glutathione Methionine (cys), phe (thy) Alanine, serine, glutamine
Proteins	Enzymatic catalysis Transport Messenger/signals Movement Structure Storage/sequestration Immunity Growth, differentiation, and gene expression	BCKADH B12-binding proteins, ceruloplasmin, apolipoproteins Insulin, growth hormones Kinesin, actin Collagens, elastin Ferritin, metallothionein Antibodies, TNF, interleukins EGF, IGFs, transcription factors

Abbreviations: BCKADH, branched-chain alpha-keto acid dehydrogenase; EGF, epidermal growth factor; GABA, γ-aminobutyric acid; IGF, insulinlike growth factor; NAG, N-acetylglutamate; PAH, phenylalanine hydroxylase; Phe, phenylalanine; TNF, tumor necrosis factor.

Data from Edelman and Wolfish.[71]

Protein Requirements and Protein-Energy Ratio During Growth

Protein is essential for growth, and its weight-based requirements (similar to total caloric requirements) are greater for VLBW neonates and gradually decrease with increasing age.[28] VLBW neonates have the highest protein requirements, often requiring up to 3.5 g/kg/d,[74,75] while term neonates

require 2 to 2.5 g/kg/d. Two approaches for determining protein requirements in these infants have been discussed in the literature, including empirical and factorial methods.[76] Nitrogen balance, which will be discussed later, is an example of an empirical approach. The factorial method is based on the sum of estimates for replacement of inevitable nitrogen losses (urinary, stool, dermal) plus lean body mass accretion needs.[76]

These and many other studies have demonstrated that adequate protein may be more critical for nutritional status and growth than total caloric requirements in preterm neonates and sick children.[18] Protein requirements can be increased by as much as 20% to 50% in critical illness, thermal injury, and catch-up growth.[77]

Early initiation of protein is beneficial in extremely low birth weight infants. Poindexter et al concluded that early amino acid administration was significant for better infant growth outcomes and neurodevelopment when evaluated at 36 weeks postmenstrual age and again at 18 months follow-up.[78] Controversy remains around whether increased protein intakes (3–4 g/kg/d) lead to increased growth or other markers of protein utilization in VLBW neonates. Several institutions have adopted these practices, but Vlaardingerbroek et al recently demonstrated that high-protein dose (3.6 g/kg/d) administration did not lead to improved nitrogen balance compared to controls receiving a conventional protein dosage (2.4 g/kg/d) in the short term (first week of life).[75]

Protein requirements in term infants are based on studies in freely breastfed infants.[79] In infancy, 55% of daily protein is dedicated to growth while 45% is for maintenance. This ratio gradually decreases, and by 4 years of age only about 10% of total protein requirement is utilized for growth and the remaining 90% is used for daily maintenance.[80] Refer to Table 5-5 for age-based protein requirements.

TABLE 5-5. Protein Requirements

Category	Protein (g/kg/d)
Very low birth weight (<1500 g)	3–3.5
Preterm	2.5–3
Infant/neonate	2–2.5
Infant	1.5–2
Preschool/school-age	1–1.5
Adolescent	0.8–1.5

Data from the American Academy of Pediatrics, Committee on Nutrition.[80]

Assessment of Protein Status

Besides the monitoring of visceral proteins (ie, albumin, TTR) and acute phase proteins (ie, CRP), nitrogen balance can be a useful tool in monitoring protein repletion and depletion in pediatric patients receiving specialized nutrition support. Nitrogen balance is an estimate of nitrogen intake minus nitrogen excretion. In adults, urinary urea nitrogen (in g/l multiplied by 1.2 to yield total urinary nitrogen [TUN]) multiplied by the urine volume (l/d) plus 2 to 4 g nitrogen (to reflect all other unmeasured nitrogen lost) results in nitrogen balance. The method for collection and calculation of nitrogen balance is altered in pediatric patients.

Nitrogen balances are best achieved in a disciplined environment, where collection can be easily reproducible. This is often achieved in a research/study setting, but it could be achieved in the hospital setting with interprofessional collaboration. Urine collections in neonates and infants are problematic, but not impossible. The use of urine bags with attentive clinician support, or collection of diapers with elution of all urinary and stool nitrogen, has been used successfully in the clinical arena to assess nitrogen output in children.[81] While 24-hour urine collections have been considered the standard, the use of 6-hour collections has been reported in pediatrics.[82] We are more comfortable using 24-hour urine collections to predict actual nitrogen balance during the observation period.

A lower percentage of nitrogen is excreted as urea in neonates and infants, making the use of adult correction factors inappropriate.[1] Several

issues, such as the previous one described, should be considered when completing nitrogen balance studies in pediatrics. Helms et al characterized nitrogen excretion in stressed pediatric intensive care unit patients and sick neonates.[83] Urea as a percentage of total nitrogen output was in the range of 40% to 60%, which is distinctly different from the 80% excretion as urea assumed in adults. Because the percentage of nitrogen excreted as urea is substantially different than in adult patients and varies with clinical conditions, the use of TUN is recommended to increase accuracy and reliability for both children and adults. Mathes et al evaluated the effects of enteral protein intake on the protein status of preterm infants measured in 2 scheduled blood samples and weekly spot urine samples.[84] Those with higher protein intake (median 4.3 g/kg/d) showed higher plasma urea concentrations and higher urinary urea to creatinine ratios at weeks 3, 5, and 7 compared to neonates receiving lower protein intakes (median 3.7 g/kg/d).

With the advent of isotopic carbon oxidation studies, new methods have been established to determine amino acid intake requirements.[85] These methods include indicator amino acid oxidation (IAAO) and the 24-hour indicator amino acid oxidation and balance method (24 h-IAAO/ IAAB). They offer the advantage of being noninvasive, with the former being a little less time-consuming than the latter. IAAO consists of a 2-day adaptation to fixed protein intakes followed by breath CO_2 measurement after 8 hourly meals enriched with [1-^{13}C]phenylalanine.[86] 24h-IAAO/IAAB consists of 6-day adaptation to fixed protein intakes followed by assessment of oxidation during 12-hour fed state and 12-hour fasted state and assessment of balance by subtraction of [1-^{13}C]leucine oxidation from intake.[87] In particular, IAAO has been compared to the factorial method to determine amino acid requirements in children. The current Dietary Reference Intake report, based on the latter, seems to underestimate mean protein requirements in healthy, school-aged children (0.76 g/kg/d) [88] compared to the IAAO method (1.3 g/kg/d).[89] More recently, a new methodology showed preliminary but promising data evaluating oral sip feeding as opposed to constant intravenous infusion of these isotope tracers.[90] Hirsch and colleagues showed significant increases in nitrogen

balance, protein synthesis, and exogenous hydroxylation during the postprandial period after protein ingestion through that method.

Given the complexity of these assessments, they may be better suited for a stable, general-ward type of patient, rather than a critically ill patient whose care is already challenging and demands more resources. As these techniques become more widely available, protein intake standards for the different age populations will change in the future.

Monitoring Plasma Amino Acids

Plasma amino acids have been widely reported in pediatric patients. Storm and Helms reviewed the hypothesis regarding normalization of plasma amino acids and its validation as a predictive tool in understanding outcomes in neonates and infants receiving PN.[91] This review led to numerous investigations suggesting normalization results in improved growth, nitrogen balance, increased calcium and phosphorus intakes, and improved liver health.[92–96] It is likely that plasma amino acids will continue to be a benchmark for the efficacy of newly developed pediatric amino acid formulations.

As introduced previously in the section "Amino Acids of the Urea Cycle," concentrations of plasma citrulline have been investigated in different GI insults and/or diseases, such as mucosal injury after chemotherapy,[97] celiac disease,[98] short bowel syndrome,[99] and transplantation.[100] Recently, several studies have evaluated plasma citrulline in patients with or without bowel resection as a marker of both intestinal mass and functionality,[101,102] identifying promising trends suggesting both properties. Most institutions can obtain whole profiles of amino acids with a rapid turnaround time, but the question remaining for clinicians is how to utilize that information.

As new research arises, certain amino acids could be monitored and serve as descriptors for certain disease states or conditions. For individual assessment of plasma amino acids to impact the clinical environment and outcomes in pediatric patients more profoundly, less expensive, less time-consuming, and more accessible analytical technologies are needed to

replace those currently used for single amino acid detection in clinical research.

Case Presentation and Discussion

A 2-week-old male was transferred to the neonatal intensive care unit today. He was born at 32 weeks gestation with a birth weight of 1.6 kg. The mother was not able to produce enough milk, so he was started on preterm infant formula, reaching full feedings about a week ago. Two days ago, the infant developed feeding intolerance and fever. This morning, the nurse noted fever, abdominal distention, tachycardia, and specks of blood in the stool. His oxygen saturation dropped, requiring intubation. He was taken to the operating room for an exploratory laparotomy, and he was diagnosed with necrotizing enterocolitis. The nutrition team was consulted to evaluate the infant's nutrition needs.

Question: Explain how the infant's symptoms could be associated with the protein content in the choice of enteral feeding.

Comment: Human milk contains IgA, which is important in host defense and can provide immunity to the infant, preventing bacterial overgrowth and possible infection. Human milk also has a higher whey content than formula. Whey is more easily digestible and promotes gastric emptying, which prevents feeding accumulation and can serve as an energy source for bacteria.

Question: What would be your initial action, and how would you monitor the effectiveness of your PN regimen?

Comment: This patient is anticipated to be NPO for an extended period. PN should be started, and L-cysteine supplementation should be considered. The best method for protein evaluation and overall nutrition status in this patient would be daily weights and longitudinal assessment of visceral proteins, such as transthyretin and albumin, and nitrogen balance if feasible.

Question: What is the estimated protein requirement for this infant?

Comment: Because this infant is preterm and critically ill due to necrotizing enterocolitis, 2.5 to 3 g/kg of protein should be provided and dosed based on the birth weight of 1.6 kg. This corresponds to a total protein dose of approximately 4 to 4.5 g/d.

Question: What are your nutrition recommendations for this infant once he is allowed to start enteral feedings?

Comment: Depending on whether bowel resection was necessary, this infant may need a specialized enteral feeding regimen. Human milk (from the mother or a donor) may confer advantages early on and is conventionally accepted as first-line compared to formula (see Chapter 11, "Human Milk"); however, the latter may be more convenient for discharge planning and because of the mother's lack of production. If formula is chosen, it would be prudent to choose one that is easier to digest, such as a hydrolyzed or amino acid–based formula.

Conclusion

The biochemical and physiologic principles of protein digestion, absorption and metabolism have not changed. New methodologies of assessment and monitoring of protein utilization are being investigated. As infants are surviving at younger gestational ages, and presumably with higher protein requirements, clinicians must combine current and newer knowledge to provide appropriate supply to meet their needs.

Test Your Knowledge Questions

1. Which amino acid is required for an infant diagnosed with phenylketonuria?
   A. Phenylalanine
   B. Cysteine
   C. Histidine
   D. Tyrosine
   E. Methionine
2. Which of the following is an advantage of human milk over cow's milk?
   A. Human milk has a higher pH because of its high bicarbonate concentration.
   B. Human milk has a higher whey content that promotes rapid gastric emptying.

C. Human milk has a higher caloric density.
D. Human milk prevents children from developing colic.
E. All of the above are advantages of human milk.

3. Which of the following is true regarding protein digestion?
   A. Occurs mostly in the small intestine.
   B. Is dependent on hydrochloric acid and pepsin to denature protein.
   C. Has been identified as early as 16 weeks gestation, but gastric acid secretion does not reach adult levels until 38 weeks gestation.
   D. Products include approximately 30% oligopeptides and 70% amino acids.
4. Which of the following is true regarding nitrogen balance?
   A. Nitrogen balance is not an accurate way to assess protein needs in a pediatric patient.
   B. A 24-hour urine collection is needed to estimate a nitrogen balance.
   C. Total urinary nitrogen is a better estimate of urinary losses compared to urinary urea nitrogen.
   D. Nitrogen balance is an estimate of nitrogen intake divided by nitrogen excreted.

References

1. Young LS, Kim DW. Protein. In: Mueller C, ed. *The ASPEN Adult Nutrition Support Core Curriculum.* 3rd ed. American Society for Parenteral and Enteral Nutrition; 2017:97–112.
2. Gilger MA. Normal gastrointestinal function. In: McMillan JA, Feigin RD, DeAngelis C, Jones MD, eds. *Oski's Pediatrics.* 4th ed. Lippincott Williams & Wilkins; 2006:1915–1921.
3. Berseth CL. Overview of the development of the gastrointestinal tract. UpToDate. Updated October 27, 2022. Accessed January 31, 2024. https://www.uptodate.com/contents/overview-of-the-development-of-the-gastrointestinal-tract?search=Overview%20of%20the%20development%20of%20the%20gastrointestinal%20tract&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

4. Lucas A, Bloom SR, Aynsley-Green A. Development of gut hormone responses to feeding in neonates. *Arch Dis Child.* 1980;55(9):678–682. https://doi.org/10.1136/adc.55.9.678
5. Berseth CL, Nordyke CK, Valdes MG, Furlow BL, Go VL. Responses of gastrointestinal peptides and motor activity to milk and water feedings in preterm and term infants. *Pediatr Res.* 1992;31(6):587–590. https://doi.org/10.1203/00006450-199206000-00010
6. Moreau H, Bernadac A, Gargouri Y, Benkouka F, Laugier R, Verger R. Immunocytolocalization of human gastric lipase in chief cells of the fundic mucosa. *Histochemistry.* 1989;91(5):419–423. https://doi.org/10.1007/bf00493829
7. Armand M, Hamosh M, Mehta NR, et al. Effect of human milk or formula on gastric function and fat digestion in the premature infant. *Pediatr Res.* 1996;40(3):429–437. https://doi.org/10.1203/00006450-199609000-00011
8. Armand M, Hamosh M, DiPalma JS, et al. Dietary fat modulates gastric lipase activity in healthy humans. *Am J Clin Nutr.* 1995;62(1):74–80. https://doi.org/10.1093/ajcn/62.1.74
9. Rudolph CD. Structure and development of the gastrointestinal tract. In: Rudolph CD, Rudolph AM, Hostetter MK, Lister GE, Siegel NJ, eds. *Rudolph's Pediatrics.* 21st ed. McGraw-Hill; 2003.
10. Wahbeh GT, Green N. Basic aspects of digestion and absorption. In: Wyllie R, Hyams JS, and Kay M, eds. *Pediatric Gastrointestinal and Liver Disease.* 6th ed. Elsevier; 2021:11–23.
11. Colaizzo-Anas T. In: Mueller C, ed. *The ASPEN Adult Nutrition Support Core Curriculum.* American Society for Parenteral and Enteral Nutrition; 2017:3–26.
12. Mason JB. Overview of nutrient absorption and etiopathogenesis of malabsorption. UpToDate. Updated July 19, 2023. Accessed January 31, 2024. https://www.uptodate.com/contents/overview-of-nutrient-absorption-and-etiopathogenesis-of-malabsorption?search=Overview%20of%20nutrient%20absorption%20and%20etiopathogenesis%20of%20malabsorption&source=search_result&selectedTitle=1%7E150&usage_type=default&display_rank=1
13. DeLegge MH, Ridley C. Nutrient digestion, absorption, and excretion. In: Gottschlich, MM, Fuhrman MP, Hammond KA, Holcombe BJ,

Seidner DL, eds. *The Science and Practice of Nutrition Support: A Case-Based Core Curriculum.* Kendall/Hunt Publishing Co; 2001:1–16.
14. Hadorn B, Tarlow MJ, Lloyd JK, Wolff OH. Intestinal enterokinase deficiency. *Lancet.* 1969;1(7599):812–813. https://doi.org/10.1016/s0140-6736(69)92071-6
15. Johnson TR, Moore WM, Jeffries JE. *Developmental Physiology.* 2nd ed. Ross Laboratories; 1978:150–152.
16. Roy CC, Silverman A, Alagille D. *Pediatric Clinical Gastroenterology.* 4th ed. Mosby-Year Book, Inc; 1995:307–309.
17. Axelsson I, Jakobsson I, Lindberg T, Polberger S, Benediktsson B, Räihä NC. Macromolecular absorption in preterm and term infants. *Acta Paediatr Scand.* 1989;78(4):532–537. https://doi.org/10.1111/j.1651-2227.1989.tb17932.x
18. Motil KJ. Meeting protein needs. In: Tsang RC, Zlotkin SH, Nichols BL, Hansen JW, eds. *Nutrition During Infancy: Principles and Practice.* 2nd ed. Digital Education Publishing, Inc; 1997:83–103.
19. Philipps AF, Sherman MP. Neonatal nutrition and gastrointestinal function. In: Rudolph CD, Rudolph AM, Hostetter MK, Lister GE, Siegel NJ, eds. *Rudolph's Pediatrics.* 21st ed. McGraw-Hill; 2003.
20. Hansen JW, Boettcher JA. Human milk substitutes. In: Tsang RC, Zlotkin SH, Nichols BL, Hansen JW, eds. *Nutrition During Infancy: Principles and Practice.* 2nd ed. Digital Education Publishing, Inc; 1997:441–466.
21. Schanler, RJ. Nutritional composition of human milk and preterm formula for the premature infant. UpToDate. Updated December 14, 2023. Accessed January 31, 2024. https://www.uptodate.com/contents/search?search=Nutritional%20composition%20of%20human%20milk%20and%20preterm%20formula%20for%20the%20premature%20infant
22. Lönnerdal B, Cederblad A, Davidsson L, Sandström B. The effect of individual components of soy formula and cow's milk formula on zinc bioavailability. *Am J Clin Nutr.* 1984;40(5):1064–1070. https://doi.org/10.1093/ajcn/40.5.1064
23. Brock, JH. Lactoferrin in human milk: its role in iron absorption and protection against enteric infection in the newborn infant. *Arch Dis*

Child. 1980;55(6):417–421. https://doi.org/10.1136/adc.55.6.417
24. Lönnerdal B. Digestibility and absorption of protein in infants. In: Räihä NC, ed. *Protein Metabolism During Infancy.* Raven Press; 1994:53–65.
25. Lindberg T, Ohlsson K, Weström B. Protease inhibitors and their relation to protease activity in human milk. *Pediatr Res.* 1982;16(6):479–483. https://doi.org/10.1203/00006450-198206000-00016
26. Davidson LA, Löonnerdal B. Fecal alpha 1-antitrypsin in breast-fed infants is derived from human milk and is not indicative of enteric protein loss. *Acta Paediatr Scand.* 1990;79(2):137–141. https://doi.org/10.1111/j.1651-2227.1990.tb11429.x
27. Thomas DW, Sinatra FR, Merritt RJ. Random fecal alpha-1-antitrypsin concentration in children with gastrointestinal disease. *Gastroenterology*. 1981;80(4):776–82. https://doi.org/10.1016/0016-5085(81)90140-2
28. Rose WC. The amino acid requirements of adult man. *Nutr Abstr Rev.* 1957;27:631–647.
29. Nasset ES, Gatewood VH. Nitrogen balance and hemoglobin of adult rats fed amino acid diets low in Land D-histidine. *J Nutr.* 1956;53:163–176. https://doi.org/10.1093/jn/53.2.163
30. Kopple JD, Swendseid ME. Evidence that histidine is an essential amino acid in normal and chronically uremic man. *J Clin Invest.* 1975;55:881–891. https://doi.org/10.1172%2FJCI108016
31. Kopple JD, Swendseid ME. Effect of histidine intake on plasma and urine histidine levels, nitrogen balance and N-methylhistidine excretion in normal and chronically uremic men. *J Nutr.* 1981;111:931–942. https://doi.org/10.1093/jn/111.6.931
32. Snyderman SE, Boyer A, Roitman E, Holt LE Jr, Prose PH. The histidine requirement of the infant. *Pediatrics.* 1963;31:786–801.
33. Heird WC, Dell RB, Helms RA, et al. Amino acid mixture designed to maintain normal plasma amino acid patterns in infants and children requiring parenteral nutrition. *Pediatrics.* 1987;80(3):401–408. https://doi.org/10.1542/peds.80.3.401
34. Heird WC, Hay W, Helms RA, Storm MC, Kashyap S, Dell, RB. Pediatric parenteral amino acid mixture in low birth weight infants.

Pediatrics. 1988;81(1):41–50. https://doi.org/10.1542/peds.81.1.41
35. ASPEN Board of Directors and the Clinical Guidelines Task Force. Practice guidelines: protein requirements. In: Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *JPEN J Parenter Enteral Nutr.* 2002;26:27SA-28SA. https://doi.org/10.1177/0148607102026001011
36. Jackson AA. Amino acids: essential and non-essential? *Lancet.* 1983;1:1034–1037. https://doi.org/10.1016/s0140-6736(83)92656-9
37. Snyderman SE. The protein and amino acid requirements of the premature infant. In: Ionxix JHP, Visser HKA, Troelstra JD, eds. *Metabolic Processes in the Fetus and Newborn Infant.* HE Stenfert Kroesse NV; 1971:128–141.
38. Pohlandt F. Cystine: a semi-essential amino acid in the newborn infant. *Acta Pediatr Scand.* 1974;63:801–804. https://doi.org/10.1111/j.1651-2227.1974.tb04866.x
39. Gaull G, Sturman JA, Raiha NCR. Development of mammalian sulfur metabolism: absence of cystathionase in human fetal tissues. *Pediatr Res.* 1972;6:538–547.
40. Sturman JA, Gaull G, Raiha NCR. Absence of cystathionase in human fetal liver: is cystine essential? *Science.* 1970;169:74–76. https://doi.org/10.1126/science.169.3940.74
41. Zlotkin SH, Anderson GH. Sulfur balances in intravenously fed infants: effects of cysteine supplementation. *Am J Clin Nutr.* 1982;36:862–867. https://doi.org/10.1093/ajcn/36.5.862
42. Lyons J, Rauh-Pfeiffer A, Ming-Yu Y, et al. Cysteine metabolism and whole blood glutathione synthesis in septic pediatric patients. *Crit Care Med*. 2001;29(4):870–877. https://doi.org/10.1097/00003246-200104000-00036
43. Courtney-Martin G, Moore AM, Ball RO, Pencharz PB. The addition of cysteine to the total sulphur amino acid as methionine does not increase erythrocytes glutathione synthesis in the parenterally fed human neonate. *Pediatr Res.* 2010;67:320–324. https://doi.org/10.1203/pdr.0b013e3181ca036f
44. Shew SB, Keshen TH, Jahoor F, Jaksic T. Assessment of cysteine in very low-birth weight neonates using a [$13C_6$] glucose tracer. *J*

Pediatr Surg. 2005;40(1):52–56. https://doi.org/10.1016/j.jpedsurg.2004.09.011
45. Helms RA, Chesney RW, Storm MC. Sulfur amino acid metabolism in infants on parenteral nutrition. *Clin Nutr.* 1995;14:381–387. https://doi.org/10.1016/s0261-5614(95)80056-5
46. Helms RA, Christensen ML, Storm MC, Chesney RW. Adequacy of sulfur amino acid intake in infants receiving parenteral nutrition. *Nutr Biochem.* 1995;6:462–466. https://doi.org/10.1016/0955-2863(95)00077-D
47. Vinton NE, Heckenlively JR, Laidlaw SA et al. Visual function in patients undergoing long-term total parenteral nutrition. *Am J Clin Nutr.* 1990;52(5):895–902. https://doi.org/10.1093/ajcn/52.5.895
48. Sturman JA, Hayes KC. The biology of taurine in nutrition and development. In: Draper HH, ed. *Advances in Nutrition Research.* Vol. 3. Plenum Publishing Co; 1980:231–299.
49. Rassin DK, Sturman JA, Gaull GE. Taurine and other free amino acids in milk of man and other mammals. *Early Hum Dev.* 1978;2:1–13.
50. Zelikovic I, Chesney RW, Freidman AL, Ahlfors CE. Taurine depletion in very low birth weight infants receiving prolonged total parenteral nutrition: role of renal immaturity. *J Pediatr.* 1990;116:301–306. https://doi.org/10.1016/s0022-3476(05)82898-7
51. Helms RA, Storm MC, Christensen ML, Hak EB, Chesney RW. Cysteine supplementation results in normalization of plasma taurine concentrations in children receiving home parenteral nutrition. *J Pediatr.* 1999; 134:358–361. https://doi.org/10.1016/s0022-3476(99)70465-8
52. Christensen ML, Helms RA, Veal DF, Boehm KA, Storm MC. Clearance of N-acetyl-L-tyrosine in infants receiving a pediatric amino acid solution. *Clin Pharm.* 1993;12:606–609.
53. Van Goudoever JB, Sulkers EJ, Timmerman M, et al. Amino acid solutions for premature neonates during the first week of life: the role of N-acetyl-L-cysteine and N-acetyl-L-tyrosine. *JPEN J Parenter Enteral Nutr.* 1994;18:404–408. https://doi.org/10.1177/0148607194018005404

54. Snyderman SE, Boyer A, Holt LE Jr. The arginine requirement of the infant. *AMA J Dis Child.* 1959;97:192–195.
55. Heird WC, Nicholson JF, Driscoll JM Jr, Schullinger JN, Winters RW. Hyperammonemia resulting from intravenous alimentation using a mixture of synthetic L-amino acids: a preliminary report. *J Pediatr.* 1972;81:162–167. https://doi.org/10.1016/s0022-3476(72)80396-2
56. Thomas DW, Sinatra FR, Hack SL, Smith TM, Platzker ACG, Merritt RJ. Hyperammonemia in neonates receiving intravenous nutrition. *JPEN J Parenter Enteral Nutr.* 1982;6:503–506. https://doi.org/10.1177/0148607182006006503
57. Motil KJ, Harmon WE, Grupe WE. Complications of essential amino acid hyperalimentation in children with acute renal failure. *JPEN J Parenter Enteral Nutr.* 1980;4:32–35. https://doi.org/10.1177/014860718000400110
58. Windmueller HG, Spaeth AE. Source and fate of circulating citrulline. *Am J Physiol.* 1981;241(6):E473–E480. https://doi.org/10.1152/ajpendo.1981.241.6.e473
59. Laidlaw SA, Kopple JD. Newer concepts of the indispensable amino acids. *Am J Clin Nutr.* 1987;46:593–605. https://doi.org/10.1093/ajcn/46.4.593
60. Raiha NCR, Suihkonen J. Development of urea-synthesizing enzymes in human liver. *Acta Pediatr Scand.* 1968;57:121–124. https://doi.org/10.1111/j.1651-2227.1968.tb04663.x
61. Raiha NCR, Lindros KO. Development of some enzymes involved in gluconeogenesis in human liver. *Ann Med Exp Biol*. 1969;47:146–150.
62. Helms RA, Dickerson RN, Ebbert ML, Christensen ML, Herrod HG. Retinol-binding protein and prealbumin: useful measures of protein repletion in critically ill, malnourished infants. *J Pediatr Gastroenteral Nutr.* 1986;5:586–592.
63. Beutler E. Nutritional and metabolic aspects of glutathione. *Annu Rev Nutr*. 1989;9:287–302. https://doi.org/10.1146/annurev.nu.09.070189.001443
64. Meister A. On the enzymology of amino acid transport. *Science.* 1973;180:33–39. https://doi.org/10.1126/science.180.4081.33

65. Svartz J, Hallin E, Soderstorm M, Hammarstrom S. Identification of regions of leukotriene C4 synthase which direct the enzyme to its nuclear envelope localization. *J Cell Biochem.* 2006;98:1517–1527. https://doi.org/10.1002/jcb.20880
66. Yamamoto H, Aikawa T, Matsutaka H, Okuda O, Ishikawa E. Interorganal relationships of amino acid metabolism in fed rats. *Am J Physiol.* 1974;226:1428–1433. https://doi.org/10.1152/ajplegacy.1974.226.6.1428
67. Munro HN. Fifth annual Jonathan E. Rhoads lecture. Metabolic integration of organs in health and disease. *J Parenter Enteral Nutr.* 1982;6(4):271. https://doi.org/10.1177/0148607182006004271
68. Melnik BC, Stremmel W, Weiskirchen R, John SM, Schmitz G. Exosome-derived microRNAs of human milk and their effects on infant health and development. *Biomolecules*. 2021;11(6):851. https://doi.org/10.3390/biom11060851
69. Rocha DM, Falona GR, Unger RH. Glucagon-stimulating activity of 20 amino acids in dogs. *J Clin Invest*. 1972;51:2346. https://doi.org/10.1172/jci107046
70. Raiha NCR, Kekomaki MP. Studies on the development of ornithine-keto acid amino transferase activity in the liver. *Biochem J.* 1968;108:521–524. https://doi.org/10.1042/bj1080521
71. Edelman CM, Wolfish NM. Dietary influence on renal maturation in premature infants. *Pediatr Res.* 1968;2:421–422.
72. Brodehl J, Gellissen K. Endogenous renal transport of free amino acids in infancy and childhood. *Pediatrics.* 1968;42:395–404.
73. Guyton AC. Protein metabolism. *Textbook of Medical Physiology.* W.B. Saunders Co; 1991:765–770.
74. Radmacher PG, Lewis SL, Adamkin DH. Early amino acids and the metabolic response of ELBW infants (< or = 1000 g) in three time periods. *J Perinatol.* 2009;29(6):433–437. https://doi.org/10.1038/jp.2009.36
75. Vlaardingerbroek H, Vermeulen MJ, Rook D, et al. Safety and efficacy of early parenteral lipid and high-dose amino acid administration to very low birth weight infants. *J Pediatr.* 2013;163(3):638–644.e1-5. https://doi.org/10.1016/j.jpeds.2013.03.059

76. Ziegler EE. Protein requirements of very low birth weight infants. *J Pediatr Gastroenterol Nutr.* 2007;45(suppl 3):S170–S174. https://doi.org/10.1097/01.mpg.0000302966.75620.91
77. Scrimshaw NS. Effect of infection on nutritional status. *Proc Natl Sci Counc Repub China B.* 1992;16:46–64.
78. Poindexter BB, Langer JC, Dusick AM, Ehrenkranz RA. Early provision of parenteral amino acids in extremely low birth weight infants: relation to growth and neurodevelopmental outcome. *J Pediatr.* 2006;148:300–305. https://doi.org/10.1016/j.jpeds.2005.10.038
79. Wu PYK, Edwards N, Storm MC. The plasma amino acid pattern of normal term breast-fed infants. *J Pediatr.* 1986;109:347–349. https://doi.org/10.1016/s0022-3476(86)80400-0
80. American Academy of Pediatrics, Committee on Nutrition. Protein. In: Kleinman RE, ed. *Pediatric Nutrition Handbook.* 8th ed. American Academy of Pediatrics; 2020:449–479.
81. Boehm KA, Helms RA, Storm MC. Assessing the validity of adjusted urinary urea nitrogen as an estimate of total urinary nitrogen in three pediatric populations. *JPEN J Parenter Enteral Nutr.* 1994;18(2):172–176. https://doi.org/10.1177/0148607194018002172
82. Lopez AM, Wolfsdorf J, Raszynski A, Contijoch-Serrano V. Estimation of nitrogen balance based on a six-hour urine collection in infants. *JPEN J Parenter Enteral Nutr.* 1986;10(5):517–518. https://doi.org/10.1177/0148607186010005517
83. Helms RA, Mowatt-Larssen CA, Boehm KA, et al. Urinary nitrogen constituents in the postsurgical preterm neonate receiving parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 1993;17:68–72. https://doi.org/10.1177/014860719301700168
84. Mathes M, Maas C, Bleeker C, et al. Effect of increased enteral protein intake on plasma and urinary urea concentrations in infants born at < 32 weeks gestation and < 1500 g birth weight enrolled in a randomized controlled trial – a secondary analysis. *BMC Pediatr.* 2018;18(1):154. https://doi.org/10.1186/s12887-018-1136-5.
85. Elango R, Ball RO, Pencharz. Recent advances in determining protein and amino acid requirements in humans. *Br J Nutr*. 2012;108(suppl 2):S22–S30. https://doi.org/10.1017/s0007114512002504

86. Kriengsinyos W, Wykes LJ, Ball RO, Pencharz PB. Oral and intravenous tracer protocols of the indicator amino acid oxidation method provide the same estimate of the lysine requirement in healthy men. *J Nutr*. 2002;132(8):2251–2257. https://doi.org/10.1093/jn/132.8.2251
87. Kurpad AV, Raj T, El-Khoury A, et al. Lysine requirements of healthy adult Indian subjects, measured by an indicator amino acid balance technique. *Am J Clin Nutr*. 2001;73(5):900–907. https://doi.org/10.1093/ajcn/73.5.900
88. Institute of Medicine, Food and Nutrition Board. *Dietary Reference Intakes: Energy*, *Carbohydrate*, *Fiber*, *Fat*, *Fatty Acids*, *Cholesterol*, *Protein and Amino Acids.* The National Academies Press; 2005.
89. Elango R, Humayun MA, Ball RO, Pencharz PB. Protein requirement of healthy school-age children determined by the indicator amino acid oxidation method. *Am J Clin Nutr*. 2011;94(6):1545–1552. https://doi.org/10.3945/ajcn.111.012815
90. Hirsch KR, Church DD, Wolfe RR and Ferrando AA. Continuous oral stable isotope ingestion to measure whole-body protein turnover. *Clin Nutr ESPEN*. 2022;49:385–389. https://doi.org/10.1016/j.clnesp.2022.03.017
91. Storm MC, Helms RA. Normalizing plasma amino acid levels in pediatric patients requiring parenteral nutrition. *Nutr Clin Pract*. 2007;22:194–203. https://doi.org/10.1177/0115426507022002194
92. Helms RA, Christensen ML, Muer EC, Storm MC. Comparison of a pediatric versus standard amino acid formulation in preterm neonates requiring parenteral nutrition. *J Pediatr.* 1987;110:466–470. https://doi.org/10.1016/s0022-3476(87)80519-x
93. Beck R. Use of a pediatric parenteral amino acid mixture in a population of extremely low birth weight neonates: frequency and spectrum of direct bilirubinemia. *Am J Perinatol*. 1990;7(1):84–86. https://doi.org/10.1055/s-2007-999453
94. Forchielli ML, Gura KM, Sandler R, Lo C. Aminosyn PF or TrophAmine: which provides more protection from cholestasis associated with total parenteral nutrition? *J Pediatr Gastroenterol Nutr.* 1995;21:374–382.

95. Pratt CA, Garcia MG, Poole RL, Kerner JA. Life-long total parenteral nutrition versus intestinal transplantation in children with microvillus inclusion disease. *J Pediatr Pharmacol Ther.* 2001;6:498–503.
96. Fitzgerald KA, MacKay MW. Calcium and phosphate solubility in neonatal parenteral nutrient solutions containing TrophAmine. *Am J Hosp Pharm.* 1986;43(1):88–93.
97. van Vliet MJ, Tissing WJ, Rings EH, et al. Citrulline as a marker for chemotherapy induced mucosal barrier injury in pediatric patients. *Pediatr Blood Cancer*. 2009;53(7):1188–1194. https://doi.org/10.1002/pbc.22210
98. Ioannou HP, Fotoulaki M, Pavlitou A, Efstratiou I, Augoustides-Savvopoulou P. Plasma citrulline levels in paediatric patients with celiac disease and the effect of a gluten-free diet. *Eur J Gastroenterol Hepatol*. 2011;23(3):245–249. https://doi.org/10.1097/meg.0b013e3283438ad7
99. Bailly-Botuha C, Colomb V, Thioulouse E, et al. Plasma citrulline concentration reflects enterocyte mass in children with short bowel syndrome. *Pediatr Res*. 2009;65(5):559–563. https://doi.org/10.1203/pdr.0b013e31819986da
100. Hibi T, Nishida S, Garcia J, et al. Citrulline level is a potent indicator of acute rejection in the long term following pediatric intestinal/multivisceral transplantation. *Am J Transplant*. 2012;12(suppl 4):S27–S32. https://doi.org/10.1111/j.1600-6143.2012.04155.x
101. Stultz J, Tillman EM, Helms RA. Plasma citrulline concentration as a biomarker for bowel loss and adaptation in hospitalized pediatric patients requiring parenteral nutrition. *Nutr Clin Pract*. 2011;26(6):681–687. https://doi.org/10.1177/0884533611425682
102. Herrera OR, Storm MC, Helms RA. Plasma citrulline concentrations in neonates/infants with or without gastrointestinal disease and bowel loss. In: *A.S.P.E.N. Clinical Nutrition Week 2014.* American Society for Parenteral and Enteral Nutrition. Abstract 1834574.

Test Your Knowledge Answers

1. The correct answer is **D**. The lack of phenylalanine hydroxylase in phenylketonuria renders the infant needing exogenous tyrosine for survival.
2. The correct answer is **B**. Casein is the most abundant protein in cow's milk. It is less readily digestible than whey, which predominates in human milk.
3. The correct answer is **A**. The endopeptidases and exopeptidases from the pancreas are released in the small bowel, which then breaks down the polypeptides primarily into oligopeptides and to a lesser degree free amino acids.
4. The correct answer is **C**. In pediatrics, the percentage of nitrogen excreted as urea only ranges from 40% to 60%, so it would underestimate the nitrogen output when determining the nitrogen balance.

The authors of this chapter wish to thank John Kerner, MD; Emma M. Tillman, PharmD; and Anup J. Patel, MD, for their contributions to previous editions of this text.

6

Minerals

Winston Koo, MBBS, FACN, CNS; May Saba, PharmD, BCNSP; Letitia Warren, RD, CSP; and Mirjana Lulic-Botica, PharmD, BCPS

Learning Objectives

1. Understand the biochemistry and physiology of calcium, phosphorus, and magnesium.
2. Identify the common risk factors for the development of deficiency and manifestations of deficiency states for these nutrients.
3. Describe the potential risks associated with excessive intake of these nutrients.
4. Apply learned knowledge to support the physiological regulation of these minerals in patients.

Introduction

Biochemistry and Physiology

Calcium (Ca) is the most abundant mineral in the body. Ca with phosphorus (P) accounts for the major inorganic content of bone, primarily as hydroxyapatite [Ca10 (PO4)6 (OH)2]. Magnesium (Mg) is the fourth most abundant cation and the second most common intracellular electrolyte after potassium.

At birth, term neonates have approximately 30 g of Ca, 20 g of P, and 0.8 g of Mg. In adults, Ca accounts for 1% to 2% of body weight with a Ca

to P ratio of about 1.7:1 by weight, and approximately 25g of Mg. The skeletal content of Ca, P, and Mg is approximately 99%, 85%, and 60%, respectively. The remainder of the body content of Ca, P, and Mg is in soft tissues, with less than 1% in the circulation.

Disturbances in the serum concentrations of these minerals are associated with disturbances in numerous biological functions with and without clinical symptoms and signs. Acute serum concentration changes likely reflect adaptive changes but not tissue storage status. However, chronic and severely lowered serum concentrations of these minerals usually suggest a deficiency state.

From a clinical perspective, the skeleton has two functions: to provide structural and mechanical support and to maintain mineral homeostasis by serving as a mineral reservoir. Infants and children who are deficient in Ca and/or vitamin D can develop osteopenia and rickets. The same is true for small preterm infants with P deficiency. Thus, the proxy for mineral homeostasis generally entails maintaining integrity of the skeleton and ensuring normal circulating concentrations of Ca, P, and Mg.[1,2]

Sources

Dietary sources of minerals, including Ca-fortified foods and beverages, are preferred to supplements alone; aside from helping to establish good dietary habits, consuming minerals in food enhances the range of nutrients available to be utilized in the body. Additionally, dietary mineral sources may be better tolerated and lessen nutrient interactions.[1–3] Natural foods and various Ca-fortified foods and beverages are good sources of these minerals. Any food that provides 20% or more of the daily recommended intake per serving for a specific nutrient is considered “high” in that nutrient.

Mineral supplements are readily available; however, their use does not compensate for poor food choices and an inadequate diet. Furthermore, the Food and Drug Administration (FDA) regulates dietary supplements under a different set of regulations than drug products (over-the-counter vs prescription). As a result, the specific contents and contaminants of dietary supplements are not as rigorously monitored.[4]

Dietary Requirements

Several unique challenges exist in maintaining mineral homeostasis during infancy, childhood, and adolescence. Mineral requirements in growing children depend on tissue synthesis needs and the balance between dietary supply, intestinal absorption, renal excretion, and bone exchange. At birth, neonates must adapt to a continuous supply of minerals from the placenta to successfully transition to extrauterine life. This adjustment is typically achieved with appropriate nutritional support, even in critically ill and preterm neonates.[5] Nutrition requirements for Ca, P, and Mg remain high until skeletal growth is complete. Infants and adolescents have the greatest requirements because of their high growth rates.[6,7] The average gain in skeletal growth over 1 year is >25 cm for an infant. This can be even greater for the preterm infant. Peak height gain is about 7 to 10 cm/y during adolescence. The recommended dietary reference intakes for Ca, P, and Mg are shown in Table 6-1.

TABLE 6-1. Dietary Reference Intake for Calcium, Phosphorus, and Magnesium

Life Stage	Calcium, mg/d[b,c]	Phosphorus, mg/d[b,c]	Magnesium, mg/d[b,c]
0–6 mo[a]	200 (1000)	100	30
7–12 mo[a]	260 (1000)	275	75
1–3 y	700 (2500)	460 (3000)	80 (65)
4–8 y	1000 (2500)	500 (3000)	130 (110)
Males			
9–13 y	1300 (3000)	1250 (4000)	240 (350)
14–18 y	1300 (3000)	1250 (4000)	410 (350)
Females			
9–13 y	1300 (3000)	1250 (4000)	240 (350)
14–18 y	1300 (3000)	1250 (4000)	360 (350)
Pregnancy			
14–18 y	1300 (3000)	1250 (3500)	400 (350)
Lactation			
14–18 y	1300 (3000)	1250 (4000)	360 (350)

The recommendations for calcium from the Institute of Medicine from 2011[2] supersede those from 1997.[1] The recommendations for phosphorus and magnesium are from the Institute of Medicine from 1997.[1]

[a] Adequate intake is an observed or experimentally determined estimate of nutrient intake by a group or groups of healthy people and is the only reference level for calcium, phosphorus, and magnesium up to age 12 months.

[b] Recommended dietary allowance is the average daily dietary intake that is sufficient to meet the requirement of 97% to 98% of healthy individuals at a specific life stage for each sex.

[c] Tolerable upper intake level for each life stage is indicated in parentheses. For magnesium, the value applies to nonfood sources only.[1] Upper intake level is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population.

Absorption and Excretion

Intestinal absorption of Ca, P, and Mg involves a passive paracellular concentration-dependent process as well as a saturable active transcellular process. Vitamin D can influence active intestinal transport, but its role under normal circumstances appears to be much less than the passive diet-dependent process in the growing child. Renal reabsorption of these minerals also has passive and active transport components. While efficient, an excessive intake can overwhelm the renal excretory capacity, leading to elevated circulating levels for each of the minerals. Conversely, deficient states—especially abnormal loss from the gastrointestinal (GI) tract or the kidney—can result in abnormally low circulating Ca, P, and Mg concentrations. Normally, the growing child has net bone (and soft tissue) accretion of these minerals. Some exchange of these minerals occurs with bone modeling. The exchangeable portion may be elevated during periods of stress and increased bone turnover. Protecting the skeleton and maintaining mineral homeostasis is not possible in extreme circumstances (eg, severe Ca or P deficiency in infants).

Metabolism

Maintaining mineral homeostasis requires sufficient dietary intake and complex interaction of hormonal and nonhormonal factors as well as adequate functioning of various body systems, particularly the renal, GI, skeletal, and endocrine systems. Intake of minerals may interact with other nutrients including protein, sodium, potassium, iron, zinc, copper, and vitamin D at the intestine-kidney-bone axis.[1,2,8,9] A significant positive or negative interaction may occur at the level of intestinal absorption, renal excretion, or metabolism. A positive effect with increased intestinal absorption and increased renal tubular reabsorption is possible at low dietary intakes, and an opposite effect is possible at high intakes primarily as dietary supplements.

Parathyroid hormone (PTH), 1,25 dihydroxy-vitamin D [1,25 $(OH)_2D$], and fibroblast growth factor-23 (FGF 23) directly regulate Ca, Mg, and P at the intestine-kidney-bone axis. Growth-regulating hormones, including thyroid and sex hormones, regulate mineral metabolism indirectly through their effect on growth and mineralization of the skeleton. Abnormally low

or high circulating concentrations of Ca, Mg, and/or P can result from numerous acquired disorders and, increasingly, from genetic disorders. These abnormal mineral concentrations can have serious clinical complications. Thus, it is vital to manage the underlying cause of abnormal circulating concentration of the minerals in addition to providing symptomatic treatment.

Deficiency States

In the United States, estimated mineral intakes from both food and dietary supplements are provided by the National Health and Nutrition Examination Survey. Mean dietary intake of minerals varies with life stage and by sex. Low dietary intake of Ca is common in older children. Groups with mean intakes below their respective estimated average requirement—and thus with a prevalence of inadequacy above 50% at the population level—include boys and girls ages 9 to 13 years and girls ages 14 to 18 years.[4,5] Preoccupation with being thin is common in adolescents, especially among girls, as is the misconception that all dairy foods are fattening. The general population would benefit from the knowledge that low-fat milk is a good source of Ca. It contains as much, if not more, Ca than whole milk.

Risks for mineral deficiency escalate with increased requirement, decreased absorption or increased losses through the GI tract or the kidney, or disturbed metabolism. All rapidly growing infants, especially very low birth weight (<1.5 kg) preterm infants, are at risk for mineral deficiency because of increased requirement, intolerance to multiple nutrients during acute illness, and therapy-related interference with mineral retention or metabolism. Critically ill neonates or children who require parenteral nutrition (PN) often do not tolerate increased nutrient intake, especially the energy load. It is unrealistic to expect a child who is critically ill to achieve normal growth (ie, normal anabolic state), and mineral intake should be less when compared with stable and growing patients.[5,10]

For preterm infants who are not receiving any medications that might interfere with mineral absorption, excretion, or metabolism, there is no convincing evidence of a clinically significant mineral deficiency if the infant is stable with adequate growth and is receiving adequate volumes (>150 mL/kg/d) of high-energy (≥24 kcal/oz) human milk fortified with a

commercial human milk fortifier containing protein, energy, and high mineral contents or preterm infant formula.[5]

Malabsorption states, chronic therapy with loop diuretics, gastric acid inhibitors, and corticosteroids as well as heritable disorders of mineral metabolism, are associated with abnormalities in mineral retention and/or metabolism. In disease states, a deficiency involving multiple minerals and additional nutrients may be unmasked during therapy. This type of deficiency is best illustrated by the simultaneous development of hypophosphatemia, hypomagnesemia, and hypokalemia with or without thiamine deficiency during refeeding of severely malnourished individuals.[11]

Excess Intake and Adverse Effects

The most common risk factor for excessive intake of minerals is associated with increased parenteral intake of minerals arising from the unrealistic expectation of normal growth in the critically ill child. Minerals delivered via parenteral routes can exceed the excretory capacity, most commonly resulting in hyperphosphatemia and hypermagnesemia with associated hypocalcemia. These findings may in part reflect "shifts" in minerals among various compartments, but they also suggest that mineral delivery can exceed the body's needs.[1,2,12]

Adverse effects from excess dietary mineral intake rarely occur in pediatric populations. However, healthy infants may develop hyperphosphatemia and secondary hypocalcemia from standard infant formula. This occurs because of higher P intake from infant formulas relative to human milk and the inability to eliminate the excess P because of immature kidney and parathyroid gland function.[12] Most of the adverse effects of excess mineral intake occur because of excessive supplement intake in pharmacologic doses and may result in serious morbidity and even mortality. The current recommendation for the upper level of intake of Mg for the population under consideration includes these potential supplemental sources.[1]

Calcium (1 mmol = 40 mg)

Biochemistry and Physiology

Ca is the most abundant mineral in the human body. More than 99% of total body Ca is stored in the bones and teeth, where it functions to support their structure. Thus, Ca is critical for normal growth and development of the skeleton and teeth. The remaining 1%, which is essential to numerous physiological functions, is present in blood, muscle, and other nonosseous tissues. In the circulation, approximately 50% of Ca is ionized, and the rest is bound to albumin or complexed to small anions, such as citrate, bicarbonate, and phosphate.

Optimal bodily function depends on maintaining the circulating total, especially the ionized Ca concentration, within a narrow range. Ca exerts its effect in two possible ways. One is through a membrane-bound Ca-sensing receptor. This receptor, which is a member of the G protein–coupled receptor family, is expressed in numerous organs and tissues. The second way is at the cellular level through the action of ionized Ca. The role of ionized Ca as a secondary messenger is critical to numerous bodily functions, including muscle contraction, blood vessel contraction and expansion, the secretion of hormones and enzymes, and message relay through the nervous system.[1,2,13]

Sources

Ca is present in many dietary sources, with dairy products having the best bioavailability and accounting for >70% of dietary Ca intake in the United States.[1–3,14] Nonfat and reduced-fat dairy products contain the same amount of Ca as regular dairy products. Some food sources (eg, fruit juices, fruit drinks, tofu, and cereals) are fortified with various Ca compounds that are well absorbed.[15–17]

The amount of Ca is relatively constant in human milk, between 200 and 250 mg/L. Various Ca salts are added to cow's milk formulas for term infants to provide at least 60 mg/100 kcal,[18] although most standard infant formulas contain more than 500 mg Ca/L. This Ca concentration is at least twofold higher than that in human milk. Ca-fortified formulas for small

preterm infants can have Ca concentrations fourfold to sixfold higher than those in human milk.[5]

Oral supplements such as Ca compounds containing carbonate and citrate are the most common, although preparations containing other anions are available. Naturally occurring products (eg, oyster shell marketed as a Ca supplement) contain high levels of lead, mercury, and other potentially toxic contaminants.[19] Common parenteral supplements include calcium gluconate and calcium chloride, but other compounds are also available. Ca gluconate but not all parenteral Ca supplements have a relatively high aluminum contamination.[20] The proportion of elemental Ca by weight varies with the Ca compound (see Table 6-2). Newer supplements with better tolerance and bioavailability are being developed.[21]

TABLE 6-2. Proportion by Weight of Elemental Calcium or Magnesium in Related Compounds*

Ca Compound	% Elemental Ca
Ca carbonate	40
Tribasic Ca phosphate	38
Ca citrate	21
Ca lactate	13
Ca gluconate	9
Ca glubionate	6.4
Mg compound	**% elemental Mg**
Mg oxide	60.3
Mg carbonate	28
Mg citrate	16
Mg chloride, acetate, and lactate	~12 each
Mg sulfate	9.7
Mg phosphate	6.8
Mg ascorbate	6.4
Mg gluconate	5.4

Abbreviations: Ca, calcium; Mg, magnesium.

* Different compounds have different bioavailability and tolerability.[4,5,12,19,21,22]

Absorption, Excretion, and Metabolism

Gastric acid aids in the digestion of Ca from natural or Ca-fortified food or drink. Some Ca compounds, such as calcium citrate, are better absorbed than calcium carbonate in individuals with decreased gastric acid. About 90% of the Ca absorbed is through the small intestine, and the large intestine can absorb the remainder.[23]

Dietary Ca absorption, particularly in young children, is primarily regulated by Ca rather than vitamin D intake.[1,2,24–26] At high dietary Ca intake, paracellular absorption takes place throughout the small intestine and depends on the concentration gradient. At low Ca intake, transcellular absorption takes place largely in the duodenum and is dependent on

$1,25(OH)_2D$.[27] The role of $1,25(OH)_2D$ in epithelial transport, including intestinal absorption of Ca, is becoming more clearly defined beyond its classic endocrine and paracrine actions.[28] Specifically, it functions as a Ca-sensing receptor[29] and calcium-selective channel in the transient receptor potential channel family.[30]

The efficiency of Ca absorption is influenced by the quantity of Ca and non-Ca components in the diet, food matrix, gastric acid production, intestinal transit time, and microbiota among other factors.[8,9,31] The non-Ca components include the type and amount of carbohydrate, phytic acid (from whole grain bread, wheat bran, beans, seeds, nuts, grains, and soy isolates), and/or oxalic acid (from spinach, collard greens, sweet potatoes, rhubarb, and beans) that may bind to Ca in the same food and reduce its absorption. These plant substances do not appear to interfere with Ca absorption from other foods.

Ca is excreted through feces, urine, and sweat. Ca excretion can be increased by many factors, including high dietary intake of sodium, protein, and caffeine. High potassium intake lowers urinary Ca, thereby affecting the net Ca retention. The effect of dietary P on Ca and bone metabolism is limited if Ca intake is adequate.[1,2,8] The detrimental effects of consuming foods high in phosphate, such as carbonated soft drinks, are probably due to milk being replaced with soda, not phosphate itself playing a role.[32] Chronic use of Mg antacids and potent loop diuretics, such as furosemide, can increase urinary Ca excretion. Aluminum antacids should not be used, especially for individuals with limited renal function, such as infants, because of potential aluminum toxicity.[33] Chronic therapy with a proton-pump inhibitor results in multiple side effects, including hypomagnesemia, and raises risks for fractures.[34,35]

Retention of Ca generally reflects the body's need, which is usually higher in individuals undergoing rapid growth and may be >60% of dietary intake.[2,12] Dietary Ca, physical activity, and the pubertal stage have independent effects on the rate of bone mineralization and therefore on mineral retention.[36,37] Ca intake should generally be in the form of foods because of the range of other nutrients present in various foods. Foods

fortified with Ca have increased the options for Ca-rich foods in the diet.[3,14–17]

Pregnant and lactating adolescents have an increased need for Ca because both bone mineralization of the mother and the fetus need support. A compensatory increase in Ca absorption occurs and any decrease in bone mass during pregnancy and lactation is replenished upon return of ovarian function. Therefore, no additional increase in dietary Ca intake is recommended.[2] However, a mother's very low dietary Ca intake can lower the fetal bone mineral content. This situation can be prevented with an adequate Ca intake from diet or Ca supplementation.[38] It is possible that perturbation in mineral homeostasis could have transgenerational effects.[38–41] Adequate intakes of Ca for nearly all members of a specific age group of either sex are shown in Table 6-1.

Ca and Mg homeostasis rely on several factors, including the following:

- dietary intake;
- absorption, excretion, and tissue accretion involving the primary target organs of the GI tract, kidney, and bone;
- the direct modulation of transport and mobilization of these minerals at the target organs, mainly by PTH and the active vitamin D metabolite, 1,25 $(OH)_2D$, and FGF 23 through their endocrine and paracrine actions; and
- regulation of Ca sensors and Ca channel proteins controlling the transport of Ca and Mg ions at the tissue level.

When assessing changes in the serum concentrations of these minerals, understanding the interrelationships among them is vital. For example, serum Ca and P have a reciprocal relationship, and hypoalbuminemia lowers Ca binding capacity, leading to lower total serum Ca although the ionized (unbound) Ca concentration remains normal. Hypomagnesemia may cause hypocalcemia due to the impaired secretion of PTH and impaired end-organ responsiveness to PTH in maintaining Ca homeostasis. The resolution of hypocalcemia may not be possible until the underlying cause, hypomagnesemia, has been corrected.

Infant formulas have higher P than human milk; however, immature renal and parathyroid functions are not able to eliminate excess P. Thus,

transient perturbation in Ca and P homeostasis with hypocalcemia and hyperphosphatemia occurs in some term infants who are fed regular infant formula. As a result of the Ca and P imbalance, these infants often present with seizures from hypocalcemia. Clinically, this perturbation is exacerbated by the early introduction of solids or whole cow's milk to the infant.[5,12] Symptomatic support with a Ca supplement for a few days and switching to an infant formula with a P content comparable to that of human milk for several months are sufficient to return serum Ca and P concentrations to the normal range.[12]

A feeding challenge with regular infant formula is warranted after a few months to ensure that the renal and PTH functions have matured sufficiently to resume increased dietary P load. If the infant does not respond quickly to this management approach, further endocrinology work-up is appropriate. A similar approach can be taken with preterm infants who develop hyperphosphatemia and hypocalcemia from excessive P load from other sources.

Deficiency States

Risk factors for a deficient state include increased need, as in the rapidly growing infant, and the presence of disease states that affect Ca digestion, absorption, or metabolism. Physically active athletes, particularly those with secondary menstrual disorders, may have lower Ca absorption and decreased bone formation, and adequate Ca intake is important to their bone health.[42] Lactose-intolerant individuals may be at risk for Ca deficiency, not because they are unable absorb Ca but rather because they avoid dairy products.[43] Drinking milk with a meal and other dietary options (eg, choosing aged cheeses such as Cheddar and Swiss, which contain little lactose; yogurt, which contains live active cultures that aid in lactose digestion; or lactose-reduced and lactose-free milk) may allow increased Ca intake. Strict vegans should include adequate amounts of nondairy sources of Ca in their daily diets; otherwise, they will likely need a Ca supplement to meet the recommended Ca intake.[44]

Dietary Ca deficiency is a risk factor for fractures,[1,2] and both Ca and vitamin D deficiency are factors in the development of rickets in infants and young children.[12,24–26] In general, hypocalcemia does not occur solely

because of low Ca intake; concomitant deficiency of vitamin D or Mg or associated medical problems are also present. Acute severe hypocalcemia may result in clinical signs and symptoms that may be subtle and vary with an individual's maturity. Preterm infants often manifest nonspecific symptomatology that may include irritability, jitteriness or lethargy, poor feeding with or without feeding intolerance, abdominal distention, apnea, cyanosis, and seizures. These features may be confused with manifestations of hypoglycemia, sepsis, meningitis, anoxia, intracranial bleeding, or narcotic withdrawal.[12] The degree of irritability of the infant does not appear to correlate with serum Ca values. In more mature individuals, other symptoms and signs may include tetany from peripheral hyperexcitability of motor nerves.[1,2]

In chronic deficient states, Ca is mobilized from the skeleton to maintain Ca levels in the blood, which is a predisposing factor for suboptimal bone accretion. In young children, both Ca and vitamin D deficiency have key roles in the development of rickets. [24–26]

Excess Intake and Adverse Effects

Adverse effects of excess Ca usually manifest as hypercalcemia and its complications. Hypercalcemia is considered mild when serum or plasma total Ca <12 mg/dL or ionized Ca is 5.6 to 8.0 mg/dL; it is severe if these values are ≥14 mg/dL and ≥10 mg/dL.[45] Severe hypercalcemia is usually the result of acquired or genetic disorders with or without excess Ca intake, usually from Ca or vitamin D supplements.[45–48] Patients with mild hypercalcemia may be asymptomatic or present with nonspecific symptoms, but they remain at risk for other complications of hypercalcemia, including polyuria and polydipsia, nephrocalcinosis, renal calculi, and metastatic calcification.

High dietary Ca intake and routine Ca supplementation generally do not cause hypercalcemia. However, high Ca intake can interfere with the absorption of other minerals, such as iron, zinc, Mg, and P. Ca supplements can interact with several prescription and over-the-counter medications. Ca decreases absorption of digoxin, fluroquinolones, levothyroxine, tetracycline, tiludronate disodium, phenytoin, and mineral oil or stimulant laxatives when taken simultaneously with these drugs. Whereas, thiazide

diuretics can interact with calcium carbonate and vitamin D supplements, increasing the risk for hypercalcemia and hypercalciuria.[1,2,45,46]

Metastatic deposits of Ca precipitate in the intravenous delivery system, lungs, kidneys, and other organs, and increased mortality has been reported in neonates who received ceftriaxone simultaneously with parenteral solutions containing Ca.[49] Hypercalcemia may be a manifestation of P deficiency (see the "Phosphorus" section).

Phosphorus (1 mmol = 31 mg)

Biochemistry and Physiology

P as phosphate is an essential constituent of all known protoplasm. "P" and "phosphate" are often used interchangeably, but phosphate refers to the inorganic freely available form. This measurable component is generally referred to as phosphorus (P).

Tissue P is approximately 0.5% of the body weight in the neonate and increases to approximately 1% in the adult because of greater bone and soft tissue mass. Structurally, P is incorporated in mineralized tissues of the skeleton and teeth, in biological membranes as phospholipids, and in cells as nucleotides and nucleic acids. About 85% of P is in the skeleton, primarily in the form of hydroxyapatite. Of the remainder, 14% is intracellular (primarily in the soft tissues) and 1% is extracellular (in the circulation and interstitial fluid). Of the extracellular P, 70% is organic and contained within phospholipids, and 30% is inorganic.[50,51] At pH 7.4, the monohydrogen and dihydrogen form is in a ratio of about 4:1. For that reason, P is usually expressed in millimole rather than milliequivalents per liter.

The serum or plasma P concentration is approximately 1 to 2 mmol/L (3.1–6.2 mg/dL) and is higher at younger ages. Plasma P concentrations of preterm infants are about 0.5 mmol higher but can be as high as 2.81 mmol/L (8.7 mg/dL) without affecting plasma Ca concentration.[1,12,52,53] This minute compartment of P is the major source of exchange of P associated with dietary uptake and absorption, renal excretion and reabsorption, and bone modeling and remodeling. This compartment is also the primary source of P for structural and high-energy phosphate in the cells

of all tissues. When extracellular fluid P concentrations are low, cellular dysfunction follows.[50,51,54,55]

A normal level of P in the extracellular fluid is necessary for cellular function and skeletal mineralization. Physiological functions include maintaining mineral and acid–base homeostasis, temporarily storing high-energy molecules from metabolic fuels, and activating many catalytic proteins through phosphorylation. Most of these processes involve recycling P. Thus, the role of dietary P is to support tissue growth and to replace excretory, cellular, and dermal losses.

Sources

P is ubiquitous in natural foods and is present in both organic and inorganic forms.[15–17] Various phosphate salts used in food processing for nonnutritive functions (eg, moisture retention, smoothness, binding) provide significant contributions to dietary P intake. Cola soft drinks contain phosphoric acid as the acidulant and provide about 50 mg of P per 12 oz serving. P intake from soft drinks can be substantial when multiple servings are consumed.[1,21,56]

Dairy and meat products have high P density. Plants, nuts, and seeds are also significant sources of P. Animal protein is more bioavailable P than soy-based or grain-based protein. P in plants (from beans, peas, cereals, and nuts) is present in the poorly digestible phytic acid. However, some phytate P is absorbed from the combined effect of food phytases, colonic bacteria enzymes, and yeast products.[1]

Human milk has low P content, which decreases further with prolonged lactation, although the P bioavailability is higher than in all other infant milk.[5] Compared to human milk, P content is higher in cow's milk by fivefold to sixfold, in standard cow's milk–based infant formula by about twofold, and in soy-based infant formula by about threefold.[18] The Ca to P ratio varies widely in natural foods.[15–17] However, both the Ca to P ratio and absolute quantities of these minerals are important to optimize mineral accretion in bone and soft tissue. P supplements are available as monophosphates and dibasic phosphates, in both oral and parenteral forms.[19] They are usually used for medical indications such as PN and inherited metabolic defects.

Absorption, Excretion, and Metabolism

Net absorption of P ranges from 55% to 70% in adults and 65% to 90% in children and infants.[5,12,56] The fractional P absorption is relatively constant across a broad range of intakes. The bulk of P absorption is passive (paracellular) and concentration dependent. A saturable, active transcellular sodium (Na+)-dependent absorption involving the type IIb Na+/phosphate cotransporter and facilitated by 1,25 (OH)2D also exists. [50–52,56] P is not absorbed in the stomach but is absorbed throughout the small bowel. The fractional absorption of P and other minerals is lower in infant formulas compared to human milk, although the absolute amounts of each mineral absorbed from infant formulas are higher because of the much higher mineral content in infant formulas. Medications or foods that bind P (antacids, phosphate binders, and Ca) can decrease the net amount of P absorbed by decreasing the free phosphate for absorption. Unabsorbed Ca complexes with phytic acid can interfere with bacterial hydrolysis of phytate, decreasing P absorption.[1]

The kidney is a major regulator of P homeostasis. Renal P is reabsorbed primarily at proximal tubular cells (70%–80%). The remaining P is reabsorbed in the distal tubules. Renal P reabsorption is increased by the abundance of type IIa Na/phosphate cotransporter (Npt2a) protein at the basolateral basement membrane, and it requires the interaction of Npt2a with various scaffolding and regulatory proteins.[48,50–52] Renal P reabsorption is also increased by growth hormone, thyroid hormone, and 1,25 (OH)2D. Renal P reabsorption is decreased by an increase in the circulating concentration of P or dietary P mediated by an increase in FGF 23. Although the effects are minor, renal P reabsorption is decreased by volume expansion, metabolic acidosis, glucocorticoids, and calcitonin.[1] FGF 23 and PTH are major phosphaturic hormones, and their secretion is increased by both dietary and circulating P.[56–58] Serum P increases as the total P intake and absorption exceeds the renal filtration and excretion for P.

The kidney can increase or decrease its P resorptive capacity to accommodate P needs. In infants and children, lower glomerular filtration rate is probably the main determinant of the higher serum P because P resorptive capacity is high even in small preterm infants.[5,12] Healthy infants who are breastfed have lower serum P compared to those fed infant

formula.[12,53] The lowest level of renal excretory work to maintain normal P homeostasis during the first year is achieved with human milk as the major source of minerals. In deficient states, renal retention of filtered phosphate is almost complete even in preterm infants.[5,12]

Deficiency States

Cellular storage of phosphate and the portion of P that can be mobilized from bone are limited. Thus, dietary P is required to maintain extracellular fluid P, which is the source of P for the tissue metabolic phosphate. Because P is ubiquitous in foods, dietary P deficiency rarely occurs unless the individual is subjected to near-total starvation. The exception is in small preterm infants with prolonged exclusive feeding of human milk without multi-nutrient fortifier or those fed infant formula with low mineral content.

In addition, P must be added to PN to prevent the development of P deficiency. Poorly managed PN with inadequate P content, inappropriate administration of fluid and electrolyte therapy that causes excessive renal P loss, or rapid refeeding in the setting of diabetic ketoacidosis or severe malnourishment (especially if accompanied by diarrhea) places individuals at risk for hypophosphatemia and other electrolyte abnormalities.[1,5,12,50–52,54,55] Individuals with chronic aluminum antacid therapy and heritable defects of P metabolism can also manifest P deficiency.[48,50–52] Chronic diuretic therapy that increases urine P can exacerbate the P deficit.[51,52]

P deficiency results in the dysfunction of numerous cell systems and clinical manifestations include

- anorexia
- general debility
- anemia
- muscle weakness (including respiratory compromise)
- bone pain
- rickets and osteomalacia
- increased susceptibility to infection
- paresthesia
- ataxia
- confusion

- death

Cellular dysfunction and clinical manifestations can occur when the extracellular fluid P is <0.65 mmol/L (2 mg/dL) and universally occurs when the extracellular fluid P is <0.3 mmol/L (0.9 mg/dL). Plasma Ca may be elevated simultaneously to hypercalcemic levels, particularly in infants.[1,12,52,54,55]

Excess Intake and Adverse Effects

All adverse effects of excess P intake from any source are the result of hyperphosphatemia.[50–52] These effects include adjustments in the hormonal control system regulating Ca homeostasis and may be complicated by hypocalcemia and its adverse effects; ectopic (metastatic) calcification, particularly of the kidney; and possible decreases in the intestinal absorption of Ca, iron, zinc, and copper.

Hyperphosphatemia usually occurs in the setting of kidney disease and rarely occurs under normal circumstances. One exception is the development of hyperphosphatemia and secondary hypocalcemia in some healthy infants who consume standard infant formulas as described in the "Calcium Absorption, Excretion, and Metabolism" section earlier in the chapter.[5,12]

Magnesium (1 mmol = 24 mg)

Biochemistry and Physiology

Mg is the fourth most abundant cation in the body and the second most abundant intracellular cation. Fetal accretion is 2.9 to 4.8 mg/kg/d (0.12–0.2 mmol/kg/d), resulting in a total body Mg content of about 0.8 g in term neonates. In adulthood, this amount increases to about 25 g (1000 mmol), with approximately 60% residing in bone. About one-third of the skeletal Mg is exchangeable and serves as a reservoir for maintaining extracellular Mg concentration. The remaining Mg is in soft tissues, such as muscle and organs, and approximately 1% is in extracellular fluid.

Cellular Mg content is 6 to 9 mmol/kg net weight, and most of this Mg is localized in membrane structures (eg, microsome, mitochondria, plasma

membrane). The much smaller pool of free Mg in the cell is maintained at approximately 1 mmol/L exchanging equilibrium with membrane-bound Mg. This unbound intracellular Mg has a critical role in cellular physiology. Intracellular Mg usually remains stable despite wide fluctuations in serum Mg. In Mg-deficient states, however, the intracellular content of Mg can be low despite normal serum concentrations. Serum Mg has a protein-bound (~30%) and an ultrafiltrable (~70%) portion. Of the latter, 70% to 80% is in ionic form. The remainder is complexed to anions, particularly phosphate, citrate, and oxalate.[1,59–62]

Mg is a required cofactor for >300 enzyme systems. It is critical for normal ATP function and glucose metabolism, and it is necessary for both aerobic and anaerobic metabolism. Mg is also important in cellular cytoskeleton contraction and at the myoneural junction; in this role, it can alter skeletal and cardiac muscle function. Among numerous other cell functions, Mg catalyzes enzymatic processes for the transfer, storage, and use of energy and regulates movement of potassium and Ca across cell membranes. Abnormalities in circulating Mg concentrations are associated with widespread cellular effects.[1,59–62]

Sources

Mg is ubiquitous in foods, but the Mg content of foods varies substantially. Green leafy vegetables are rich in Mg because chlorophyll is the Mg chelate of porphyrin. Unpolished grains and nuts also have high Mg content, whereas meats and milk have intermediate levels. Refined foods generally have the lowest Mg content.[15–17] Water is a variable source of Mg, but "hard" water has higher concentrations of Mg salts.[1] Human milk contains adequate amounts of Mg, and infant formulas are mandated to contain at least 6 mg/100 kcal.[18] Supplements containing various Mg salts are readily available in oral forms. Magnesium sulfate is available in parenteral form. Inorganic Mg (eg, Mg oxide) provides a high amount of elemental Mg but has limited bioavailability. Organic sources of Mg salts (eg, Mg Citrate) have higher solubility but with limited elemental Mg.[22]

The proportion of elemental Mg by weight in various Mg compounds is shown in Table 6-2. Mg supplements may contribute a substantial portion to

the daily intake. This factor is taken into consideration when deriving the tolerable upper intake limits.[1]

Absorption, Excretion, and Metabolism

The net absorption of Mg is about 40% to 60%. Fractional intestinal absorption is inversely proportional to the amount of Mg ingested. Intestinal absorption occurs via a passive gradient-dependent paracellular and an active saturable vitamin D–dependent transcellular mechanism. Mg is absorbed throughout the entire intestinal tract, with maximal absorption at the distal jejunum and ileum. Mg absorption is not significantly affected by other nutrients at usual dietary intake levels. It is lowered with high P intake, particularly in association with a high fiber and phytate intake, and at low protein intake.[1]

The kidney plays an important role in the homeostasis of divalent ions. The majority (>85%) of filtered free ionized and anion-complexed Ca and Mg are reabsorbed from the proximal tubules and the thick ascending limb (TAL) of Henle's loop via paracellular pathway through junctional pores formed by claudin proteins. However, the distal convolute tubule and the connecting tubule are the sites where ionized Ca and ionized Mg are reabsorbed via active transcellular transport, and this process determines the final plasma Mg concentrations. The largest fraction of filtered Ca is reabsorbed from the proximal tubule (65%), while the largest fraction of filtered Mg is reclaimed from the TAL (60%).[63–65]

Mg is often considered "a natural Ca antagonist," and Mg homeostasis is regulated similarly to but less tightly than Ca homeostasis. Renal Mg transport is also affected by both hormonal (PTH, calcitonin, glucagon, arginine vasopressin, 17β estradiol) and nonhormonal factors. High intake of glucose, sodium, Ca, and Mg and chronic excessive alcohol intake as well as elevated serum Mg or Ca, depletion of potassium and phosphate, and metabolic acidosis inhibit Mg and Ca reabsorption, leading to increased urine excretion of both cations.[1,2,8,9,62–65]

Mg is intimately involved in Ca homeostasis, and when hypocalcemia coexists with hypomagnesemia, the former may not respond to therapy until hypomagnesemia is corrected. There are also increasing reports of Mg action beyond mineral homeostasis, such as immune modulation,

bronchodilation used as adjunct therapy for asthma,[66] cystic fibrosis,[67] sickle cell disease,[68] and Mg therapy for mothers at imminent risk for preterm delivery is used to provide fetal neuroprotection.[69] However, intravenous Mg sulfate given in ED did not lower the hospitalization rate for children with refractory or mild asthma,[66] and it had varied benefits in other conditions.[69] The exact mechanisms of supplemental Mg therapy in these states remain to be elucidated.

Deficiency States

Mg deficiency is usually associated with insufficient dietary intake, malabsorption, increased losses from the gut or kidney, or upon refeeding of severe and chronically malnourished individuals. Mg deficiency is associated with obesity, metabolic syndrome, and type 2 diabetes.[70] Loop diuretics, cisplatin, tacrolimus, amphotericin B, aminoglycosides, and proton pump inhibitors are among the medications that result in increased renal Mg excretion and predisposition to Mg deficiency.[71] There are also increasing reports of patients with heritable defects of Mg transport that lead to Mg wasting and deficiency states.[72–75]

Hypomagnesemia is usually associated with a significant Mg deficit and correlates with the development of symptoms.[76] The typical deficit required to produce symptomatic hypomagnesemia is approximately 0.5 to 1 mmol (12–24 mg)/kg of body weight.[74] Hypomagnesemia and hypocalcemia may have similar clinical manifestations. Prolonged dietary Mg deprivation in human adults leads to personality change, tremor, muscle fasciculation, spontaneous carpopedal spasm, and generalized spasticity as well as hypomagnesemia, hypocalcemia, and hypokalemia.[1,62,76] In infants, acute complications associated with clinical manifestations include poor growth, seizure, apnea, cyanosis and hypoxia, electrocardiographic changes, bradycardia, and hypotension.[5,12] Thus, any patient at risk for Mg deficiency from the multiple conditions described previously should be monitored for hypomagnesemia. In addition, plasma Mg should be checked in patients with hypocalcemia unresponsive to standard Ca therapy.[1,12,62,71,72]

Excess Intake and Adverse Effects

Ingestion of Mg from natural foods has not been shown to exert any adverse effects. However, adverse effects of excess Mg intake have been reported for nonfood sources, such as various Mg salts for pharmacologic purposes, particularly in patients with renal dysfunction. The amount of Mg supplement is the basis from which the current upper limit of Mg intake is derived.[1] The primary initial manifestation of excessive Mg intake from nonfood sources is diarrhea (probably from its osmotic effect), which may be accompanied by nausea and abdominal cramping. Neuromuscular depression with floppiness and lethargy and respiratory depression are frequent clinical manifestations of severe neonatal hypermagnesemia in infants born to mothers who received Mg therapy prior to delivery.[1,12] Acute hypotonia, apnea, hypotension, and refractory bradycardia mimicking septic shock syndrome has been reported in preterm infants accidentally overdosed with Mg in PN.[77] In adults with hypermagnesemia, hypotension and urinary retention occur at serum Mg concentrations of 1.67 to 2.5 mmol/L (4–6 mg/dL); central nervous system depression, hyporeflexia, and electrocardiographic abnormalities (ie, increased atrioventricular and ventricular conduction time) occur at 2.5 to 5 mmol/L (6–12 mg/dL); and respiratory depression, coma, and cardiac arrest occur above 5 mmol/L (12 mg/dL).[62,78]

Conclusion

Calcium, phosphorus, and magnesium have an important place in the big picture of patient health. These minerals are critical to the maintenance of a normal skeleton and normal function of every organ system. Both mineral deficiencies and excesses highlights the importance of balance in dietary planning and supplementation. This chapter provides the biochemical and physiological basis to understand the interactions between these minerals and with other dietary components necessary for developing comprehensive nutritional strategies that support overall health and recovery from illnesses.

Test Your Knowledge Questions

1. Which of the following statements on the bioavailability of calcium is incorrect?
   A. Low-fat dairy products are a good source of bioavailable calcium
   B. The presence of phytate in plants can decrease calcium bioavailability
   C. Calcium in fortified foods is bioavailable
   D. Vitamin D is a major determinant of calcium bioavailability
2. Which of the following statements regarding calcium absorption is incorrect?
   A. Calcium absorption is inversely related to dietary content of calcium
   B. Calcium absorption is related to growth rate
   C. Calcium absorption is decreased with lactose intolerance
   D. Dietary zinc does not impair calcium absorption
3. Which of the following statements about phosphorus is incorrect?
   A. It is ubiquitous in natural foods
   B. Dietary intake of phosphorus is increased with increased consumption of processed foods
   C. Soy or grain-based protein has more bioavailable phosphorus than animal protein
   D. Phosphorus deficiency can result in hypercalcemia
4. Which of the following is not associated with low serum inorganic phosphate?
   A. Increased PTH
   B. Increased FGF 23
   C. Vitamin D deficiency
   D. Decreased renal function
5. Which of the following findings is not associated with magnesium deficiency?
   A. decreased fecal fat loss
   B. Chronic gastrointestinal losses
   C. Deficiency of other nutrients
   D. Hypocalcemia
6. Which of the following is not increased by hypermagnesemia?
   A. Hypotonia

B. Increased tendon reflex
C. Hypotension
D. Central nervous system depression

References

1. Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Intake for Reference Intakes. *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride.* National Academy Press; 1997. https://doi.org/10.17226/5776
2. Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes; Ross AC, Taylor CL, Yaktine AL, Del Valle HB, eds. *Dietary Reference Intakes for Vitamin D and Calcium*; s. National Academy Press; 2011.
3. Dietary guidelines for Americans 2020–2025. 9th ed. U.S. Department of Agriculture and U.S. Department of Health and Human Services. Published 2020. Accessed July 6, 2022. https://www.dietaryguidelines.gov
4. Dietary supplements. U.S. Food and Drug Administration. Accessed July 18, 2022. https://www.fda.gov/food/dietary-supplements.
5. American Academy of Pediatrics Committee on Nutrition. Calcium, phosphorus, and magnesium. In: Kleinman RE, Greer FR, eds. *Pediatric Nutrition*. 8th ed. American Academy of Pediatrics; 2019:541–56.
6. Koo W, Walyat N. Vitamin D and skeletal growth and development. *Curr Osteoporos Rep*. 2013;11:188–193. https://doi.org/10.1007/s11914-013-0156-1
7. Golden N, Abrams S; Committee on Nutrition. Optimizing bone health in children and adolescents. *Pediatrics*. 2014;134(4):e1229–e1243. https://doi.org/10.1542/peds.2014-2173
8. Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes; Food and Nutrition Board, Committee to Review the Dietary Reference Intakes for Sodium and Potassium; Oria M, Harrison M, Stallings VA, eds. *Dietary Reference*

Intakes for Water, Potassium, Sodium, Chloride, and Sulfate. National Academy Press; 2005.
9. Gagnon KB, Delpire E. Sodium transporters in human health and disease. *Front Physiol*. 2021;11:588664. https://doi.org/10.3389/fphys.2020.588664
10. Mihatsch W, Fewtrell M, Goulet O, Molgaard C, Picaud JC, Senterre T, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: calcium, phosphorus and magnesium. *Clin Nutr*. 2018;37(6 Pt B):2360–2365. https://doi.org/10.1016/j.clnu.2018.06.950
11. Da Silva JS, Seres D, Sabino K, et al; Parenteral nutrition safety and clinical practice committees, American Society for Parenteral and Enteral Nutrition. ASPEN consensus recommendations for refeeding syndrome. *Nutr Clin Pract*. 2020;35:178–195. https://doi.org/10.1002/ncp.10474
12. Koo WWK, Tsang RC. Calcium and magnesium homeostasis. In: MacDonald MG, Seshia MMK, eds. *Avery's Neonatology—Pathophysiology and Management of the Newborn*. 7th ed. Lippincott-Williams and Wilkins. 2016:646–669.
13. Matikainen N, Pekkarinen T, Ryhänen EM, Schalin-Jäntti C. Physiology of Calcium Homeostasis: An Overview. *Endocrinol Metab Clin North Am*. 2021;50:575–590. https://doi.org/10.1016/j.ecl.2021.07.005
14. Fulgoni VL 3rd, Keast DR, Auestad N, Quann EE. Nutrients from dairy foods are difficult to replace in diets of Americans: food pattern modeling and an analyses of the National Health and Nutrition Examination Survey 2003–2006. *Nutr Res*. 2011;31:759–765. https://doi.org/10.1016/j.nutres.2011.09.017
15. Pennington JAT, Douglass JS. Bowes & Church's Food Values of Portions Commonly Used. 19th ed. Lippincott Williams & Wilkins, 2014.
16. Calcium content in foods. CalorieKing™ for Food Awareness. Accessed July 19, 2022. http://www.calorieking.com
17. FoodData Central. National nutrient database for standard reference – 2018. U.S. Department of Agriculture, Agriculture Research Service. Accessed August 22, 2022. https://fdc.nal.usda.gov/fdc-app.html#/

18. Code of Federal Regulations Title 21. Nutrient specifications for infant formula. 21 CFR Part 107.100 Subpart D. U.S. Food and Drug Administration. Accessed October 27, 2023.
19. Dietary supplement label database. National Institutes of Health, Office of Dietary Supplements. Accessed July 31, 2022. https://dsld.od.nih.gov/
20. Koo WWK, Kaplan LA, Horn J, Tsang RC, Steichen JJ. Aluminum in parenteral nutrition solution—sources and possible alternatives. *JPEN*. 1986;10:591–5. https://doi.org/10.1177/0148607186010006591
21. An J, Zhang Y, Ying Z, Li H, Liu W, Wang J, Liu X. The formation, structural characteristics, absorption pathways and bioavailability of calcium-peptide chelates. *Foods*. 2022;11(18):2762. https://doi.org/10.3390/foods11182762
22. Pardo MR, Garicano Vilar E, San Mauro Martín I, Camina Martín MA. Bioavailability of magnesium food supplements: a systematic review. *Nutrition*. 2021;89:111294. https://doi.org/10.1016/j.nut.2021.111294
23. Beggs MR, Bhullar H, Dimke H, Alexander RT. The contribution of regulated colonic calcium absorption to the maintenance of calcium homeostasis. *J Steroid Biochem Mol Biol*. 2022;220:106098. https://doi.org/10.1016/j.jsbmb.2022.106098
24. Fischer PR, Thacher TD, Pettifor JM. Pediatric vitamin D and calcium nutrition in developing countries. *Rev Endocr Metab Disord*. 2008;9:181–192. https://doi.org/10.1007/s11154-008-9085-1
25. Oramasionwu GE, Thacher TD, Pam SD, Pettifor JM, Abrams SA. Adaptation of calcium absorption during treatment of nutritional rickets in Nigerian children. *Br J Nutr*. 2008;100:387–392. https://doi.org/10.1017/s0007114507901233
26. Thacher TD, Obadofin MO, O'Brien KO, Abrams SA. The effect of vitamin D2 and vitamin D3 on intestinal calcium absorption in Nigerian children with rickets. *J Clin Endocrinol Metab*. 2009;94:3314–3321. https://doi.org/10.1210%2Fjc.2009-0018
27. Fleet JC. Vitamin D-mediated regulation of intestinal calcium absorption. *Nutrients*. 2022 16;14(16):3351. https://doi.org/10.3390/nu14163351
28. Christakos S. Vitamin D: A Critical Regulator of Intestinal Physiology. *JBMR Plus*. 2021;5(12):e10554. https://doi.org/10.1002/jbm4.10554

29. Chanpaisaeng K, Teerapornpuntakit J, Wongdee K, Charoenphandhu N. Emerging roles of calcium-sensing receptor in the local regulation of intestinal transport of ions and calcium. *Am J Physiol Cell Physiol*. 2021;320(3):C270–C278. https://doi.org/10.1152/ajpcell.00485.2020
30. Khattar V, Wang L, Peng JB. Calcium selective channel TRPV6: structure, function, and implications in health and disease. *Gene*. 2022;817:146192. https://doi.org/10.1016/j.gene.2022.146192
31. Shkembi B, Huppertz T. Calcium absorption from food products: food matrix effects. *Nutrients*. 2021;14(1):180. https://doi.org/10.3390/nu14010180
32. Heaney RP, Rafferty K. Carbonated beverages and urinary calcium excretion. *Am J Clin Nutr*. 2001;74:343–347. https://doi.org/10.1093/ajcn/74.3.343
33. Koo WWK, Kaplan LA. Aluminum and bone disorders: with specific reference to aluminum contamination of infant nutrients. *J Am Coll Nutr*. 1988;7:199–214. https://doi.org/10.1080/07315724.1988.10720237
34. Gommers LMM, Hoenderop JGJ, de Baaij JHF. Mechanisms of proton pump inhibitor-induced hypomagnesemia. *Acta Physiol (Oxf)*. 2022;235(4):e13846. https://doi.org/10.1111/apha.13846
35. FDA drug safety communication: Possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors. U.S. Food and Drug Administration. Accessed August 25, 2022. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-drug-safety-communication-possible-increased-risk-fractures-hip-wrist-and-spine-use-proton-pump
36. Slemenda CW, Reister TK, Hui SL, Miller JZ, Christian JC, Johnston CC Jr. Influences on skeletal mineralization in children and adolescents: evidence for varying effects of sexual maturation and physical activity. *J Pediatr*. 1994;125:201–207. https://doi.org/10.1016/s0022-3476(94)70193-8
37. Specker BL. Evidence for an interaction between calcium intake and physical activity on changes in bone mineral density. *J Bone Miner Res*. 1996;11:1539–1544. https://doi.org/10.1002/jbmr.5650111022
38. Koo WWK, Walters JC, Esterlitz J, Levine RJ, Bush AJ, Sibai B. Maternal calcium supplementation and fetal bone mineralization.

Obstet Gynecol. 1999;94:577–582. https://doi.org/10.1016/s0029-7844(99)00371-3
39. Ryan BA, Kovacs CS. Maternal and fetal vitamin D and their roles in mineral homeostasis and fetal bone development. *J Endocrinol Invest*. 2021;44(4):643–659. https://doi.org/10.1007/s40618-020-01387-2
40. Stenhouse C, Suva LJ, Gaddy D, Wu G, Bazer FW. Phosphate, calcium, and vitamin D: key regulators of fetal and placental development in mammals. *Adv Exp Med Biol*. 2022;1354:77–107. https://doi.org/10.1007/978-3-030-85686-1_5
41. Fanni D, Gerosa C, Nurchi VM, Manchia M, Saba L, Coghe F, et al. The role of magnesium in pregnancy and in fetal programming of adult diseases. *Biol Trace Elem Res*. 2021;199(10):3647–3657. https://doi.org/10.1007/s12011-020-02513-0
42. Nattiv A. Stress fractures and bone health in track and field athletes. *J Sci Med Sport*. 2000;3:268–279. https://doi.org/10.1016/s1440-2440(00)80036-5
43. Lactose intolerance. National Institute of Diabetes and Digestive and Kidney Diseases. Accessed July 10, 2022. https://www.niddk.nih.gov/health-information/digestive-diseases/lactose-intolerance
44. Bakaloudi DR, Halloran A, Rippin HL, Oikonomidou AC, Dardavesis TI, Williams J, Wickramasinghe K, Breda J, Chourdakis M. Intake and adequacy of the vegan diet. A systematic review of the evidence. *Clin Nutr.* 2021;40:3503–3521. https://doi.org/10.1016/j.clnu.2020.11.035
45. Walker MD, Shane E. Hypercalcemia: A Review. *JAMA*. 2022;328:1624–1636. https://doi.org/10.1001/jama.2022.18331
46. Lecoq AL, Livrozet M, Blanchard A, Kamenický P. Drug-related hypercalcemia. *Endocrinol Metab Clin North Am*. 2021;50:743–752. https://doi.org/10.1016/j.ecl.2021.08.001
47. Gorvin CM. Genetic causes of neonatal and infantile hypercalcemia. *Pediatr Nephrol*. 2022;37:289–301. https://doi.org/10.1007/s00467-021-05082-z
48. Papadopoulou A, Bountouvi E, Karachaliou FE. The molecular basis of calcium and phosphorus inherited metabolic disorders. *Genes (Basel)*. 2021;12(5):734. https://doi.org/10.3390/genes12050734

49. Monte SV, Prescott WA, Johnson KK, Kuhman L, Paladino JA. Safety of ceftriaxone sodium at extremes of age. *Expert Opin Drug Saf*. 2008;7:515–523. https://doi.org/10.1517/14740338.7.5.515
50. Lederer E. Regulation of serum phosphate. *J Physiol*. 2014;592(Pt 18):3985–3995. https://doi.org/10.1113/jphysiol.2014.273979
51. Peacock M. Phosphate Metabolism in Health and Disease. *Calcif Tissue Int*. 2021;108:3–15. https://doi.org/10.1007/s00223-020-00686-3
52. Koumakis E, Cormier C, Roux C, Briot K. The Causes of Hypo- and Hyperphosphatemia in Humans. *Calcif Tissue Int*. 2021;108:41–73. https://doi.org/10.1007/s00223-020-00664-9
53. Specker BL, Lichtenstein P, Mimouni F, Gormley C, Tsang RC. Calcium-regulating hormones and minerals from birth to 18 months of age: a cross-sectional study. II. Effects of sex, race, age, season, and diet on serum minerals, parathyroid hormone, and calcitonin. *Pediatrics*. 1986;77:891–896. https://doi.org/10.1542/peds.77.6.891
54. Lotz M, Zisman E, Bartter FC. Evidence for a phosphorus-depletion syndrome in man. *N Engl J Med*. 1968;278:409–415. https://doi.org/10.1056/nejm196802222780802
55. Freiman I, Pettifor JM, Moodley GM. Serum phosphorus in protein energy malnutrition. *J Pediatr Gastroenterol Nutr*. 1982;1:547–550. https://doi.org/10.1097/00005176-198212000-00016
56. Hill Gallant KM, Vorland CJ. Intestinal phosphorus absorption: recent findings in translational and clinical research. *Curr Opin Nephrol Hypertens*. 2021;30(4):404–410. https://doi.org/10.1097/mnh.0000000000000719
57. Takashi Y, Fukumoto S. Phosphate-sensing and regulatory mechanism of FGF23 production. *J Endocrinol Invest*. 2020;43:877–883. https://doi.org/10.1007/s40618-020-01205-9
58. Rausch S, Föller M. The regulation of FGF23 under physiological and pathophysiological conditions. *Pflugers Arch*. 2022;474(3):281–292. https://doi.org/10.1007/s00424-022-02668-w
59. Picone G, Cappadone C, Farruggia G, Malucelli E, Iotti S. The assessment of intracellular magnesium: different strategies to answer different questions. *Magnes Res*. 2020;33(1):1–11. https://doi.org/10.1684/mrh.2020.0464

60. Pelczyńska M, Moszak M, Bogdański P. The role of magnesium in the pathogenesis of metabolic disorders. *Nutrients*. 2022;14(9):1714. https://doi.org/10.3390/nu14091714
61. Carpenter TO. Dent A, Selvaratnam R. Measuring magnesium—physiological, clinical and analytical perspectives. *Clin Biochem*. 2022;105–106:1–15. https://doi.org/10.1016/j.clinbiochem.2022.04.001
62. Dent A, Selvaratnam R. Measuring magnesium - Physiological, clinical and analytical perspectives. *Clin Biochem*. 2022;105–106:1–15. https://doi.org/10.1016/j.clinbiochem.2022.04.001
63. Alexander RT, Dimke H. Molecular mechanisms underlying paracellular calcium and magnesium reabsorption in the proximal tubule and thick ascending limb. *Ann N Y Acad Sci*. 2022;1518:69–83. https://doi.org/10.1111/nyas.14909
64. Ellison DH, Maeoka Y, McCormick JA. Molecular mechanisms of renal magnesium reabsorption. *J Am Soc Nephrol*. 2021;32(9):2125–2136. https://doi.org/10.1681/asn.2021010042
65. Franken GAC, Huynen MA, Martínez-Cruz LA, Bindels RJM, de Baaij JHF. Structural and functional comparison of magnesium transporters throughout evolution. *Cell Mol Life Sci*. 2022;79(8):418. https://doi.org/10.1007/s00018-022-04442-8
66. Schuh S, Freedman SB, Zemek R, Plint AC, Johnson DW, Ducharme F, et al. Association between intravenous magnesium in the emergency department and subsequent hospitalization among pediatric patients with refractory active asthma: secondary analysis of a randomized clinical trial. *JAMA Netw Open*. 2021;4(7):e2117542. https://doi.org/10.1001/jamanetworkopen.2021.17542
67. Sankararaman S, Hendrix SJ, Schindler T. Update on the management of vitamins and minerals in cystic fibrosis. *Nutr Clin Pract*. 2022 Oct;37(5):1074–1087. https://doi.org/10.1002/ncp.10899
68. Than NN, Soe HHK, Palaniappan SK, Abas AB, De Franceschi L. Magnesium for treating sickle cell disease. *Cochrane Database Syst Rev*. 2017;4(4):CD011358. https://doi.org/10.1002/14651858.cd011358.pub2
69. Wolf HT, Huusom LD, Henriksen TB, Hegaard HK, Brok J, Pinborg A. Magnesium sulphate for fetal neuroprotection at imminent risk for preterm delivery: a systematic review with meta-analysis and trial

sequential analysis. *BJOG 2020*;127(10):1180–1188. https://doi.org/10.1111/1471-0528.16238
70. Piuri G, Zocchi M, Porta MD, Ficara V, Manoni M, Zuccotti GV, et al. Magnesium in obesity, metabolic syndrome, and type 2 diabetes. *Nutrients*. 2021;13(2):320. https://doi.org/10.3390/nu13020320
71. Rosner MH, Ha N, Palmer BF, Perazella MA. Acquired disorders of hypomagnesemia. *Mayo Clin Proc*. 2023;98:581–596. https://doi.org/10.1016/j.mayocp.2022.12.002
72. Wolf MT. Inherited and acquired disorders of magnesium homeostasis. *Curr Opin Pediatr*. 2017;29:187–198. https://doi.org/10.1097/mop.0000000000000450
73. Viering DHHM, de Baaij JHF, Walsh SB, Kleta R, Bockenhauer D. Genetic causes of hypomagnesemia, a clinical overview. *Pediatr Nephrol*. 2017 Jul;32(7):1123–1135. https://doi.org/10.1007/s00467-016-3416-3
74. Tseng MH, Konrad M, Ding JJ, Lin SH. Clinical and genetic approach to renal hypomagnesemia. *Biomed J*. 2022;45(1):74–87. https://doi.org/10.1016/j.bj.2021.11.002
75. Nuñez-Gonzalez L, Carrera N, Garcia-Gonzalez MA. Molecular basis, diagnostic challenges and therapeutic approaches of Bartter and Gitelman syndromes: a primer for clinicians. *Int J Mol Sci*. 2021;22(21):11414. https://doi.org/10.3390/ijms222111414
76. Shils ME. Experimental human magnesium depletion. *Medicine*. 1969;48:61–85. https://doi.org/10.1097/00005792-196901000-00003
77. Ali A, Walentik C, Mantych GJ, Sadiq HF, Keenan WJ, Noguchi A. Iatrogenic acute hypermagnesemia after total parenteral nutrition infusion mimicking septic shock syndrome: two case reports. *Pediatrics*. 2003;112:e70–e72. https://doi.org/10.1542/peds.112.1.e70
78. Mordes JP, Wacker WE. Excess magnesium. *Pharmacol Rev*. 1978;29:273–300.

Test Your Knowledge Answers

1. The correct answer is **D**. Vitamin D affects the active component of calcium absorption, which is quantitatively much less than passive

calcium absorption and does not directly influence calcium bioavailability. The preferred source of calcium is from the diet because diets with high bioavailable calcium are generally nutrient-dense, with multiple other critical nutrients. Foods fortified with Ca have increased the options for Ca-rich foods in the diet. Naturally occurring products (eg, oyster shells) marketed as calcium supplements have disadvantages and may contain high levels of lead, mercury, and other potentially toxic contaminants.

2. The correct answer is **C**. No evidence exists that lactose-intolerant individuals have intrinsically impaired Ca absorption. Lactose-intolerant individuals may be at risk for Ca deficiency, not because they are unable to absorb Ca but rather because they avoid dairy products. Drinking milk with a meal and other dietary options (eg, aged cheeses, such as cheddar and Swiss, which contain little lactose; yogurt, which contains live active cultures that aid in lactose digestion; or lactose-reduced and lactose-free milk) may allow increased Ca intake. Intestinal calcium absorption is higher with growth and with a lower calcium intake. A high Ca intake may decrease zinc absorption, but no convincing evidence exists that a normal dietary zinc intake affects Ca absorption.
3. The correct answer is **C**. Animal protein has more bioavailable phosphorus than soy- or grain-based protein. Phosphorus in plants (from beans, peas, cereals, and nuts) is present in poorly digestible phytic acid and is less bioavailable than P from animal protein. Various phosphate salts used in food processing for nonnutritive functions (eg, moisture retention, smoothness, and binding) provide significant contributions to dietary P intake. Phosphorus deficiency occurs in selected clinical situations and can have serious consequences, including hypercalcemia.
4. The correct answer is **D**. The kidney is a major regulator of circulating P, and impaired renal function results in hyperphosphatemia. PTH and FGF are phosphaturic, and an increase in either can lower serum P. Vitamin D deficiency in infants results in rickets and can be associated with hypophosphatemia.
5. The correct answer is **A**. Magnesium absorption is independent of fat absorption. Gastrointestinal secretions have high Mg content.

Magnesium deficiency can occur with chronic losses from the gastrointestinal tract and concomitantly with deficiency of multiple other nutrients. Magnesium deficiency can have serious consequences, including hypocalcemia. The latter may not resolve unless Mg deficiency has been corrected.

6. The correct answer is **B**. Hypermagnesemia is associated with neuromuscular depression and hypotonia and therefore decreases tendon reflex and respiratory and central nervous system depression. It lowers blood pressure as well.

7

Water-Soluble Vitamins and Related Compounds

Winston Koo, MBBS, FACN, CNS; Judith Christie, RN, MSN; May Saba, PharmD, BCNSP; Letitia Warren, RD, CSP; and Mirjana Lulic-Botica, PharmD, BCPS

Learning Objectives

1. Understand the physiological basis shared among water-soluble essential micronutrients, encompassing both their common functions and individual, specific requirements.
2. Identify prevalent risk factors and special considerations contributing to the development of deficiency states in these micronutrients.
3. Discern the typical signs, symptoms, and methods for diagnosis of deficiency states associated with these micronutrients.
4. Assess and predict the potential risks associated with the excessive intake of these micronutrients.

Introduction

Water-soluble essential micronutrients include the 8 B-complex vitamins as well as vitamin C and choline:

1. Thiamin (vitamin B_1)
2. Riboflavin (vitamin B_2)
3. Niacin (vitamin B_3)
4. Pantothenic acid (vitamin B_5)
5. Vitamin B_6 (pyridoxine)
6. Biotin (vitamin B_7)
7. Folate (vitamin B_9)
8. Vitamin B_{12}

These micronutrients are generally considered water-soluble vitamins (WSVs). They affect the function of all cells, and many have interrelated transport mechanisms, metabolisms, and functions. In pediatric participants, these cellular functions additionally affect growth and development.[1–3] This chapter provides the biochemical and physiologic basis to develop nutrition support strategies to maintain normal WSV status and restore health in patients with deficient states.

Sources

Some WSVs can be synthesized de novo from other nutrients (eg, niacin from tryptophan, choline from methylation of phosphatidylethanolamine) or by intestinal bacteria (eg, thiamin, riboflavin, pantothenic acid, biotin, pyridoxine, and vitamin B_{12}), although in amounts inadequate to meet physiological demands.

WSVs produced by in-vitro chemical synthesis or bacteria fermentation can be added to foods or taken as dietary supplements to achieve adequate intake. Low- and middle-income countries are increasingly using biofortification through plant breeding and genetic engineering technology to enhance the nutritional value of crops. WSVs are widely distributed in foods. [4,5] Processing, storing, and cooking foods (especially prolonged boiling with liquid disposal), negatively affects their WSV content.,[2,6,7] However, changes in the manufacturing process might be able to lower these negative effects.[8] Many food and drink products are fortified with one

or more of these micronutrients. Some nutrients, such as choline, are added to foods as a component of an emulsifying agent.

WSVs are available as individual supplements, as part of multivitamin or multi-nutrient supplements, and as oral and parenteral preparations. Vitamin B_{12} is also available as an intranasal gel and liquid preparation.[9] Multivitamin preparations used for parenteral nutrition (PN) are shown in Table 7-1.

TABLE 7-1. Water-Soluble Vitamin Content per Unit Dose of Multivitamin Preparations for Parenteral Nutrition

Ingredient/Dose	Infuvite Pediatric	Infuvite Adult
Unit dose volume, mL	5[a]	10[b]
Vitamin B_1 (thiamin), mg	1.2	6
Vitamin B_2 (riboflavin), mg	1.4	3.6
Vitamin B_3 (niacinamide), mg	17	40
Vitamin B_6 (pyridoxine), mg	1	6
Folic acid (vitamin B_9), mcg	140	600
Vitamin B_{12} (cyanocobalamin), mcg	1	5
Vitamin C (ascorbic acid), mg	80	200
Dexpanthenol (D-pentothenyl alcohol), mg	5	15
Biotin, mcg	20	60

Data from manufacturer product inserts: Baxter Inc for Infuvite Pediatric and Infuvite Adult. Manufacturers, products, and product information can change frequently, so please consult the manufacturer's website for the most current information.

[a] 2 single-dose vials: vial 2 (1 mL) contains folic acid, biotin, and vitamin B, and vial 1 (4 mL) contains all the other vitamins. The daily dose for infants and children weighing 3 kg or more up to age 11 y is 5 mL, for infants weighing 1–3 kg is 3.25 mL (65% of daily dose), and for infants weighing <1 kg is 1.5 mL (30% of daily dose).

[b] Supplied as unit vials or dual vials. Unit vial is a 2-chambered single-dose vial that must be mixed just before use and will provide one 10-mL dose. Dual vial is 2 vials labeled vial 1 (5 mL) and vial 2 (5 mL), with both vials to be used for a single 10-mL dose.

Multiple product shortages are an ongoing issue. The American Society for Parenteral and Enteral Nutrition (ASPEN) provides guidelines on the use of pediatric intravenous multivitamins when there is a shortage and nonavailability as follows:

- Shortage: Prioritize use for neonates <2.5 kg or <36 weeks post-menstrual age due to the presence of propylene glycol, and higher content of polysorbate and aluminum in adult preparations.
- Non-availability:
  - For infants < 2.5 kg or < 36 weeks postmenstrual age, use an adult intravenous multivitamin at a daily dose of 1 mL/kg up to a maximum of 2.5 mL/d. Additional vitamin K also needs to be added.

– For infants >2.5 kg or >36 weeks gestation, add 5 mL of adult preparation plus vitamin K to make a total of 200 mcg/d.

For updates, consult the U.S. Food and Drug Administration and professional organizations, including the American Society of Health-System Pharmacists and ASPEN.

For healthy near-term or term infants, human milk from mothers who are well nourished with a varied diet should be sufficient to provide all water-soluble essential micronutrients for their daily needs. Because of minimal or absent reserves and the need for catch-up growth, small preterm infants have greater needs for these and other nutrients. Human milk fortifier added to human milk raises the concentration of these and many other nutrients to multiple times higher than in unfortified human milk, and the result should be sufficient for preterm infants tolerating an adequate volume of enteral intake.[3]

For formula-fed infants, the use of commercial milk-based formula designed for term and preterm infants is expected to be adequate.[3,10] Beyond infancy, a culturally appropriate varied diet ensures the adequacy of intake at all life stages because these essential nutrients are present in a wide range of food products. [1,2,4,5,11] However, most adults and children do not consume enough WSV-rich fruits and vegetables and are at risk for deficiencies. Absorption of vitamin B_{12} may be lower in older adults.[11–13]

Digestion, Absorption, and Metabolism

After digestion releases WSVs from foods, the body absorbs them in free form or as small molecular complexes. Absorption usually occurs by active transport at low nutrient intake and by passive diffusion at high nutrient intake. Absorption of WSVs occurs mainly in the jejunum, except for cobalamin, which under physiological conditions, is absorbed only in the ileum. Some absorption also occurs in the stomach (niacin) and proximal colon (riboflavin, biotin).[1,2,6,7] After absorption, WSVs are transported as part of an enzyme complex or are bound to proteins. Erythrocytes may serve both as transporters and storage sources. Tissue uptake via membrane transporters is usually specific to each nutrient.

The metabolism and function of some WSVs are interrelated and are affected by environmental factors. Notable metabolic or functional interactions include those between thiamin and biotin and among riboflavin, niacin, folate, and pyridoxine. The environmental factors include photooxidation of riboflavin in PN infusate. Oxidative products, in turn, increase the oxidation of amino acids and chelate divalent cations, such as copper, zinc, iron, and manganese. Photoprotection of PN for premature infants is recommended because of the potential for clinical complications resulting from oxidative stress in this high-risk group.[14,15] The bioavailability of WSV supplements is generally similar to or better than that from dietary sources when tested under the same conditions.[1,2,6,7]

Dietary Reference Intake

The current dietary reference intakes (DRIs) of WSVs for pediatric populations are provided in Table 7-2.[1,2] The current reference values are subject to change as understanding of the relationship among various nutrients increases and more data are available on the type and bioavailability of specific nutrients from naturally occurring dietary sources, fortification of foods and drinks, and dietary supplements.

TABLE 7-2. Dietary Reference Intake of Water-Soluble Essential Micronutrients in Pediatric Populations[1,2]

Life Stage	Thiamin B_1 mg	Riboflavin B_2 mg	Niacin B_3 mg	Pyridoxine B_6 mg	Folate B_9 mcg	Cobalamin B_{12} mcg	Vitamin C mg	Pantothenic Acid B_5 mg[a]	Biotin B_7 mcg[a]	Choline mg[a]
0–6 m[a]	0.2	0.3	2	0.1	65	0.4	40	1.7	5	125
7–12 m[a]	0.3	0.4	4	0.3	80	0.5	50	1.8	6	150
1–3 y[b]	0.5	0.5	6 (15)	0.5 (30)	150 (300)	0.9	15 (400)	2	8	200 (1000)
4–8 y[b]	0.6	0.6	8 (20)	0.6 (40)	200 (400)	1.2	25 (650)	3	12	250 (1000)
Males										
9–13 y[b]	0.9	0.9	12 (20)	1.0 (60)	300 (600)	1.8	45 (1200)	4	20	375 (2000)
14–18 y[b]	1.2	1.3	16 (30)	1.3 (80)	400 (800)	2.4	75 (1800)	5	25	550 (3000)
Females										
9–13 y[b]	0.9	0.9	12 (20)	1.0 (60)	300 (600)	1.8	45 (1200)	4	20	375 (2000)
14–18 y[b]	1.0	1.0	14 (30)	1.2 (80)	400 (800)	2.4	65 (1800)	5	25	400 (3000)
Pregnancy										
14–18 y[b]	1.4	1.4	18 (30)	1.9 (80)	600 (800)	2.6	80 (1800)	6	30	450 (3000)
Lactation										
14–18 y[b]	1.4	1.6	17 (30)	2.0 (80)	500 (800)	2.8	115 (1800)	7	35	550 (3000)
Highest intake[c]	11 mg at >51 y	11 mg at >70 y	35 mg at 51–70 y	3.9 mg at 19–30 y	1000 mcg at 51–70 y	36.8 mcg at 14–55 y	656 mg at 51–70 y	NA	NA	NA
UL[d]	NA	NA	[e]	[e]	[e]	NA	[e]	NA	NA	[e]

[a] AI is the observed or experimentally determined estimate of nutrient intake by a group or groups of healthy people. AI is the only reference level provided for infants < 12 months and for pantothenic acid, biotin, and choline at all life stages and for both sexes.

[b] RDA is calculated as + 2 standard deviations of the estimated average requirement, or in its absence, a coefficient of variation of 10%–15% for each standard deviation is assumed for a life stage and by sex.

[c] Highest intake is the highest reported daily mean intake from both food and supplements at the 95th percentile for any life stage or sex.

[d] UL is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population.

[e] Upper limit of intake for each life stage is indicated in parentheses.

For a dietary niacin equivalent, 1 niacin equivalent (NE) = 60 mg tryptophan. However, preformed niacin, not NE, is needed at age 0–6 m.

For dietary folate equivalents, 1 µg food folate = 0.6 µg of folic acid from fortified food or as a supplement consumed with food = 0.5 µg of a supplement taken on an empty stomach. All women capable of becoming pregnant are recommended to consume 400 µg from

supplements or fortified foods in addition to intake of food folate until pregnancy is confirmed and they enter prenatal care.

The DRI of each essential micronutrient is based on several sets of reference values including adequate intake (AI), estimated average requirement (EAR), recommended dietary allowance (RDA), and upper tolerable levels of intake (UL). AI is the average daily intake of a specific nutrient. Establishing AI for specific micronutrients relies on having access to food composition data that includes accurate micronutrient content. Additionally, large-scale epidemiologic studies are necessary to identify dietary and supplement intake of nutrients among healthy individuals of different genders and life stages.

During the first year of life for healthy infants, AI is based on specific nutrients principally from human milk. After 1 year of age, EAR and RDA are used for references in addition to AI. EAR is a daily nutrient intake value estimated to meet the requirement of half of healthy individuals. RDA is the average daily dietary intake level that is sufficient to meet the nutrient requirement of nearly all (97%–98%) healthy individuals. Assessing dose-response risk to high intakes and setting UL depends on the availability of sufficient data. Limited data in children and adolescents often necessitates the derivation of EAR, RDA, and UL by extrapolation from adult data. AI is used when RDA cannot be determined.[1,2]

Predisposition to Deficiency States

Isolated WSV deficiency is rare and stems mainly from nutrition product manufacturing issues (eg, thiamin and pyridoxine deficiency). Restrictive dietary practices (eg, thiamin and vitamin B_{12} deficiency) and inborn errors of metabolism (IEM) or certain gene polymorphisms are associated with perturbation in various aspects of digestion, absorption, transport, and metabolism of specific essential micronutrients. Heritable predispositions to deficiency or dependency states have been reported for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, biotin, and vitamin C. The number

of disorders is expected to increase with improvements in molecular diagnostic techniques.

In all populations, most deficiency states are associated with deficiencies in more than one WSV, either from poor intake, digestion, or absorption or because of interrelated metabolisms (Exhibit 7-1). For example, nutrient deficiency in HIV and AIDS is likely the result of dietary deficiency, antiretroviral-induced or concomitant diarrheal diseases, and inflammation-suppressed circulating nutrient biomarkers. However, not all children with HIV infection have micronutrient deficiencies.[16]

EXHIBIT 7-1. Predispositions to Deficiency of Water-Soluble Essential Micronutrients[a]

- Limited body store, particularly in infants and young children
- Inadequate endogenous synthesis
- Decreased intake
  - Production shortage of parenteral multivitamin preparations
  - Manufacturer error in infant formula resulting in lack of selected vitamin=Manufacturer error in infant formula resulting in lack of selected vitamin
  - Food faddism or severe dietary restrictions including vegan diet
  - Food refusal
  - Anorexia nervosa
- Decreased bioavailability
  - Cooking and storage of foods at high temperatures and prolonged periods
  - Addition of baking soda to vegetables
  - Decreased absorption and/or increased loss (eg, Celiac disease, Crohn's disease, cystic fibrosis, gastrointestinal bypass surgery, and any malabsorption states)
  - Heritable metabolic defect and gene polymorphism
- Nutrient–nutrient and nutrient–drug interaction (see Table 7-4)
- Mixed predispositions including some or all of above
  - Hyperemesis gravidarum
  - Chronic renal dialysis
  - Alcohol abuse
  - Human immunodeficiency virus infection

[a] More than one predisposition to the development of a deficiency state is usually present.

Requirements for many WSVs increase with growth, pregnancy, lactation, physical exertion, fever, and conditions associated with increased metabolic needs. Deficiency of multiple micronutrients particularly in women and young children is highly prevalent in low-income and middle-income countries.[17,18] Other predisposing conditions that may result in poorer WSV status include the following:

- Health and dietary fads, including diets with high fat and a preponderance of low-nutrient-density foods, and strict veganism.
- Medical conditions involving malabsorption states such as celiac disease, Crohn's disease, and cystic fibrosis.[6,7,19,20]
- Bariatric surgery involving the stomach or small intestine.[21]

Prolonged therapy with certain medications (eg, chronic diuretic, metformin therapy), also predisposes individuals to deficiency states through their actions on excretion or metabolism of certain nutrients.[9,22,23]

Tobacco and alcohol affect the need for these nutrients. Tobacco use is the leading cause of preventable disease, disability, and death in the United States.[24] The association between cigarette smoking and dieting in adolescents exists even in individuals who are not overweight.[25] Oxidative stress from smoking increases the need for antioxidant vitamins, while inappropriate dieting may decrease intake. Alcohol is the most used substance among young people in the United States, even more so than tobacco and illicit drugs.[26] Alcohol abuse is often associated with poor dietary intake of many essential nutrients. In addition, alcohol can directly or indirectly interfere with the digestion, absorption, and metabolism of multiple essential water-soluble micronutrients.[1,2,6,19]

Deficiency and toxicity states for WSVs have many biochemical and clinical manifestations (see Table 7-3). Diagnosing a deficiency state may be complicated by overlapping clinical manifestations, which commonly include skin disorders, anemia, diarrhea, and impaired neurologic function.[1,2,6,7,19,27,28] Biochemical indicators of deficiency may be affected by laboratory technique and by varied normal ranges of laboratory values from different life stages and possibly other physiologic factors such as sex. For example, using streptavidin-biotin-based assays to measure plasma hormones in patients who consume large amounts of biotin may produce

erroneous results. These results may, in turn, lead to potentially dangerous therapies.[29–31] The value of techniques that directly measure the concentration of selected vitamins in clinical diagnosis and management remains to be determined.[32] Molecular diagnosis and genetic counseling are appropriate for heritable defects.[28,33]

TABLE 7-3. Characteristics of Water-Soluble Essential Micronutrients[a]

Micro-nutrient	Adult Tissue Store	Biological Half-Life	Deficiency—Major Clinical Manifestations	Deficiency—Biochemical RC, WB, P, U	Toxicity
Thiamin (B_1)	~30 mg, mostly red cells and liver	9–18 d	Beriberi: wet, dry; Wernicke encephalopathy	↓ RC or WB TPP; ↑ RC transketolase activity with TPP	Rapid injection: anaphylactoidlike reaction
Riboflavin (B_2)	Very low	2–3 d	Ariboflavinosis: pharyngitis, cheilosis, angular stomatitis, glossitis, seborrheic dermatitis	↓ RC riboflavin; ↑ RC erythrocyte glutathione reductase activity coefficient with FAD stimulation; ↓ 24 h U riboflavin	Photooxidation of some amino acids
Niacin (B_3)	NA	P nicotinamide 7–9 h	Pellegra: diarrhea, dementia, dermatitis	↓ RC nicotinamide adenine dinucleotide: nicotinamide adenine dinucleotide phosphate ratio; ↓ 24 h U niacin and its metabolites	Vasodilatory, nausea, vomiting, hepatitis, neurovisual disturbance, glucose intolerance
B_6 (pyridoxine)	160 mg, muscle ~80%	25 d	Seizures	↓ P pyridoxal phosphate, ↓ RC aspartate and alanine transferase saturation	Peripheral sensory neuropathy
Folate	12–30 mg, liver ~50%	RC ~8 wk	Seizures, neuromotor disorder, developmental delay, megaloblastic anemia	↓ RC folate, ↑ P homocysteine	Exacerbates B_{12}-deficient neuropathy
B_{12} (cobalamin)	2–3 mg, liver ≥ 50%	6 d	Macrocystic megaloblastic anemia, nervous system involvement	↓ P B_{12} and holotranscobalamine, ↑ P and U methylmalonic acid, and ↑ P homocysteine	Skin eruptions include urticaria, anaphylaxis
Vitamin C	2–5g	8–40 d	Scurvy	↓ P ascorbate < 0.2 mg/dL, ↓ RC and leukocyte ascorbate	Nausea, abdominal cramps, and diarrhea; urinary oxalate stones
Pantothenic acid	NA	NA	Gastrointestinal and nervous system	No consistent changes in RC, WB, or P	NA

Micro-nutrient	Adult Tissue Store	Biological Half-Life	Deficiency—Major Clinical Manifestations	Deficiency—Biochemical RC, WB, P, U	Toxicity
Biotin	NA	2 h (post ingestion elimination)	Seizures, developmental delay, rash, alopecia	U ↓ biotin, ↑ 3 hydroxyisovaleric acid	NA
Choline	NA	43 h	Nonspecific	↓ P, RC, and tissue choline and phosphatidylcholine	Hypotension, cholinergic, fishy odor

Abbreviations: FAD, flavin adenine dinucleotide; NA, not available; P, plasma; RC, red cells; TPP, thiamin pyrophosphate; U, urine; WB, blood.

[a] Insufficient data to provide quantitative data in some cells.

Management of Deficiency States

Treating a deficiency state requires an understanding of the primary cause, the possibility of deficiency in other nutrients, and concomitant therapies that may interfere with effective replacement therapy. Because all vitamins are pharmacologically active substances, potential nutrient–nutrient and nutrient–drug interactions (see Table 7-4) can increase the likelihood of deficiency and toxicity, sometimes with serious consequences.

TABLE 7-4. Potential Nutrient–Nutrient and Nutrient–Drug Interactions of Water-Soluble Essential Micronutrients[a]

Micronutrient	Nutrient–nutrient interaction	Nutrient–drug Interaction
Thiamin (B_1)	Not available	↓ Plasma B_1 with or without ↑ requirement from excess alcohol, caffeine, chronic diuretics, and phenytoin
Riboflavin (B_2)	Deficiency can impair metabolism of vitamin B_6, folate, niacin, and iron. Divalent cations may chelate B_2 from tryptophan	↑ B_2 metabolism from tricyclic antidepressant, phenothiazines, phenytoin, quinacrine, adriamycin, chronic alcohol
Niacin (B_3)	Riboflavin, pyridoxine, and iron needed for B_3 endogenous synthesis	↓ Endogenous production from isoniazid, 5-fluorouracil, or 6-mercaptopurine
B_6 (pyridoxine)	B_6 metabolism interacts closely with metabolism of riboflavin, niacin, zinc, and folate	↓ Plasma B_6 from binding to isoniazid, hydralazine, oral contraceptives, penicillamine, cycloserine, theophylline, L-dopa. B_6 ↓ plasma phenobarbital, phenytoin, L-dopa
Folate	Interacts closely with choline and B_{12} metabolism in the transfer of methyl group	↓ Plasma folate from aspirin, ibuprofen, naproxene, methotrexate, 5-fluoruracil, phenobarbital, phenytoin, primidone, pyrimethamine
B_{12} (cobalamin)	Interacts closely with folate and choline metabolism in the transfer of methyl group	↓ Plasma or altered B_{12} metabolism from zidovudine, bile acid sequestrants, H_2 receptor antagonists, proton pump inhibitors, metformin, nitrous oxide
Vitamin C	Participates in redox reactions with glutathione, tocopherol, flavanoid, iron, copper; ↑ iron absorption	↓ Vitamin C cellular transport from proton pump inhibitors; ↑ vitamin C excretion from aspirin; vitamin C ↑ excretion of aspirin and acetaminophen but ↓ activity of β blocker, protease inhibitors, warfarin, and chemotherapy drugs that generate free

Micronutrient	Nutrient–nutrient interaction	Nutrient–drug Interaction
		radicals (eg, cyclophosphamide, chlorambucil, carmustine, busulfan, thiotepa, and doxorubicin)
Pantothenic acid (vitamin B_5)	Potential to compete with B_7 for intestinal and cellular uptake due to their similar structures	Not available
Biotin (vitamin B_7)	May compete with B_5 for intestinal and cellular uptake due to their similar structures. Avidin (a protein in raw egg white) binds biotin.	Not available
Choline	Interacts closely with folate and B_{12} metabolism in the transfer of methyl group	Choline need may ↑ from methotrexate limiting methyl groups donation from folate derivatives

[a] Insufficient data in some cells. Clinically significant adverse effects from these interactions are poorly defined in many instances. However, clinically significant adverse effects are more likely from certain medications in the presence of marginal nutrition status or excess use of selected water-soluble essential micronutrients. Chronic alcohol or tobacco use will exacerbate any clinical adverse effects.

The initial treatment may require an amount of micronutrient that is 10 to 100 times greater or more than the daily requirement. The administration route should ensure delivery to the tissues. For example, parenteral or intranasal delivery (rather than oral) should be used during a significant malabsorption state. Correcting the underlying cause (if possible) is warranted, as is continued monitoring for a clinical response and normalization of laboratory parameters.

Direct supplement of the deficient WSV to the breastfed infant (and to the mother if appropriate) is most appropriate because maternal

micronutrient supplementation has a variable effect on the human milk content.[34] Fortification of selected nutrients (eg, adding folic acid to the diet) effectively improves folate status of the population.

Managing the ongoing shortage of various components, in particular micronutrients, for PN is difficult. Unfortunately, adult products are not interchangeable with pediatric preparations because of different requirements and greater quantities of toxic excipients in adult preparations.[35] In the extreme situation when an individual parenteral vitamin is used, daily administration of thiamin, ascorbic acid, pyridoxine, and folic acid (along with less frequent administration of vitamins K and B_{12}) is recommended.[36] Other vitamins may be needed depending on the underlying reason for total PN as well as total PN duration. Closely monitoring patients who require total PN is critical, particularly for those with abnormal gastrointestinal losses, organ failure, or preexisting nutrient deficiency.

Supplementation and Toxicity

No evidence exists for adverse effects from the consumption of naturally occurring water-soluble nutrients in foods, presumably in part because of lowered fractional absorption at high intakes and concomitant increase in urinary excretion. Ingesting multi-nutrient supplements to provide a similar intake to daily needs has no documented long-term benefit but is unlikely to result in any long-term side effects. Children at risk for WSV deficiencies may benefit from supplemental multivitamin preparations providing 50% to 100% of the RDA with minimal risks.[3]

The number of vitamins and minerals varies widely in commercial multivitamins/minerals (MVMs) preparations. Liquid preparations for children tend to have fewer micronutrients than adult tablets. One report on MVMs for children shows 59% of 281 products provide >50% of the daily age-appropriate requirement in at least one nutrient, most frequently vitamin D. The same study reports 49% of 197 products exceed the UL in at least one nutrient, notably folic acid, vitamin A, and/or zinc. Most MVMs contain many of the 16 vitamins and minerals identified in national surveys as already abundant in children's diets.[36] Findings for prenatal MVMs are

similar, although fewer products provide potentially excess quantities.[37] Some supplements, particularly those from natural sources such as oyster shells, may be contaminated by heavy metals including lead.[38] Because the manufacturing of dietary supplements is not well regulated, accurately determining the content of intended nutrients and the extent of toxic contaminants will require legislation and independent third-party testing.

A multiple-micronutrient prenatal supplement, including at least iron and folic acid, probably provides some overall benefits to mothers' disease burden and pregnancy outcomes while preventing noncommunicable diseases in the next generation.[17,18] The transgenerational effect is probably mediated via epigenetic effects.[39] However, supplement use does not compensate for poor food choices and inadequate diet.[1–3,11]

Energy drinks and vitamin-water products contain variable—and possibly extremely high—amounts of WSVs. For example, a 2-oz energy shot has an excess of the daily requirement by 2000% for vitamin B_6 and >8000% for vitamin B_{12}.[3] This degree of intake can lead to clinically adverse effects due to nutrient–nutrient and drug–nutrient interactions. This is especially true in the case of an underlying metabolic disorder that enhances or interferes with the action of a specific nutrient or drug (see Table 7-4). Understanding is limited regarding the biochemical and genetic mechanisms whereby impaired metabolism of these essential micronutrients increases the risk for developmental anomalies and disease. Similarly, understanding of the mechanisms whereby elevated intake of these nutrients protects against these pathologies is also limited. Current initiatives to increase the intake of some essential nutrients, such as folic acid in human populations to ameliorate developmental anomalies and prevent disease,[17,41] while effective, lack predictive value for unintended adverse outcomes.

Clinical side effects from the therapeutic use of some WSVs (eg, niacin for hyperlipidemia) are well known. However, systematic studies of excessive intake of some WSVs for prolonged periods are extremely limited.[1–3] The absence of reported adverse effects does not negate the possibility that negative outcomes may arise from extended periods of high

intake. Nevertheless, sufficient data are available to set the UL of intake for niacin, vitamin B_6, folate, vitamin C, and choline (see Table 7-2).

Thiamin (Vitamin B_1)

Biochemistry and Physiology

Chemically, thiamin consists of substituted pyrimidine and thiazole rings linked by a methylene bridge. Thiamin exists mainly in various interconvertible phosphorylated forms: thiamin monophosphate, thiamin triphosphate, and approximately 80% as thiamin pyrophosphate (TPP). TPP, the coenzyme form of thiamin, is involved in 2 main types of metabolic reactions: decarboxylation of α-keto acids (eg, pyruvate, α-ketoglutarate, branch-chain keto acids) and transketolation (eg, among hexose, pentose phosphates).

Thiamin requirement increases as carbohydrate intake increases. Thiamin is critical to the metabolism of carbohydrates and branched-chain amino acids and the synthesis of neurotransmitters glutamate and γ-amino butyric acid, nicotinamide adenine dinucleotide phosphate (NADPH), and the pentose sugars deoxyribose and ribose.[1,6,19] TPP is also present in nerve membranes and activates a chloride channel for nerve conduction. Some of the newer lipid-soluble derivatives of thiamin may have effects on additional signaling pathways.[41]

Sources

Thiamin in the diet includes free thiamin, phosphorylated thiamin, and protein-phosphate complexes. Dietary sources[4,5,42] include whole grain rice, pasta and cereals, pork, eggs, yeast, legumes, and nuts. Thiamin is lost during the processing of wheat flour into white flour, during the milling of brown rice, and especially during cooking, particularly when boiling for an extended period.

Breads and cereals can have added thiamin. Dairy products and most fruits contain little thiamin. Thiamin content in human milk is reported to be 0.14 to 0.21 mg/L and is dependent on maternal diet.[34,42] Both thiamin and TPP can be synthesized by microbiota. However, the ability to meet the

nutritional needs for thiamin from bacteria synthesis is not well defined. Thiamin in fortified foods and pharmaceutical preparations is usually chemically synthesized as thiamin salts: thiamin hydrochloride and thiamin mononitrate. Biofortification through breeding and genetic engineering of plants is not yet commercially cost-effective. Thiamin supplements are available in oral and injectable forms as thiamin salts or as part of multivitamin preparations. Lipid-soluble thiamin derivatives are also available over the counter and are better absorbed at higher intakes.[41]

Absorption, Metabolism, and Excretion

Phosphorylated thiamin is hydrolyzed by intestinal phosphatases and absorbed mainly at the jejunum. Thiamin uptake by the small intestine and by cells within various organs is mediated by saturable, high-affinity transporters encoded by the solute carrier (SLC) gene family.[43,44] Thiamin transporters are upregulated in thiamin deficiency. At high intake, absorption can occur by passive diffusion. Thiamin and TPP produced from microbiota in the large intestine are absorbed through colonocytes using a similar mechanism to that employed in the small intestine.

Thiamin is transported by blood in both erythrocytes (~80%) and plasma. Nonphosphorylated thiamin is weakly bound to plasma proteins. Free thiamin is phosphorated to TPP by a specific cytosolic thiamin pyrophosphokinase[45] and requires magnesium and adenosine triphosphate. The liver appears to be the major organ for phosphorylation of thiamin, although it can occur in all tissues. Transport of metabolic active TPP into mitochondria is also mediated via the SLC genes.[6,43,44] Thiamin reuptake occurs in proximal tubule and excess is excreted. It is also excreted in feces, sweat, and human milk.

After an oral dose of thiamin, peak urine excretion occurs in about 2 hours and is nearly complete after 4 to 6 hours. The biological half-life of the vitamin, however, is much longer, estimated to be between 9 and 18 days. The total thiamin content in adults is estimated to be approximately 30 mg.

Deficiency State

Thiamin deficiency can occur with inadequate intake, particularly during PN, without added WSVs,[46] and from impaired absorption, defective vitamin transport, and excessive loss from other causes.[6,33,42,43] It can also occur as part of the refeeding syndrome in malnourished patients receiving rapid and excessive replacement of calories.[47] Multiple drugs (eg, metformin, 5-fluorouracil, and Janus kinase 2 inhibitors) can disrupt thiamin absorption, excretion, and metabolism, ultimately contributing to a deficiency state.

Antithiamin factors can be heat labile (thiaminases) or heat stable (thiamin antagonists). Regular consumption of several food products containing antithiamin factors has been implicated in thiamin deficiency.[42] Antithiamin factors such as thiaminases are heat-labile enzymes that cleave thiamin and render it inactive. They are found in certain raw and fermented fish, shellfish, ferns, and some bacteria species. Antithiamin factors such as thiamin antagonists are heat stable and block absorption of thiamin. They include phenolic compounds and methylxanthines, and are found in some foods such as blueberries, betel nuts, coffee, and tea. They react with thiamin to yield the nonabsorbable thiamin disulfide. The destructive process of thiamin antagonists can be prevented by ascorbic acid and other acidifying agents present in many vegetables and fruits. It can also be prevented by increasing the interval between ingestion of thiamin and anti-thiamin factors. Thiamin decomposition is also accelerated by food and drink preservatives (eg, sulfites, bisulfites) and ions (eg, chlorine, copper) in drinking water.

Severe depletion may occur in under 3 weeks from a strict thiamin-deficient diet, but the most common cause of thiamin deficiency in affluent countries is alcoholism.[1,6,19,42] Alcohol abuse often leads to essential nutrient deficiencies. While poor dietary intake may partially explain this, it can also result from reduced intestinal absorption and transport partly from the inhibition of SLC family transporter proteins, along with decreased thiamin phosphorylation. Patients with end-stage organ failure (especially liver) are at risk for deficiency of thiamin and multiple nutrients.

The classic clinical syndromes associated with thiamin deficiency include beriberi and Wernicke's encephalopathy. Beriberi is traditionally

classified as a “dry” or “wet” form. Dry beriberi is characterized by a symmetrical peripheral neuropathy with progressive weakness, muscle wasting, difficulty walking, and ataxia, and is accompanied by paresthesia and loss of deep tendon reflex. Wet beriberi is secondary to cardiomyopathic congestive cardiac failure and edema. Infantile beriberi is characterized by shock in a breastfed infant at 2 to 3 months of age, with or without a preceding history of a weak cry and poor feeding.

In exclusively breastfed infants, thiamin deficiency generally occurs when the mother has subclinical thiamin deficiency from factors such as poor diet, food preparation, and cooking practices. Additional food restrictions of some postpartum mothers may precipitate symptomatic thiamin deficiency in their infants.[48–50] Wernicke’s encephalopathy is characterized by altered consciousness as well as the triad of ophthalmoplegia, nystagmus, and ataxia. It is generally seen in adults with alcohol abuse and weight loss, although it has been reported in infants and children.

A manufacturing error that omitted thiamin fortification in soy infant formula resulted in thiamin deficiency in infants between the ages of 2 and 12 months. Initial manifestations were nonspecific and included the following:

- vomiting
- lethargy
- irritability
- abdominal distention
- diarrhea
- respiratory symptoms
- developmental delay
- malnutrition

Respiratory and gastrointestinal infections were noted in many of the reported cases. Classic manifestation of ophthalmoplegia or death also occurred in several infants.[51–53]

Negative outcomes have been reported during shortages of intravenous multivitamin preparation. Severe lactic acidosis leading to death in some cases can occur in children and adults requiring total PN. Additionally,

adults requiring total PN can develop clinical manifestations of beriberi or Wernicke's encephalopathy.[46] The onset of clinical manifestation begins within weeks, but clinical recovery has been noted within days after the provision of parenteral thiamin.

Laboratory investigations show abnormal magnetic resonance imaging at the frontal lobes, basal ganglia, periaqueductal region, thalami, and mammillary bodies, while magnetic resonance spectroscopy demonstrates a characteristic lactate peak.[53] Biochemical diagnosis of thiamin deficiency is by low TPP in erythrocyte and whole blood[54] or by the transketolase activation test.[55] The latter measures the whole blood or erythrocyte transketolase activity at baseline, which is increased after TPP is added if the individual is deficient.

For simple deficiency states, acute symptomatic improvement occurs rapidly within 1 day of treatment.[51] However, neurodevelopmental delay, particularly in receptive and expressive language,[56] and recurrent seizures[57] have been noted at up to 6 years of follow-up.

The number of cases reported for IEM for thiamin with varying morbidity and mortality is increasing.[33,43,58,59] Some patients with an autosomal recessive defect in the folate-thiamin transporter SLC family[43] experience a clinical triad of diabetes mellitus, sensorineural deafness, and thiamin-responsive megaloblastic anemia with ringed sideroblasts. Some of these patients may show clinical improvement with pharmacologic doses of thiamin. Another mutation in the SLC19A3 gene is associated with basal ganglia disease. It has variable onset from the neonatal period to adulthood and includes seizures, ataxia, dystonia, and dysphagia. Patients with this mutation show partial or complete improvement within days of biotin and thiamin administration.[58]

Supplementation

Thiamin supplementation is part of the treatment for refeeding syndrome and may be given prophylactically in malabsorption disorders. High-dose supplementation can result in interactions with chemotherapy agents or other high-dose vitamins.[1,6,60] Anaphylactic reaction with parenteral administration of thiamin has occasionally been reported, but toxic effects

of thiamin excess have not been studied systematically. The use of thiamin in the treatment of neurological disorders such as Parkinson's disease, Freidrich's ataxia, and multiple sclerosis remains ill-defined.

Riboflavin (Vitamin B_2)

Biochemistry and Physiology

Riboflavin (7, 8-dimethyl-10-ribityl-isoalloxazine) is a water-soluble, yellow, fluorescent compound. The primary form of riboflavin is an integral component of the coenzymes flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), the predominant flavoenzyme in body tissues. These coenzymes are involved in multiple oxidation-reduction reactions integral to carbohydrate, protein, and fat metabolism and are involved in the metabolism of folate, pyridoxine, and niacin. Riboflavin-binding proteins expressed in fetuses of different species are essential to normal fetal development.

Sources

Over 90% of dietary riboflavin comes from food proteins bound to FAD and FMN. The remaining percentage comes from free vitamins and traces of glycosides and esters. Animal protein (ie, meat, dairy, eggs) as well as green vegetables and fortified cereals are abundant sources.[4,5] Riboflavin may be synthesized by colonic bacteria, but the extent of its contribution to human needs is not known. Biofortification of food during fermentation is also possible.[61]

Absorption, Metabolism, and Excretion

FAD and FMN from dietary protein are released by gastric acid digestion. They are then hydrolyzed to riboflavin by nonspecific pyrophosphatases and phosphatases in the upper small intestine. Riboflavin absorption is relatively poor compared to other WSVs but increases when ingested along with other foods and in the presence of bile salts. Some divalent cations (eg, copper, zinc, iron, manganese) form chelates with riboflavin, lowering its absorption. Most absorption occurs in the small intestine via an active or facilitated transport system from the SLC gene family at low intakes and

passive diffusion at high intakes. A small amount is absorbed in the large intestine, where endogenous synthesis of riboflavin occurs. A small component of enterohepatic circulation also exists.

Riboflavin is transported in the circulation bound to albumin and immunoglobulins. It is phosphorylated to FMN and FAD in most tissues, particularly in the small intestine, liver, kidney, and heart. Intracellular phosphorylation is regulated by thyroid hormone, and production of FAD is under negative feedback control. The metabolism of riboflavin is affected by some medications (see Table 7-4). The body stores very little riboflavin. Excess riboflavin is mainly excreted in urine through both glomerular filtration and active tubular secretion, primarily as riboflavin (around 60%–70%) as well as various related products.

Riboflavin is more heat stable than thiamin, but it is very photosensitive. It increases the photooxidation of amino acids.[6,14] Protection of PN infusate used for preterm infants is recommended to minimize the negative effect of photooxidation of multiple nutrient components in PN.[15]

Deficiency State

A latent subclinical riboflavin deficiency can result in a significant clinical phenotype when combined with inborn genetic disturbances or environmental and physiological factors such as infections, exercise, diet, aging, and pregnancy.[62]

Riboflavin deficiency is often accompanied by deficiencies of one or more of the other B vitamins, in part because of its role in the metabolism of niacin, pyridoxine, and folate. Chronically limited dietary meat or dairy intake (including infants after weaning) is a specific risk factor for riboflavin deficiency. Riboflavin deficiency is also found in protein energy malnutrition states, such as kwashiorkor and anorexia nervosa, and in patients with other risk factors such as malabsorptive states that are common to all water-soluble micronutrients. Nucleoside analogues have been associated with riboflavin deficiency and manifest as lactic acidosis responsive to riboflavin therapy.[63]

Symptoms and signs of a mild deficiency state can be nonspecific. The more characteristic features of a severe deficiency state of ariboflavinosis include the following: pharyngitis; cheilosis; angular stomatitis; glossitis

(magenta tongue); seborrheic dermatitis involving the nasolabial folds, the flexural area of extremities, and the genital areas; and possibly lactic acidosis.[27,28,62,64]

Riboflavin deficiency is diagnosed by low erythrocyte riboflavin quantified by high-performance liquid chromatography and low 24-hour urinary excretion of riboflavin. The erythrocyte glutathione reductase activity coefficient (stimulated in vitro with FAD in a lab setting), is used to assess riboflavin status. Increases above 40% indicate deficiency while those between 20% and 40% indicate low status. Increases below 20% indicate acceptable riboflavin status. Biochemical deficiency has been reported in infants receiving short-term phototherapy.[14]

Supplementation

Excess riboflavin turns urine yellow, although no functional or structural adverse effects have been demonstrated in vivo after excess riboflavin intake. This is in part because of the limited absorption of ingested riboflavin. In theory, excess riboflavin could heighten sensitivity to UV radiation, potentially intensifying the light-induced oxidation of amino acids and proteins in newborns undergoing phototherapy for hyperbilirubinemia. Riboflavin supplementation in pharmacologic doses is a viable therapeutic option for several IEM, either by compensating for transport or synthesis of flavin cofactors or by improving the folding or stability of flavoproteins. Limited systematic studies in humans have reported the efficacy of riboflavin, either in pharmacological doses or as part of combination therapy in treating various clinical conditions, including a mild form of multiple acyl-coenzyme A dehydrogenase deficiency, genetic neuropathies from deficient riboflavin transporters, and several other clinical conditions.[6,62,64,65]

Niacin (Vitamin B_3)

Biochemistry and Physiology

Niacin refers to nicotinamide (nicotinic acid amide), nicotinic acid (pyridine-3-carboxylic acid), and derivatives that exhibit the biological activity of nicotinamide. None of the forms are related to the nicotine found

in tobacco although their names are similar. The two major forms of niacin are chemically modified in the mitochondria to form coenzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP).

About 200 enzymes require NAD and NADP, mainly to accept or donate electrons in the energy-producing oxidation-reduction (redox) reactions. NAD functions most often in energy-producing reactions during degradation (catabolism) of carbohydrate, fat, protein, and alcohol. NADP and its reduced form (NADPH) function in biosynthetic (anabolic) reactions, such as in the synthesis of macromolecules including fatty acids, cholesterol, bile acid, steroids and glyconeogenesis. Nonredox enzymatic reactions important to DNA repair and stress responses, cell signaling, transcription, regulation of apoptosis, chromatin structure, and cell differentiation require separation of the niacin moiety from NAD and integration of ADP-ribose in these functions.[1,6,66,67]

Sources

Good sources of niacin include liver, meats, poultry, red fish (eg, tuna, salmon), yeast, cereals, legumes, and seeds. In corn and wheat, niacin may be bound to sugar molecules as glycosides, which significantly decrease niacin bioavailability. Dairy products and green leafy vegetables have lesser amounts of niacin.

Niacin in both forms (nicotinic acid and nicotinamide) is the most stable water-soluble vitamin, and it is normally highly resistant to atmospheric oxygen, acids, heat, and light in both aqueous and solid systems. Processing, especially milling, decreases the niacin content although roasting of green coffee beans and sweet corn releases niacin from its precursors.[68] Bread, cereal, and pasta are often fortified with niacin although the bioavailability of esterified bound forms of niacin may vary.

Endogenous synthesis of nicotinamide in the liver and kidney from tryptophan is possible in the presence of adequate amounts of riboflavin, pyridoxine, and iron. Dairy products and eggs are good sources of tryptophan. However, tryptophan is also used for protein synthesis, which takes priority over NAD and NADP synthesis. An estimated average of 60

mg of tryptophan produces 1 mg of niacin or niacin equivalent. Dietary intake of niacin is needed to meet the daily requirements.

Absorption, Metabolism, and Excretion

Nicotinic acid and nicotinamide are absorbed from the stomach and the intestine by simple diffusion and by sodium-dependent facilitated transport (at low niacin concentrations). The transport of nicotinic acid and nicotinamide across erythrocytes and other cells is based on the same mechanisms. Nicotinamide released by intestinal glycohydrolases and during many biochemical reactions involving NAD is reutilized, together with nicotinic acid, for the synthesis of the coenzymes NAD and NADP. NADP synthesis depends on the availability of NAD, and NADPH (the reduced form of NADP) synthesis depends on the availability of NADH.[6,67]

Tissue stores of niacin are either in the form of NAD that is not bound to enzymes or as nicotinamide adenine mononucleotide synthesized from tryptophan and nicotinic acid. Hepatic NAD is hydrolyzed to provide nicotinamide for tissues that cannot synthesize nicotinamide from tryptophan. Excess niacin is methylated in the liver to N_1-methyl-nicotinamide and excreted in the urine either unchanged or as its 2-pyridone derivative. At very high intakes of niacin, some unmetabolized niacin may be excreted in the urine.

Deficiency State

Several conditions uniquely predispose to niacin deficiency. These include carcinoid syndrome in which tryptophan is preferentially oxidized to 5-hydroxytryptophan and serotonin; prolonged treatment with isoniazid, 5-fluorouracil, or 6-mercaptopurine, which competes with the pyridoxine-derived coenzyme required in the tryptophan-niacin pathway; and Hartnup's disease, an autosomal recessive disorder that interferes with the absorption of the neutral amino acid, tryptophan. A deficient state has also been reported with alcoholism and chronic medication use.[69]

The classic manifestation of severe niacin deficiency is pellagra, an Italian term meaning "rough skin." It is characterized by the triad of diarrhea, dermatitis, and dementia.[70] Gastrointestinal manifestations include glossitis, angular stomatitis, chelitis, and diarrhea in about 50% of patients.

Skin lesions begin as painful erythema in sun-exposed areas. Vesicle or bullae formation may occur with reexposure to the sun, and the skin eventually becomes rough, hard, and scaly. Hair and nails tend to be spared.[27,28] Neuropsychiatric manifestations include insomnia, fatigue, nervousness, irritability, apathy, and memory impairment. Dementia and death may occur in untreated cases.[66]

Niacin status is determined by the erythrocyte concentration of NAD relative to NADP. Deficiency exists when the "niacin number" (NAD/NADP × 100) is <130. Additionally, a 24-hour urine sample will contain small amounts of niacin, its metabolite N_1-methyl-nicotinamide, and another niacin derivative, 2-pyridone.

Supplementation

Niacin as a supplement or pharmacologic agent used primarily in the treatment of hyperlipidemia can result in clinical side effects. Both forms of niacin may result in similar side effects, although nicotinamide results in less vasodilatory effects. High-dose niacin, as seen in energy drinks and energy shots, also causes flushing. Nicotinic acid as low as 30 mg/d is associated with vasodilatory effects including flushing, burning, tingling, an itching sensation, and gastrointestinal effects of nausea and vomiting. Some improvement may occur with a gradual increase in dosage, co-ingestion of food, or the slow-release form of the supplement. Liver dysfunction is more common with the slow-release form. At high intakes of niacin, fulminant hepatitis and encephalopathy, glucose intolerance, and ocular effects of blurred vision, toxic amblyopia, macular edema, and cystic maculopathy also may occur. Other potential pharmacological actions, such as those involving signaling pathways, aging, and cancer are not well defined.[1,6,60,71]

Vitamin B_6

Biochemistry and Physiology

Vitamin B_6 comprises a group of 6 related compounds: Pyridoxal (PL), pyridoxine (Pn), pyridoxamine (PM), and their respective 5′-phosphates

(PLP, PnP, and PMP). The major forms in animal tissues are PLP and PMP; the forms in plant-derived foods are primarily Pn and PnP, sometimes in the form of a glucoside.

PLP is a coenzyme for a multitude of enzymes involved in amino acid metabolism, including aminotransferases, decarboxylases, racemases, and dehydratases. It is required for the conversion of tryptophan to both niacin and the neurotransmitter serotonin, homocysteine to cysteine, and dopa to dopamine. It is also needed for the synthesis of the inhibitory neurotransmitter γ-aminobutyric acid. Pyridoxine is a coenzyme for δ-aminolevulinate synthase, the rate-limiting first step in heme synthesis.

Sources

Foods rich in pyridoxine include fruits and nuts (bananas, cantaloupe, walnuts), plants (green leafy vegetables, broccoli, peas, carrots, rice husks, brown rice, maize, wheat germ, yeast), and animal products (eggs, chicken, fish, beef), as well as fortified cereals. Microbial synthesis of vitamin B_6 is possible, but the extent to which it contributes to the physiological need is not known.

Absorption, Metabolism, and Excretion

Bioavailability of vitamin B_6 in a mixed diet is approximately 75% after intestinal phosphatase-mediated hydrolysis of PLP and PMP to nonphosphorylated B_6. Absorption occurs primarily at the jejunum and ileum by a nonsaturable passive diffusion transport. Pyridoxine glucoside is absorbed after deconjugation by a mucosal glucosidase, and some is absorbed intact and then hydrolyzed in various tissues. The unphosphorylated forms of B_6 absorbed are converted to 5′-phosphate forms by pyridoxal kinase, primarily in the liver. PnP and PMP are oxidized to PLP by PnP oxidase. PMP is also generated from PLP via aminotransferase reactions. PLP is bound to various proteins in tissues, which protects it from the action of phosphatases. Muscle, plasma, and erythrocytes (hemoglobin) have high capacities for PLP-protein binding. Albumin is the major PLP-binding protein in plasma.

When the capacity for protein binding is exceeded, free PLP is rapidly hydrolyzed, and nonphosphorylated forms of B_6 are released. Free PLP in

the circulation is also dephosphorylated and then reabsorbed or carried in the erythrocyte. Vitamin B_6 is found in various subcellular compartments but primarily in the mitochondria and cytosol.

In humans, the major excretory form is 4-pyridoxic acid, which accounts for about half of the B_6 compounds in the urine. At high doses of pyridoxine, much of the dose is excreted unchanged. The body's B_6 content is estimated to be about 167 mg based on muscle biopsy data, and the assumption is that muscle represents about 80% of the store. The overall half-life of vitamin B_6 is about 25 days, but its muscle turnover for B_6 is much slower.[72,73]

Deficiency State

An isolated deficiency of pyridoxine is rare because its metabolism is intimately involved with multiple other nutrients including riboflavin, niacin, zinc, and folate. Lower plasma PLP may result from PLP binding to certain drugs: isoniazid, hydralazine, oral contraceptives, penicillamine, cycloserine, theophylline, and L-dopa (which reacts with the PLP's carbonyl group). Acetaldehyde, but not ethanol, decreases net PLP formation and may compete with PLP for protein binding. However, the extent to which these situations increase B_6 requirements is not known. Vitamin B_6 status is inversely associated with markers of inflammation, oxidative stress, and chronic inflammatory conditions, but the cause-and-effect relationship remains ill-defined. Multiple autosomal recessive mutations in several genes that increase degradation of Pn (a deficiency of α-aminoadipic semialdolase dehydrogenase [antiquitin] encoded by the ALDH7A1 gene) or decrease the production of PLP (a deficiency of pyridox(am)ine 5′-phosphate oxidase by the PNPO gene) result in deficiency of the respective vitamin B_6.

Clinical manifestations of a B_6-deficient state include seizures in infants (ie, those who are fed milk formulas without pyridoxine fortification due to manufacturing errors)[74,75] and abnormal electroencephalograms in adults (from experimental B_6 deficiency).[76] Reintroducing B_6 reverses symptoms and signs of deficiency. Intractable neonatal or infantile seizure unresponsive to standard therapy should raise concern for the presence of

IEM in vitamin B_6. They can be categorized as pyridoxine-dependent, pyridoxine-responsive, and pyridoxal phosphate–responsive conditions, depending on the type of mutation and whether partial or complete expression of the gene mutation occurs. Plasma and cerebrospinal fluid samples should be collected for diagnostic testing before and after empiric therapy using Pn and adding PLP if unresponsive to Pn.[77] Oral folinic acid (vitamin B_9) may be needed to improve the response to Pn. Simultaneous administration of Pn, PLP, and folinic acid may be needed before definitive biochemical and genetic diagnosis. Other clinical manifestations of B_6 deficiency are nonspecific and may include microcytic anemia, glossitis, seborrheic dermatitis, and depression.

Plasma PLP is probably the best indicator of B_6 status because it appears to reflect tissue stores.[72] Erythrocyte aspartate and alanine aminotransferase activity with or without PLP or tryptophan are also useful indicators of relative B_6 status. Other biochemical markers and genetic testing may be needed with IEM for vitamin B_6.[77]

Supplementation

Pyridoxine has been used as an emergency antidote for isoniazid and hydralazine overdose, as well as for ethylene glycol and gyromitrin mushroom poisoning.[78,79] The UL for vitamin B_6 is set at 80 mg daily;[1] peripheral sensory neuropathy may result from high-dose pyridoxine supplementation at 2 to 6 g daily for 2 to 40 months[80] or chronic intake at doses <500 mg/d.[81] The latter may improve slowly upon withdrawal of the supplement. The combination of high doses of vitamin B_6 with vitamin B_{12} may result in a severe rosacea fulminans.[27,28,60,82]

Folate (Vitamin B_9)

Biochemistry and Physiology

Folate is a generic term for this water-soluble B-complex vitamin. Most naturally occurring food folates are pteroyl glutamates containing 1 to 6 glutamate molecules joined in a peptide linkage to the γ-carboxyl of

glutamate. Folinic acid (5-formyl tetrahydrofolate) is found in foods. Folic acid (pteroylmonoglutamic acid) is the most oxidized and stable form of folate. It consists of a p-aminobenzoic acid molecule linked at one end to a pteridine ring and at the other end to a glutamic acid molecule. It occurs rarely in food but is the synthetic form used in vitamin supplements and fortified food products.

Folate is critical to the metabolism of nucleic and amino acids. It promotes cellular growth in general and is necessary for erythrocyte maturation. Folate is a substrate (5-methyl-tetrahydrofolate), and vitamin B_{12} is a coenzyme in the formation of 5,10-methylenetetrahydrofolate (MTHF) and thymidylate synthesis. In either folate or vitamin B_{12} deficiency, the megaloblastic changes in bone marrow and other replicating cells result from a lack of MTHF. Folate and vitamin B_{12} deficiency are independent risk factors for neural tube defects including anencephaly and spina bifida. Folic acid is the only WSV mandated as part of prenatal supplements for the prevention of neural tube defects.

Sources

Natural sources of folate include fresh green vegetables, liver, yeast, cereals, egg yolk, and citrus fruits. In 1998, the U.S. Food and Drug Administration mandated the addition of folic acid to all enriched breads, cereals, flours, corn meal, pasta products, rice, and other cereal grain products sold in the United States. Biofortification of food during fermentation is also possible.[61]

Absorption, Metabolism, and Excretion

Dietary folate equivalent has approximately 50% lower bioavailability compared with folic acid supplement. Food folates (polyglutamate derivatives) are hydrolyzed by conjugase enzymes to monoglutamate forms and then enter various cells by membrane carrier or folate-binding protein-mediated system. The folate transporter derives from the SLC19 gene family of solute carriers and shares structural homology with the thiamin transporter.[43,83] Monoglutamates, mainly 5-methyl-tetrahydrofolate, are metabolized in the liver and other tissues to polyglutamate derivatives by the enzyme folylpolyglutamate synthetase. Polyglutamates are the forms

retained in various tissues or found in blood or bile and are the forms needed for function as a coenzyme in single-carbon transfer reactions.

Folate catabolism involves the cleavage of intracellular and circulatory polyglutamates to the monoglutamate form. Approximately two-thirds of the folate in plasma is protein-bound, and albumin accounts for approximately 50% of the bound folate. Folates filter freely through the glomeruli and are secreted and reabsorbed by the renal tubules. The bulk of the urine excretory products are folate cleavage products, mainly in the monoglutamate form. Extensive enterohepatic circulation of folate occurs.[84] The estimated total body folate content is between 12 and 28 mg, of which approximately 50% is in the liver.

Deficiency State

In the normal population, about 60% of children consume fewer fruits than recommended, and 93% of children consume fewer vegetables than recommended.[11] This generally lower intake of vegetables and fruits contributes to the potentially inadequate intake of folate. Cooking, particularly boiling, destroys large amounts of folate.

Some patients are predisposed to folate deficiency and require monitoring of folate status. Such patients include those with malabsorptive states and those receiving the following drugs:

- folate antagonists such as methotrexate
- drugs with antifolate activity, including pyrimethamine, trimethoprim, triamterene, trimetrexate, sulfasalazine, anticonvulsants (phenobarbital, phenytoin)
- large doses of nonsteroidal anti-inflammatory medications

Several inborn errors in folate metabolism predispose affected individuals to folate deficiency, including the following:

- MTHF reductase deficiency associated with mutations of alleles on chromosome 1[33,83,85,86]
- folate transport defects to the central nervous system
- autoantibody to folate receptor and other folate transport defects to the central nervous system (cerebral folate deficiency)

With cerebral folate deficiency,[33,83,87] serum folate is normal but cerebral spinal fluid 5MTHF is low. Folinic acid treatment normalizes 5MTHF levels.[87]

Clinical features of folate deficiency may begin during infancy and include the following:

- delayed psychomotor development
- poor social interaction
- decelerating head growth
- hypotonia
- ataxia
- dyskinesia
- irritability
- visual and hearing deficiency
- seizures.

Some neurological manifestations may be reversible with folinic acid supplement. Megaloblastic anemia is the primary sign of deficiency. Anemia onset is usually gradual, and clinical manifestations typically appear at advanced stages of anemia.

Deficiency states are confirmed with low red cell folate, which reflects tissue folate stores. Plasma folate reflects concurrent folate balance. Plasma total homocysteine concentrations increase when folate status is inadequate to convert homocysteine to methionine. Significantly improved folate status, indicated by population survey of red cell and serum folate, has been reported since the mandate for folic acid fortification of selected foods.

Supplementation

Taking folate supplements in the preconception period and during pregnancy (for the prevention of neural tube defects) is an established practice.[40] Excessive folate intake may precipitate or exacerbate neuropathy in individuals with vitamin B_{12} deficiency. Folate supplementation has been implicated in delayed diagnosis of pernicious anemia until after irreversible neurological damage has occurred.[83,86] These risks are increased in cases of reduced hepatic transformation of folic acid (eg, caused by genetic variants or during some pharmacotherapies). 5-MTHF may be a better alternative to

folic acid supplementation because it is immediately available as a methyl donor in many metabolic reactions. Additionally, it does not accumulate in blood like folic acid does in cases of reduced hepatic transformation. However, the use of 5-MTHF instead of folate supplement under various clinical conditions remains to be determined.[86]

Vitamin B_{12} (Cobalamin)

Biochemistry and Physiology

The term vitamin B_{12} is usually restricted to cyanocobalamin but can be used to refer to all potentially biologically active cobalamins, a group of cobalt-containing compounds (corrinoids) that contain the sugar ribose, phosphate, and a base (5,6-dimethyl benzimidazole) attached to the corrin ring. Bioavailable cobalamine requires 2 enzymatic conversions (via methionine synthase and methylmalonyl-CoA-mutase) into cofactor forms methylcobalamin and adenosylcobalamin, which are both needed for human metabolism.

An adequate supply of B_{12} is essential for bone marrow, particularly the production of normal erythrocytes, and for neurological function. Vitamin B_{12} and folate balance is vital for one-carbon metabolism, which is essential for DNA methylation and the purine/pyrimidine synthesis of nucleic acids. Folate and vitamin B_{12} deficiency are independent risk factors for neural tube defects including anencephaly and spina bifida.

Sources

Cobalamin is only found in foods of animal origin. Meat, fish, poultry, cheese, milk, and eggs are good sources. Cereal and soy milk are fortified with varied amounts of vitamin B_{12}. Vitamin B_{12} content in human milk is dependent on maternal diet, and colostrum has higher content than mature milk. Cyanocobalamin is mostly used in supplements and pharmaceuticals. Other forms of cobalamin in supplements include hydroxocobalamin, adenosylcobalamin, and methylcobalamin. Vitamin B_{12} can be synthesized by intestinal bacteria, but this contribution to the body pool is not known and is likely to be limited.

Absorption, Metabolism, and Excretion

Cobalamin absorption and cellular uptake require an intact stomach, adequate transport proteins, pancreatic sufficiency, and a normally functioning terminal ileum. Haptocorrin (HC, also known as transcobalamin I), gastric intrinsic factor (IF), and transcobalamin (TC, also known as transcobalamin II) are critical to B_{12} transport from food to cell. IF and HC are glycosylated proteins, but not TC. Increasing specificity exists for binding to cobalamin in the order HC, TC, and IF.[88]

Cobalamin bound to protein in food is released by the activity of hydrochloric acid and gastric protease in the stomach. Free cobalamin then binds to IF to form a cobalamin-IF complex. When synthetic vitamin B_{12} is added to fortified foods and dietary supplements, it is already in free form and binds to salivary HC. Bioavailability of a B_{12} supplement is about 50% higher than food sources and is higher from dairy products and meat than other food sources.[89]

After proteolysis of HC in the duodenum, free cobalamin then binds to gastric parietal cell–produced IF. The cobalamin-IF complex is absorbed only in the distal ileum under physiological conditions via endocytosis mediated by cubam receptors comprised of amnionless and cubilin protein moieties on intestinal mucosal cells. Only about 1% to 2% of an oral dose can be absorbed passively. Vitamin B_{12} absorption decreases markedly when the capacity of IF is exceeded (at 1−2 mcg of vitamin B_{12}). In the enterocyte, the cobalamin-IF complex is degraded, and cobalamin is transported to the cells bound to TCs and taken up via endocytosis by a specific receptor on most cell types.[90]

Vitamin B_{12} appears in circulation several hours after ingestion. If the circulating B_{12} exceeds the B_{12}-binding capacity of the blood, the excess is excreted in the urine. About 80% of circulating B_{12} is bound to the protein transcobalamin I (TCI), and the remainder to TCII or III. TCII is the form that delivers B_{12} to the tissues (~50% taken up by the liver) through specific receptors for TCII. HC in plasma cannot facilitate cellular uptake of cobalamin, except in hepatocytes.

In the presence of IF, an active enterohepatic circulation reabsorbs almost all B_{12} secreted into the bile. Unlike other WSVs, a large store of

B_{12} exists, primarily in the liver. The average B_{12} content of the liver is approximately 1 mcg/g in healthy adults. The average total body pool of B_{12} is estimated to be 2 to 3 mg. Daily loss of B_{12} is approximately 0.1% to 0.2% of the B_{12} pool regardless of the size of the store, with the 0.2% value generally applicable to those with pernicious anemia.[91]

Deficiency State

On the basis of population, deficiency of multiple micronutrients including vitamin B_{12} is common in low-income and middle-income countries.[17] Breastfed infants of mothers following a strict vegan diet, children receiving macrobiotic diets, and elderly individuals are at risk for B_{12} deficiency as are individuals lacking an intact stomach, distal ileum, pancreatic exocrine function, or IF.[91,92]

Chronic use of proton pump inhibitors and possibly histamine receptor antagonists can lower serum B_{12} levels by inhibiting intragastric proteolysis from releasing B_{12} and inhibiting B_{12} from binding to gastric IF.[88,93] However, the risk of progression to biochemical deficiency (ie, elevated blood concentrations of homocysteine and methymalonic acid) or clinical deficiency (ie, megaloblastic anemia and neurologic disorders) remains ill defined.[22]

Vitamin B_{12} deficiency has been reported following surgical gastric bypass or ileal resection due to interference with digestion and absorption of vitamin B_{12}.[21] Maternal B_{12} deficiency from gastrointestinal surgery can secondarily affect the fetus. [94,95]

The presence of autoantibodies against parietal cell H+K+-adenosine triphosphate is another predisposition to B_{12} deficiency. These autoantibodies deplete gastric parietal cells and block the B_{12} binding site for IF. Genetic defects associated with disturbed vitamin B_{12} metabolism can lead to a deficiency state. These include deletions or defects of methylmalonic acid-CoA mutase, IF, TCII, enzymes in the pathway of cobalamin adenosyllation, and cubilin or amnionless genes involved in the intestinal handling of B_{12}.[33,88,90]

Clinical manifestations of B_{12} deficiency include the following:

- macrocytic megaloblastic anemia
- glossitis
- stomatitis
- weight loss
- neurological problems

Neurological problems include

- ataxia
- muscle weakness
- spasticity
- incontinence
- vision problems
- dementia
- psychosis
- mood disturbance

Adolescents with marginal cobalamin status have shown impaired cognitive function.[96] Infants born to mothers who were B_{12}-deficient during pregnancy are at risk of congenital anomalies, including neural tube and orofacial defects, postnatal development of involuntary movements, delayed speech development, and growth failure.[95] Vitamin B_{12} deficiency may also precipitate acute visual loss from optic atrophy in asymptomatic carriers of the mtDNA mutation for Leber hereditary optic neuropathy.[97]

Vitamin B_{12} status is commonly assessed through the measurement of serum B_{12} bound to its protein carrier and by holotranscobalamine, which represents the bioactive form of B_{12}. Functional markers indicating B_{12} deficiency include elevated levels of plasma and urine methylmalonic acid, as well as elevated plasma homocysteine. Relying solely on a single test to diagnose B_{12} deficiency is subject to potential errors. Moreover, it does not effectively differentiate between insufficient and deficient states. To mitigate the risk of misinterpreting vitamin B_{12} status, it is necessary to employ a combination of one marker indicating vitamin B_{12} status and one

functional marker, along with clinical information including family history.[91]

Supplementation

In adults and children, oral or intranasal B_{12} supplement can raise plasma B_{12} concentrations similar to what is achieved by intramuscular vitamin B_{12}.[98,99] All B_{12} preparations have been used to treat clinical B_{12} deficiency.[100] However, periodic parenteral administration of high-dose B_{12} (1–5 mg) is still needed for patients with pernicious anemia (lack of IF) or malabsorptive defects.

Energy drinks and energy shots contain vitamin B_{12} in variable amounts but can contain >8000% of the daily value.[3] Toxic reactions include anaphylaxis, urticaria, and the exacerbation of and precipitation of acneiform eruptions. High-dose vitamin B_{12} in combination with pyridoxine may cause the severe skin lesion rosacea fulminans.[27,28,60,82]

Vitamin C

Biochemistry and Physiology

Ascorbic acid is the enolic form of an α-ketolactone (2,3-didehydro-L-threo-hexano-1,4-lactone). The 2 enolic hydrogen atoms give the compound its acidic character and provide electrons for its function as a reductant and antioxidant. Vitamin C refers to both ascorbic acid and dehydroascorbic acid. Ascorbic acid is the functional and primary in vivo form of the vitamin. Ascorbate is the free reduced form of ascorbic acid. Ascorbyl radical and dehydroascorbic acid are 1-electron or 2-electron oxidation products that readily reduce back to ascorbic acid in vivo by glutathione, and NADH-dependent and NADPH-dependent reductases, thus a relatively small amount of the vitamin is lost through catabolism.

Vitamin C is known to be an electron donor for 8 human enzymes. Three enzymes participate in collagen hydroxylation, which also requires the presence of iron. These enzymes play a role in the biosynthesis of other connective tissues including elastin, fibronectin, proteoglycans, the bone matrix, and a protein called elastin-associated fibrillin. Two enzymes along

with iron are required in carnitine synthesis, and 3 enzymes, dopamine-β-hydroxylase, peptidyl-glycine monooxygenase, and 4-hydroxyphenylpyruvatedioxygenase, are required in hormone and amino acid biosynthesis.[2,7]

Vitamin C is an effective antioxidant because of its ability to donate electrons; its antioxidant effect operates both intracellularly and extracellularly in the aqueous phase. It participates in redox reactions with many other dietary and physiological compounds including glutathione, tocopherol, flavonoids, and the trace metals iron and copper. Antioxidation activities at the tissue level include protection of the eye, neutrophils, and sperm DNA, among others. In circulation, it protects against oxidation of plasma low-density lipoprotein. Ascorbate also provides antioxidant protection indirectly by regenerating other biological antioxidants such as glutathione and α-tocopherol back to their active state. Ascorbic acid acts as a reducing agent within the microsomal drug-metabolizing system, particularly for mixed-function oxidases. This action helps neutralize or deactivate various substances, including naturally occurring hormones and foreign compounds like drugs, pesticides, and carcinogens that are not normally found in the human body. Vitamin C participates in biosynthesis of corticosteroids and aldosterone as well as microsomal hydroxylation of cholesterol to bile acids. One form of hereditary methemoglobinemia is reported to be responsive to vitamin C.[101]

Sources

Vitamin C content is relatively high (10−100 mg/100 g) in various foods although it can vary with the growing condition, season, stage of maturity, cooking practice, and storage time before consumption. Almost 90% of vitamin C in the typical diet comes from fruits and vegetables. Citrus fruits, tomatoes, and tomato juice are excellent sources. Other sources include Brussels sprouts, cauliflower, broccoli, strawberries, cabbage, and spinach. Potatoes have varied ascorbic acid and total phenolic contents and antioxidant activity[102] and could be a major source of vitamin C depending on the amount consumed. Vitamin C content in fermented cabbage (sauerkraut) is even higher than in most fresh vegetables.[103] Animal sources

generally have low vitamin C content, except for livestock livers and some fresh eggs.[4,5]

Absorption, Metabolism, and Excretion

Seventy to ninety percent of the usual dietary intake of ascorbic acid is absorbed primarily in the distal ileum via a sodium-dependent saturable vitamin C transporter 1 (SVCT1), which is a member of the solute transporter SLC family. Some passive diffusion in the intestinal tract cannot be excluded. Vitamin C exists in the form of dehydroascorbic acid, which is the main form that crosses the membranes of both blood and intestinal cells. Once inside the cells, it is reduced back to its active form, ascorbic acid, mainly found in the cytosol. Intestinal absorption of vitamin C is nonlinear; bioavailability is close to 100% at a low intake but significantly decreases when intake exceeds 500 mg.[104] With large intakes of vitamin C, unabsorbed ascorbate is degraded in the intestine, which may lead to diarrhea and intestinal discomfort.

Cellular transport of ascorbic acid and dehydroascorbic acid is mediated by tissue-specific SVCT transporters that allow for a wide variation of tissue ascorbate concentrations. High concentrations are maintained in the pituitary and adrenal glands, leukocytes, eyes, and the brain, while low concentrations are found in plasma and saliva. Both intracellular and plasma vitamin C exist predominantly in the free reduced form as ascorbate monoanion. Vitamin C is actively secreted in human gastric juice. Proton pump inhibitor therapy lowers the concentration of vitamin C in gastric juice and may reduce the bioavailability of ingested vitamin C.[7]

The kidney is capable of reabsorbing ascorbate, but renal excretion of ascorbate is greater with increased intake. Aspirin may increase urinary ascorbate. Due to homeostatic regulation, the biological half-life of ascorbate varies widely from 8 to 40 days and is inversely related to the ascorbate body pool. A body pool of <300 mg is associated with scurvy, while maximum body pools are estimated to be about 2 g[2] and may be as high as 5 g.[105]

Deficiency State

In developed countries, population surveys indicate that serum vitamin C concentrations are significantly lower in individuals who smoke and those in low-income populations, presumably because of oxidative stress from smoking and low dietary consumption of foods rich in vitamin C.[105] Clinical manifestation of vitamin C deficiency is quite rare but has been reported in children with severely restricted diets related to food faddism, psychiatric or developmental problems,[106] or end-stage organ disease with severely compromised nutrition.[107] Deficiency has been reported in young children who ingest only well-cooked foods and few fruits and vegetables and who are supplemented with ultra heat-processed milk.[108] Vitamin C insufficiency may occur in patients on prolonged PN, particularly when there is a limited supply of intravenous vitamin preparations.[109]

The primary clinical manifestation of vitamin C deficiency is scurvy, which reflects deterioration of elastic tissues. Clinical features include the following:

- follicular hyperkeratosis
- petechiae
- ecchymoses
- brittle coiled hairs
- inflamed and bleeding gums
- perifollicular hemorrhages
- impaired wound healing

Refusal to walk (with or without joint effusions and arthralgia), dyspnea, edema, weakness, fatigue, depression, and Sjögren syndrome (dry eyes and mouth) may also occur. Other features may include impaired bone growth, disturbed ossification, subperiosteal hemorrhage,[7,27,28,110] and possibly pulmonary hypertension.[111] In experimental participants, the most sensitive markers of deficiency short of advanced scurvy were gingival inflammation and fatigue. Scurvy usually occurs at a plasma concentration of <0.2 mg/dL (11 μmol/L), although leukocyte ascorbate concentration might be a better measure of tissue reserve than plasma ascorbate concentration.

Supplementation

Gastrointestinal disturbances such as nausea, abdominal cramps, and diarrhea have been reported at a vitamin C intake of >3 g/d likely because of the osmotic effect of unabsorbed vitamin C. In vivo data do not clearly show a causal relationship between excess vitamin C intake by apparently healthy individuals and other adverse effects,[2] although increased urine oxalate excretion and development of oxalate stones may be possible.[112] However, individuals with hemochromatosis, glucose-6-phosphate dehydrogenase deficiency, and renal disorders may be more susceptible to adverse effects of excess vitamin C intake. Adverse effects include excess iron absorption, pro-oxidant effects, and kidney (oxalate) stone formation. Additional risks associated with excessive vitamin C intake are reduced vitamin B_{12} and copper levels, increased oxygen demand, dental enamel erosion, allergic response, and inhibited action of warfarin.[2,7]

A daily vitamin C intake of 250 mg/d or higher has been associated with false-negative occult blood test results for stool and gastric contents.[113] Therefore, individuals should discontinue high-dose vitamin C supplements before undergoing these laboratory tests. This recommendation considers vitamin C's biological half-life (~8 d) when the body's ascorbate pool is well supplied.

Pantothenic Acid (Vitamin B_5)

Biochemistry and Physiology

Pantothenic acid is a component of coenzyme A (CoA), which is involved in more than 70 enzymatic pathways. CoA exists in various forms, including acetyl-CoA and succinyl-CoA. It plays a crucial role in multiple biological processes, such as:

- tricarboxylic acid cycle
- synthesis of fatty acids
- membrane phospholipids
- amino acids
- steroid hormones
- vitamins A/D

- porphyrin/corrin rings
- neurotransmitters
- acetylation/acylation of proteins

Additionally, it contributes to the synthesis of α-tubulin.

Sources

Pantothenic acid is widely distributed in foods[4,5] and is found in high concentrations in beef, chicken, dairy products, egg yolk, fresh vegetables, yeast, whole grains, and legumes. Intestinal microflora can synthesize pantothenic acid, but this contribution has not been quantified in humans.

Absorption, Metabolism, and Excretion

CoA in the diet is hydrolyzed in the intestinal lumen to dephospho-CoA, phosphopantethine, and pantethine, with the latter subsequently hydrolyzed to pantothenic acid. When pantothenic acid intake is low, its absorption in the intestines is facilitated by a sodium-dependent multivitamin transporter, belonging to the sodium-glucose transporter family. This mechanism is saturable. At high intakes, the absorption is by passive diffusion. Pantothenic acid can also be absorbed in the colon via the same mechanisms.

Pantothenic acid is hydrolyzed to pantothenate during absorption and is transported in the free form in blood and rapidly taken up by tissues and erythrocytes. The latter probably serve as transporters because they have limited ability to metabolize pantothenate. Muscle and the liver have high pantothenate content. Tissue CoA synthesis is regulated primarily by pantothenate kinase, an enzyme inhibited by feedback from the pathway end products, CoA, and acyl-CoA. CoA is hydrolyzed to pantothenic acid in a multiple-step reaction and is excreted intact in the urine in proportion to dietary intake. Renal tubular reabsorption is possible.[1,6]

Deficiency State

Pantothenic acid deficiency is rare and may be part of multi-nutrient deficiency with severe malnutrition. Experimentally, deficiency occurs with feeding semisynthetic diets[114] or an analog vitamin Ω-methyl pantothenic

acid.[115] Clinical manifestations may be nonspecific and include the following:

- irritability
- restlessness
- fatigue
- apathy
- malaise
- sleep disturbances
- nausea, vomiting, and abdominal cramps
- numbness, paresthesia
- staggering gait
- increased sensitivity to insulin

Historically, pantothenic acid was implicated in the "burning feet" syndrome that affected prisoners of war in Asia during World War II.[116] Gene mutation of pantothenate kinase 2 is associated with neurodegeneration and dementia.[117]

No data support the use of whole blood, plasma, or red cell concentrations as a marker of deficiency state. Urinary excretion of pantothenic acid is strongly dependent on dietary pantothenic acid.[114,115]

Supplementation

No subgroups of the population are distinctly susceptible to adverse effects of excess pantothenic acid.

Biotin (Vitamin B_7)

Biochemistry and Physiology

Biotin is a cofactor for 5 mammalian carboxylases. These carboxylases are important for the metabolism of fatty acids, carbohydrate, and amino acids through the production of intermediates for the tricarboxylic acid cycle and the formation of substrates for fatty acid elongation. Biotin also has a possible role in gene regulation, cell signaling, and reproduction.[19,29,118]

Sources

Biotin is widely distributed in natural foodstuffs, but its concentration varies substantially.[4,5] Liver and whole egg have the highest content, while fruits and most meats contain small amounts. Plant variety and season can affect the biotin content of cereal, and certain processing techniques (eg, canning) decrease biotin content. The contribution of biotin synthesized by intestinal microflora to the body's needs has not been defined.

Absorption, Metabolism, and Excretion

Most dietary biotin is protein-bound, although it also exists in free form. Biotinidase is responsible for freeing biotin from the protein to which it is bound, allowing it to be absorbed by the body. This absorption primarily takes place in the proximal small intestine, but some absorption also occurs in the proximal colon. The process of absorption involves active transport when biotin concentrations are low and passive diffusion when concentrations are high. Avidin, a glycoprotein found in appreciable amounts in raw egg whites, binds to biotin and prevents its absorption. Cooking denatures avidin, making it unable to interfere with biotin absorption. Specific receptors are probably involved in tissue uptake of biotin.[29]

About half of biotin undergoes metabolism to bisnorbiotin and biotin sulfoxide before excretion. In human urine and plasma, they are present in molar proportions of approximately 3:2:1. Two additional minor metabolites, bisnorbiotin methyl ketone and biotin sulfone, are also present in urine. The serum concentrations and urinary excretion of biotin and its metabolites increase roughly in the same proportion in response to either intravenous or oral administration of large doses of biotin.

During normal breakdown of cellular proteins, biotin-containing enzymes are degraded to biocytin (ε-Nbiotinyl-L-lysine) or short oligopeptides containing biotin-linked lysyl residues. Biotin is released from these oligopeptides by biotinidase, and the biotin is reused.

Deficiency State

Clinical deficiency of biotin is uncommon but has been reported in individuals who consume raw egg whites over long periods[119] or receive

PN without biotin supplementation.[120] Infantile seizures either alone or with other neurological or cutaneous findings, particularly in the presence of ketolactic acidosis and organic aciduria, are typical of biotinidase deficiency.[121] Infants manifest rash around the mouth, nose, and eyes as "biotin deficiency facies" after several months of biotin-free PN. This rash may extend to the ears and perineal orifices. Alopecia totalis, hypotonia, lethargy, developmental delay, and withdrawn behavior may also occur. Similar manifestations, including ataxia and paresthesia, may occur in older children and adults. IEM resulting in biotin dependency and various degrees of neurological and dermatologic abnormalities are increasing, and include holocarboxylase synthetase deficiency and a defect in biotin transport.[33,122]

Biochemically, lymphocyte biotinylated 3-methylcrotonyl-CoA carboxylase and propionyl-CoA carboxylase are the most reliable single markers of biotin status. Urinary 3-hydroxyisovaleric acid is increased with biotin deficiency, but there is too much interindividual variation to have clinical utility. Urinary excretion of biotin may be useful to detect biotin supplementation.[123]

Biotinidase deficiency results in a relative biotin deficiency through a lack of adequate digestion of protein-bound biotin. It is treated with free (unbound) biotin at the estimated typical dietary intake of 50 to 150 mcg/d.[124]

Supplementation

Intakes of biotin at >10 mg/d in a variety of participants at different life stages have no documented adverse effects. Urinary biotin metabolites increase in humans during chronic supplementation.[125] Immunoassays using a biotinylated reagent and biotin-binding proteins including troponins, thyroid function, and vitamin D tests are liable to have erroneous results in samples from individuals receiving biotin supplement. [29–31]

Choline

Biochemistry and Physiology

Choline is the major source of methyl groups in the diet. It is a precursor for acetylcholine, phospholipids, and the methyl donor betaine. Functionally, it plays a critical role in the structural integrity of cell membranes, methyl metabolism, cholinergic neurotransmission, transmembrane signaling, and lipid and cholesterol transport and metabolism.

Sources

Dietary choline is available as free choline or is bound as water-soluble esters (eg, phosphocholine, glycerophosphocholine) or lipid-soluble esters (eg, sphingomyelin, phosphotidylcholine). Phosphatidylcholine, primarily found in cell membranes, is widely available in foods. Foods especially rich in choline compounds are milk, liver, eggs, and peanuts.[4,5] Lecithin, a phosphatidylcholine-rich fraction prepared during commercial purification of phospholipids, is often used interchangeably with phosphatidylcholine. It is frequently added to food as an emulsifying agent and may be a significant source of choline.

Endogenous synthesis of choline occurs via sequential methylation of phosphatidylethanolamine catalyzed by the enzyme phosphatidylethanolamine N-methyltransferase and with S-adenosylmethionine as the methyl donor. However, endogenously synthesized choline does not compensate for inadequate dietary choline.

Absorption, Metabolism, and Excretion

Choline can be absorbed as lipid-soluble esters through the lymph or as free choline into portal circulation. Pancreatic enzymes can liberate choline from its ester forms. The absorption through the small intestinal mucosa is by transporter proteins. Some choline may be metabolized by intestinal bacteria to form betaine (which may be absorbed and used as a methyl donor) and methyl amines (which are not methyl donors). Metabolism of choline, folate, and vitamin B_{12} involves interactions necessary for transferring methyl groups from MTHF to homocysteine, resulting in the formation of methionine and tetrahydrofolate via the enzyme methionine synthase. Thus, the need for choline is modified by methionine, folic acid,

and vitamin B_{12} and may be influenced by polymorphisms in genes involved in the metabolism of these nutrients.[126,127]

All tissues accumulate choline by diffusion and mediated transport. A specific carrier mechanism transports free choline across the blood–brain barrier at a rate proportional to the serum choline concentration. Choline is required to form the phosphatidylcholine portion of very low-density lipoprotein particles needed for the transport of fat from the liver to the tissues. Choline is also readily taken up by the liver and kidney, where a large proportion of choline is oxidized to betaine. The methyl groups of betaine can be scavenged and reused in single-carbon metabolism.

Deficiency State

Although many foods contain choline, dietary intake varies at least twofold in humans. When deprived of dietary choline, most men and postmenopausal women will develop signs of organ dysfunction (eg, fatty liver, muscle damage), while less than half of premenopausal women develop such signs. This outcome is likely a result of estrogen inducing the gene (phosphatidylethanolamine-N-methyltransferase) that catalyzes endogenous synthesis of phosphatidylcholine, which can subsequently yield choline. [126]

Individuals receiving PN devoid of choline but adequate for methionine and folate develop hepatic steatosis and elevated alanine aminotransferase. These abnormalities resolved in some individuals when a source of dietary choline was provided.[128] In addition to the sex-based influence, genetic polymorphisms and epigenetics also appear to influence susceptibility to choline deficiency.[127,129] Along with other critical nutrients (eg, folate, docasahexenoic acid), both prenatal and postnatal choline are important to early childhood neurodevelopment.[127,130] Choline status can be determined using the following markers: fasting plasma, erythrocyte, and tissue content of choline and phosphatidylcholine.

Supplementation

The critical adverse effect of high intake of choline is hypotension, with corroborative evidence of cholinergic side effects (eg, sweating, diarrhea, fishy body odor).[1]

Conclusion

WSVs include the 8 B-complex vitamins, vitamin C, and choline. They are essential to all bodily functions primarily via their actions as enzymes in all metabolic pathways, stress responses, cell signaling, transcription, regulation of apoptosis, chromatin structure, and cell differentiation. Their actions support cellular activities, growth, development, and reproduction.

WSVs are widely available in the normal diet although most WSVs have limited total body storage. Deficiency in one or more WSVs is often associated with serious morbidity and even death. It usually occurs in individuals with underlying illnesses or extenuating circumstances such as extreme dietary restrictions and is increasingly reported as a result of IEM of specific WSVs.

Clinical manifestations of WSV deficiency often reflect its role in bodily function (eg, anemia, seizure) or changes in body tissues (mucocutaneous bruising, bleeding). Adverse effects usually occur only with intake at pharmacological doses of some WSVs.

Test Your Knowledge Questions

1. Which of the following conditions has the least effect on bioavailability of water-soluble vitamins (WSVs)?
   A. Temperature and duration of cooking
   B. Storage
   C. Source from food or supplement
   D. Exposure to light
2. Which of the following organs does NOT need to function normally to prevent WSV deficiency?
   A. Stomach
   B. Pancreas
   C. Small bowel
   D. Large bowel
3. Which of the following statements is false?
   A. Deficiency in WSVs can occur with a high-fat, low-nutrient-density diet and excess consumption of alcohol and tobacco use.

B. After the initial treatment of an IEM of a specific WSV, clinical manifestation can be prevented with the intake of the same vitamin at the level of the RDA.
C. For nutrition deficiency in WSVs, after initial treatment and correction of the predisposing cause, recurrence can be prevented with the intake of the same vitamins at the level of the RDA.
D. Excessive intake of some WSVs can mask or delay the manifestation of deficiency in other WSVs.

4. Which of the following is not a manifestation of inherited metabolic defects in water-soluble essential micronutrients?
   A. Rickets
   B. Intractable seizures
   C. Skin disorders
   D. Anemia
5. Which of the following samples obtained before/after treatment of suspected IEM for a WSV is least useful?
   A. Nail
   B. Cerebrospinal fluid
   C. Plasma
   D. Urine
6. Which one of the following statements is incorrect?
   A. Folic acid supplementation is universally recommended from the preconception period throughout pregnancy to prevent neural tube defects in the fetus.
   B. Deficiency of 5,10-methylenetetrahydrofolate is responsible for development of anemia in folate and vitamin B_{12} deficiency.
   C. Vitamin B_{12} is absorbed primarily at the jejunum.
   D. Chronic use of proton pump inhibitors and H2 receptor antagonists is associated with lower plasma vitamin B_{12} concentration.

References

1. Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary intake for Reference Intakes and its Panel on Folate, Other B Vitamins, and Choline. Dietary Reference Intakes for

Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline. National Academies Press; 1998.
2. Institute of Medicine (US) Panel on Dietary Antioxidants and Related Compounds. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. National Academies Press; 2000. https://doi.org/10.17226/9810
3. American Academy of Pediatrics Committee on Nutrition. Water soluble vitamins. In: Kleinman RE, Greer FR, eds. Pediatric Nutrition. 8th ed. Elk American Academy of Pediatrics 2019:655–677.
4. Pennington JAT, Douglass JS. Bowes & Church's Food Values of Portions Commonly Used. 20th ed. Lippincott Williams & Wilkins; 2014.
5. FoodData Central. National nutrient database for standard reference - 2018. U.S. Department of Agriculture, Agriculture Research Service. Accessed September 21, 2022. https://fdc.nal.usda.gov/fdc-app.html#/
6. Hrubsa M, Siatka T, Nejmanova I, et al. Biological properties of vitamins of the B-complex, Part 1: vitamins $B_{1,}$ $B_{2,}$ $B_{3,}$ $B_{5.}$ *Nutrients*. 2022:14:484. https://doi.org/10.3390%2Fnu14030484
7. Doseděl M, Jirkovský E, Macáková K, et al. Vitamin C—sources, physiological role, kinetics, deficiency, use, toxicity, and determination. *Nutrients*. 2021;13:615. https://doi.org/10.3390/nu13020615
8. Coelho SC, Estevinho BN, Rocha F. Recent advances in water-soluble vitamins delivery systems prepared by mechanical processes (electrospinning and spray-drying techniques) for food and nutraceuticals applications—a review. *Foods*. 2022;11:1271. https://doi.org/10.3390/foods11091271
9. Dietary supplement label database. National Institutes of Health, Office of Dietary Supplements. Accessed July 8, 2022. https://dsld.od.nih.gov/
10. Code of Federal Regulations Title 21. Nutrient specifications for infant formula. 21 CFR Part 107.100 Subpart D. National Archives and Records Administration. Accessed October 27, 2023.

https://www.ecfr.gov/current/title-21/chapter-I/subchapter-B/part-107/subpart-D/section-107.100
11. Dietary guidelines for Americans 2020–2025. 9th ed. U.S. Department of Agriculture and U.S. Department of Health and Human Services. Published 2020. Accessed July 6, 2022. https://www.dietaryguidelines.gov
12. Centers for Disease Control and Prevention. *State Indicator Report on Fruits and Vegetables, 2018*. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services; 2018. https://www.cdc.gov/nutrition/downloads/fruits-vegetables/2018/2018-fruit-vegetable-report-508.pdf
13. Lee SH, Moore LV, Park S, Harris DM, Blanck HM. Adults meeting fruit and vegetable intake recommendations – United States 2019. *MMWR Morb Mortal Wkly Rep*. 2022;71:1–9. https://doi.org/10.15585/mmwr.mm7101a1
14. Amin HJ, Shukla AK, Snyder F, Fung E, Anderson NM, Parsons HG. Significance of phototherapy-induced riboflavin deficiency in the full-term neonate. *Biol Neonate*. 1992;61:76–81. https://doi.org/10.1159/000243534
15. Robinson DT, Ayers P, Fleming B, et al. Recommendations for photoprotection of parenteral nutrition for premature infants: an ASPEN position paper. *Nutr Clin Pract*. 2021;36:927–941. https://doi.org/10.1002/ncp.10747
16. Malik ZA, Abadi J, Sansary J, Rosenberg M. Elevated levels of vitamin B_{12} and folate in vertically infected children with HIV-1. *AIDS*. 2009;23:403–407. https://doi.org/10.1097/qad.0b013e32831ef4f7
17. Oh C, Keats EC, Bhutta ZA. Vitamin and mineral supplementation during pregnancy on maternal, birth, child health and development outcomes in low- and middle-income countries: a systematic review and meta-analysis. *Nutrients*. 2020;12(2):491. https://doi.org/10.3390%2Fnu12020491
18. Blakstad MM, Fawzi WW, Castro MC, Thompson A, Arabi M, Danaei G. Scaling up prenatal nutrition could reduce the global burden of noncommunicable diseases in the next generation: a

modeling analysis. *Am J Clin Nutr.* 2022;116:1291–1302. https://doi.org/10.1093/ajcn/nqac214
19. Hanna M, Jaqua E, Nguyen V, Clay J. B vitamins: functions and uses in medicine. *Perm J* 2022;26:89–97. https://doi.org/10.7812/tpp/21.204
20. Erlich S, Guz-Mark A, Rinawi F, et al. Micronutrients deficiencies in children with inflammatory bowel diseases. *Nutr Clin Pract*. 2020;35:3150322. https://doi.org/10.1002/ncp.10373
21. Xanthakos SA, Khoury JC, Inge TH, Jenkins TM, Modi AC, Michalsky MP, et al. Nutritional risks in adolescents after bariatric surgery. *Clin Gastroenterol Hepatol*. 2020;18:1070–1081. https://doi.org/10.1016/j.cgh.2019.10.048
22. Miller JW. Proton pump inhibitors, H2-receptor antagonists, metformin, and vitamin B12 deficiency: clinical implications. *Adv Nutr*. 2018:9:511S-518S. https://doi.org/10.1093/advances/nmy023
23. Owen MD, Baker BC, Scott EM, Forbes K. Interaction between metformin, folate and vitamin B12 and the potential impact on fetal growth and long-term metabolic health in diabetic pregnancies. *Int J Mol Sci*. 2021;22:5759. https://doi.org/10.3390/ijms22115759
24. Gentzke AS, Wang TW, Cornelius M, et al. Tobacco product use and associated factors among middle and high school students—National Youth Tobacco Survey, United States, 2021. *MMWR Surveill Summ.* 2022;71:1–29.
25. Seo DC, Jiang N. Associations between smoking and extreme dieting among adolescents. *J Youth Adolesc*. 2009;38:1364–1373. https://doi.org/10.1007/s10964-009-9421-0
26. Substance Abuse and Mental Health Services Administration. *Key substance use and mental health indicators in the United States: Results from the 2020 National Survey on Drug Use and Health (HHS Publication No. PEP21-07-01-003, NSDUH Series H-56)*. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; 2021. Accessed August 2, 2022. https://www.samhsa.gov/data/
27. Jen M, Yan AC. Syndromes associated with nutritional deficiency and excess. *Clin Dermatol*. 2010;28:669–685. https://doi.org/10.1016/j.clindermatol.2010.03.029

28. Nosewicz J, Spaccarelli N, Roberts KM, et al. The epidemiology, impact, and diagnosis of micronutrient nutritional dermatoses. Part 2: B-complex vitamins. *J Am Acad Dermatol*. 2022;86:281–292. https://doi.org/10.1016/j.jaad.2021.06.900
29. Mock DM. Biotin: from nutrition to therapeutics. *J Nutr*. 2017;147:1487–1492. https://doi.org/10.3945/jn.116.238956
30. Ghazal K, Brabant S, Prie D, Piketty ML. Hormone immunoassay interference: a 2021 update. *Ann Lab Med*. 2022;42:3–23. https://doi.org/10.3343/alm.2022.42.1.3
31. Moerman A, Delanghe JR. Sense and nonsense concerning biotin interference in laboratory tests. *Acta Clin Belg*. 2022;77:204–210. https://doi.org/10.1080/17843286.2020.1780770
32. Gheorghe DC, Stefan-van Staden RI, van Staden JKF. Mini-review: electrochemical sensors used for the determination of water- and fat-Ssoluble vitamins: B, D, K. *Crit Rev Anal Chem*: 2022;26:1–10. https://doi.org/10.1080/10408347.2022.2045557
33. National Institutes of Health, National Library of Medicine, National Center for Biotechnology Information (multiple databases). Online Mendelian Inheritance in Man (OMIM®).
34. Hampel D, Shahab-Ferdows S, Islam MM, Peerson JM, Allen LH. Vitamin concentrations in human milk vary with time within feed, circadian rhythm, and single-dose supplementation. *J Nutr*. 2017;147:603–611. https://doi.org/10.3945/jn.116.242941
35. ASPEN guidelines and clinical resources, Parenteral nutrition product shortages. American Society for Parenteral and Enteral Nutrition. Accessed September 1, 2022. https://www.nutritioncare.org/Guidelines_and_Clinical_Resources/Product_Shortages/
36. Dwyer JT, Saldanha LG, Bailen RA, Gahche JJ, Potischman N, Bailey RL, et al. Do multivitamin/mineral dietary supplements for young children fill critical nutrient gaps? *J Acad Nutr Diet*. 2022;122:525–532. https://doi.org/10.1016/j.jand.2021.10.019
37. Adams JB, Kirby JK, Sorensen JC, Pollard EL, Audhya T. Evidence based recommendations for an optimal prenatal supplement for women in the US: vitamins and related nutrients. *Matern Health*

Neonatol Perinatol. 2022;8(1):4. https://doi.org/10.1186/s40748-022-00139-9
38. White CM. Lead in mineral or multivitamin-multimineral products. *Ann Pharmacother*. 2022;56:339–345. https://doi.org/10.1177/10600280211023328
39. Martorell R. Expanding the already strong rationale for prenatal multiple micronutrient supplementation in low- and middle-income countries. *Am J Clin Nutr*. 2022;116:1191–1192. https://doi.org/10.1093/ajcn/nqac243
40. Tsakiridis I, Kasapidou E, Dagklis T, et al. Nutrition in pregnancy: a comparative review of major guidelines. *Obstet Gynecol Surv*. 2020;75:692–702. https://doi.org/10.1097/ogx.0000000000000836
41. Raj V, Ojha S, Howarth FC, Belur PD, Subramanya SB. Therapeutic potential of benfotiamine and its molecular targets. *Eur Rev Med Pharmacol Sci*. 2018;22:3261–3273. https://doi.org/10.26355/eurrev_201805_15089
42. Whitfield KC, Bourassa MW, Adamolekun B, et al. Thiamine deficiency disorders: diagnosis, prevalence, and a roadmap for global control programs. *Ann NY Acad Sci*. 2018;1430:3–43. https://doi.org/10.1111/nyas.13919
43. Ganapathy V, Smith SB, Prasad PD. SLC19: the folate/thiamin transporter family. *Pflugers Arch*. 2004;447:641–646. https://doi.org/10.1007/s00424-003-1068-1
44. Liu X. SLC family transporters. *Adv Exp Med Biol*. 2019:1141:101–202. https://doi.org/10.1007/978-981-13-7647-4_3
45. Zhao R, Gao F, Goldman ID. Molecular cloning of human thiamin pyrophosphokinase. *Biochim Biophys Acta* 2001;1517:320–322. https://doi.org/10.1016/s0167-4781(00)00264-5
46. Centers for Disease Control and Prevention. Lactic acidosis traced to thiamin deficiency related to nationwide shortage of multivitamins for total parenteral nutrition—United States, 1997. *MMWR Morb Mortal Wkly Rep*. 1997;46:523–528.
47. Da Silva JS, Seres D, Sabino K, et al; and Parenteral nutrition safety and clinical practice committees, American society for parenteral and enteral nutrition. ASPEN consensus recommendations for refeeding

syndrome. *Nutr Clin Pract*. 2020;35:178–195. https://doi.org/10.1002/ncp.10474
48. Davis RA, Wolf A. Infantile beriberi associated with Wernicke's encephalopathy. *Pediatrics*. 1958;21:409–420. https://doi.org/10.1542/peds.21.3.409
49. Luxemburger C, White NJ, ter Kuile F, et al. Beri-beri: the major cause of infant mortality in Karen refugees. *Trans R Soc Trop Med Hyg*. 2003;97:251–255. https://doi.org/10.1016/s0035-9203(03)90134-9
50. Smith TJ, Hess SY. Infantile thiamine deficiency in South and Southeast Asia: an age-old problem needing new solutions. *Nutr Bull*. 2021;46:12–25. https://doi.org/10.1111/nbu.12481
51. Fattal-Valevski A, Kesler A, Sela BA, et al. Outbreak of life-threatening thiamin deficiency in infants in Israel caused by a defective soy-based formula. *Pediatrics*. 2005;115:e233–e238. https://doi.org/10.1542/peds.2004-1255
52. Shamir R. Thiamin-deficient infant formula: what happened and what have we learned? *Ann Nutr Metab* 2012;60:185–187. https://doi.org/10.1159/000338211
53. Kornreich L, Bron-Harlev E, Hoffmann C, et al. Thiamin deficiency in infants: MR findings in the brain. *Am J Neuroradiol.* 2005;26:1668–1674. http://www.ncbi.nlm.nih.gov/pmc/articles/pmc7975150/
54. Talwar D, Davidson H, Cooney J, St JO'Reilly D. Vitamin B(1) status assessed by direct measurement of thiamin pyrophosphate in erythrocytes or whole blood by HPLC: comparison with erythrocyte transketolase activation assay. *Clin Chem*. 2000;46:704–710. https://doi.org/10.1093/clinchem/46.5.704
55. Bayoumi RA, Rosalki SB. Evaluation of methods of coenzyme activation of erythrocyte enzymes for detection of deficiency of vitamins B_1, B_2, and B_6. *Clin Chem*. 1976;22:327–335. http://dx.doi.org/10.1093/clinchem/22.3.327
56. Fattal-Valevski A, Azouri-Fattal I, Greenstein YJ, Guindy M, Blau A, Zelnik N. Delayed language development due to infantile thiamine

deficiency. *Dev Med Child Neurol.* 2009;51:629–634. https://doi.org/10.1111/j.1469-8749.2008.03161.x
57. Fattal-Valevski A, Bloch-Mimouni A, Kivity S, et al. Epilepsy in children with infantile thiamine deficiency. *Neurology*. 2009;73:828–833. https://doi.org/10.1212/wnl.0b013e3181b121f5
58. Tabarki B, Al-Hashem A, Alfadhel M. Biotin-thiamin-responsive basal ganglia disease. Gene reviews. Published November 21, 2013. Accessed August 1, 2022. http://www.ncbi.nlm.nih.gov/books/NBK169615/.
59. Au LWC, Lee HHC, Sheng B, et al. Movement disorders associated with thiamine pyrophosphokinase deficiency: intrafamilial variability in the phenotype. *Clin Neurol Neurosurg*. 2020;199:106258. https://doi.org/10.1016/j.clineuro.2020.106258
60. Rogovik AL, Vohra S, Goldman RD. Safety considerations and potential interactions of vitamins: should vitamins be considered drugs? *Ann Pharmacother*. 2010;44:311–324. https://doi.org/10.1345/aph.1m238
61. Levit R, Savoy de Giori G, de Moreno de LeBlanc A, LeBlanc JG. Recent update on lactic acid bacteria producing riboflavin and folates: application for food fortification and treatment of intestinal inflammation. *J Appl Microbiol*. 2021;130:1412–1424. https://doi.org/10.1111/jam.14854
62. Mosegaard S, Dipace G, Bross P, Carlsen J, Gregersen N, Olsen RKJ. Riboflavin deficiency-implications for general human health and inborn errors of metabolism. *Int J Mol Sci*. 2020;21:3847. https://doi.org/10.3390%2Fijms21113847
63. Dalton SD, Rahimi AR. Emerging role of riboflavin in the treatment of nucleoside analogue-induced type B lactic acidosis. *AIDS Patient Care STDS*. 2001;15:611–614. https://doi.org/10.1089/108729101753354608
64. Suwannasom N, Kao I, Pruß A, Georgieva R, Bäumler H. Riboflavin: The health benefits of a forgotten natural vitamin. *Int J Mol Sci*. 2020;21:950. https://doi.org/10.3390/ijms21030950
65. Liang WC, Nishino I. Lipid storage myopathy. *Curr Neurol Neurosci Rep*. 2011;11:97–103. https://doi.org/10.1007/s11910-010-0154-y

66. Gasperi V, Sibilano M, Savini I, Catani MV. Niacin in the central nervous system: an update of biological aspects and clinical applications. *Int J Mol Sci*. 2019;20:974. https://doi.org/10.3390/ijms20040974
67. Jiang Y, Liu J, Chen D, Yan L, Zheng W. Sirtuin inhibition: strategies, inhibitors, and therapeutic potential. *Trends Pharmacol Sci*. 2017;38:459–472. https://doi.org/10.1016/j.tips.2017.01.009
68. Adrian J, Frangne R. Synthesis and availability of niacin in roasted coffee. *Adv Exp Med Biol*. 1991;289:49–59. https://doi.org/10.1007/978-1-4899-2626-5_4
69. Li R, Yu K, Wang Q, et al. Pellagra secondary to medication and alcoholism: a case report and review of the literature. *Nutr Clin Pract*. 2016;31:785–789. https://doi.org/10.1177/0884533616660991
70. Hegyi J, Schwartz RA, Hegyi V. Pellagra: dermatitis, dementia, and diarrhea. *Int J Dermatol*. 2004;43:1–5. https://doi.org/10.1111/j.1365-4632.2004.01959.x
71. Hwang ES, Song SB. Possible adverse effects of high-dose nicotinamide: mechanisms and safety assessment. *Biomolecules*. 2020;10:687. https://doi.org/10.3390/biom10050687
72. Lui A, Lumeng L, Aronoff GR, Li TK. Relationship between body store of vitamin B6 and plasma pyridoxal-P clearance: metabolic balance studies in humans. *J Lab Clin Med*. 1985;106:491–497.
73. Coburn SP. Location and turnover of vitamin B6 pools and vitamin B6 requirements of humans. *Ann NY Acad Sci*. 1990;585:76–85. https://doi.org/10.1111/j.1749-6632.1990.tb28043.x
74. Coursin DB. Convulsive seizures in infants with pyridoxine-deficient diet. *J Am Med Assoc*. 1954;154:406–408. https://doi.org/10.1001/jama.1954.02940390030009
75. Bessey OA, Adam DJ, Hansen AE. Intake of vitamin B6 and infantile convulsions: a first approximation of requirements of pyridoxine in infants. *Pediatrics*. 1957;20:33–44.
76. Kretsch MJ, Sauberlich HE, Newbrun E. Electroencephalographic changes and periodontal status during short-term vitamin B-6 depletion of young, nonpregnant women. *Am J Clin Nutr*. 1991;53:1266–1274. https://doi.org/10.1093/ajcn/53.5.1266

77. Dakshinamurti K, Dakshinamurti S. Neonatal epileptic encephalopathy: role of vitamin B-6 vitamers in diagnosis and therapy. *Am J Clin Nutr.* 2014;100:505–506. https://doi.org/10.3945/ajcn.114.092445
78. Romero JA, Kuczler FJ. Isoniazid overdose: recognition and management. *Am Fam Physician*. 1998;57:749–752.
79. Lheureux P, Penaloza A, Gris M. Pyridoxine in clinical toxicology: a review. *Eur J Emerg Med*. 2005;12:78–85. https://doi.org/10.1097/00063110-200504000-00007
80. Schaumburg H, Kaplan J, Windebank A, et al. Sensory neuropathy from pyridoxine abuse. A new megavitamin syndrome. *N Engl J Med*. 1983;309:445–448. https://doi.org/10.1056/nejm198308253090801
81. Parry GJ, Bredesen DE. Sensory neuropathy with low-dose pyridoxine. *Neurology*. 1985;35:1466–1468. https://doi.org/10.1212/wnl.35.10.1466
82. Veraldi S, Benardon S, Diani M, Barbareschi M. Acneiform eruptions caused by vitamin B12: a report of five cases and review of the literature. *J Cosmet Dermatol*. 2018;17:112–115. https://doi.org/10.1111/jocd.12360
83. Chan YM, Bailey R, O'Connor DL. Folate. *Adv Nutr.* 2013;4:123–125. https://doi.org/10.3945/an.112.003392
84. Weir DG, McGing PG, Scott JM. Folate metabolism, the enterohepatic circulation and alcohol. *Biochem Pharmacol.* 1985;34:1–7. https://doi.org/10.1016/0006-2952(85)90092-9
85. Tonetti C, Burtscher A, Bories D, Tulliez M, Zittoun J. Methylenetetrahydrofolate reductase deficiency in four siblings: a clinical, biochemical, and molecular study of the family. *Am J Med Genet*. 2000;91:363–367. https://doi.org/10.1002/(SICI)1096-8628(20000424)91:5%3C363::AID-AJMG9%3E3.0.CO;2-X
86. Ferrazzi E, Tiso G, Di Martino D. Folic acid versus 5-methyl tetrahydrofolate supplementation in pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 2020;253:312–319. https://doi.org/10.1016/j.ejogrb.2020.06.012
87. Ramaekers VT, Rothenberg SP, Sequeira JM, et al. Autoantibodies to folate receptors in the cerebral folate deficiency syndrome. *N Engl J Med.* 2005;352:1985–1991. https://doi.org/10.1056/nejmoa043160

88. Guéant JL, Guéant-Rodriguez RM, Alpers DH. Vitamin B12 absorption and malabsorption. *Vitam Horm*. 2022;119:241–274. https://doi.org/10.1016/bs.vh.2022.01.016
89. Doets EL, In't Veld PH, Szczecińska A, et al. Systematic review on daily vitamin B12 losses and bioavailability for deriving recommendations on vitamin B12 intake with the factorial approach. *Ann Nutr Metab.* 2013;62:311–22. https://doi.org/10.1159/000346968
90. Hannibal L, Jacobsen DW. Intracellular processing of vitamin B12 by MMACHC (CblC). *Vitam Horm.* 2022;119:275–298. https://doi.org/10.1016/bs.vh.2022.02.001
91. Sobczyńska-Malefora A, Delvin E, McCaddon A, Ahmadi KR, Harrington DJ. Vitamin B12 status in health and disease: a critical review. Diagnosis of deficiency and insufficiency—clinical and laboratory pitfalls. *Crit Rev Clin Lab Sci.* 2021;58:399–429. https://doi.org/10.1080/10408363.2021.1885339
92. Specker BL, Black A, Allen L, Morrow F. Vitamin B-12: low milk concentrations are related to low serum concentrations in vegetarian women and to methylmalonic aciduria in their infants. *Am J Clin Nutr*. 1990;52:1073–1076. https://doi.org/10.1093/ajcn/52.6.1073
93. Termanini B, Gibril F, Sutliff VE, Yu F, Venzon DJ, Jensen RT. Effect of long-term gastric acid suppressive therapy on serum vitamin B12 levels in patients with Zollinger-Ellison syndrome. *Am J Med*. 1998;104:422–430. https://doi.org/10.1016/s0002-9343(98)00087-4
94. Falcone V, Stopp T, Feichtinger M, et al. Pregnancy after bariatric surgery: a narrative literature review and discussion of impact on pregnancy management and outcome. BMC Pregnancy Childbirth 2018;18:507. https://doi.org/10.1186/s12884-018-2124-3
95. Finkelstein JL, Layden AJ, Stover PJ. Vitamin B-12 and perinatal health. *Adv Nutr.* 2015;6 :552–563. https://doi.org/10.3945/an.115.008201
96. Briani C, Dalla Torre C, Citton V, et al. Cobalamin deficiency: clinical picture and radiological findings. *Nutrients*. 2013;5:4521–4539. https://doi.org/10.3390/nu5114521
97. Zibold J, von Livonius B, Kolarova H, et al. Vitamin B12 in Leber hereditary optic neuropathy mutation carriers: a prospective cohort

study. *Orphanet J Rare Dis*. 2022;17:310–322. https://doi.org/10.1186/s13023-022-02453-z

98. Andrès E, Zulfiqar A, Vogel T. State of the art review: oral and nasal vitamin B12 therapy in the elderly. *QJM*. 2020;113:5–15. https://doi.org/10.1093/qjmed/hcz046
99. Estourgie-van Burk GF, van der Kuy PHM, de Meij TG, Benninga MA, Kneepkens CMF. Intranasal treatment of vitamin B_{12} deficiency in children. *Eur T Pediatr*. 2020;179:349–352. https://doi.org/10.1007/s00431-019-03519-0
100. Wang H, Li L, Qin LL, Song Y, Vidal-Alaball J, Liu TH. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. *Cochrane Database Syst Rev*. 2018:3:CD004655. https://doi.org/10.1002/14651858.cd004655.pub3
101. Jamal A. Hereditary methemoglobinemia. *J Coll Physicians Surg Pak*. 2006;16:157–159.
102. Külen O, Stushnoff C, Holm DG. Effect of cold storage on total phenolics content, antioxidant activity and vitamin C level of selected potato clones. *J Sci Food Agric*. 2013;93:2437–2444. https://doi.org/10.1002/jsfa.6053
103. Peñas E, Frias J, Sidro, B, Vidal-Valverde C. Chemical evaluation and sensory quality of sauerkrauts obtained by natural and induced fermentations at different NaCl levels from Brassica oleracea Var. capitata Cv. Bronco grown in eastern Spain. Effect of storage. *J Agric Food Chem*. 2010;58:3549–3557. https://doi.org/10.1021/jf903739a
104. Graumlich JF, Ludden TM, Conry-Cantilena C, Cantilena LR Jr, Wang Y, Levine M. Pharmacokinetic model of ascorbic acid in healthy male volunteers during depletion and repletion. *Pharm Res*. 1997;14:1133–1139. https://doi.org/10.1023/a:1012186203165
105. Carr AC, Lykkesfeldt J. Discrepancies in global vitamin C recommendations: a review of RDA criteria and underlying health perspectives. *Crit Rev Food Sci Nutr*. 2021;61:742–755. https://doi.org/10.1080/10408398.2020.1744513
106. Willmott NS, Bryan RA. Case report: scurvy in an epileptic child on a ketogenic diet with oral complications. *Eur Arch Paediatr Dent*. 2008;9:148–152. https://doi.org/10.1007/bf03262627

107. Samonte VA, Sherman PM, Taylor GP, et al. Scurvy diagnosed in a pediatric liver transplant patient awaiting combined kidney and liver retransplantation. *Pediatr Transplant.* 2008;12:363–367. https://doi.org/10.1111/j.1399-3046.2007.00800.x
108. Ratanachu-Ek S, Sukswai P, Jeerathanyasakun Y, Wongtapradit L. Scurvy in pediatric patients: a review of 28 cases. *J Med Assoc Thai.* 2003;86:S734–S740.
109. Grillot J, Ait S, Bergoin C, et al. Vitamin C in home parenteral nutrition: a need for monitoring. *Nutrients*. 2020;12:1667. https://doi.org/10.3390%2Fnu12061667
110. Fain O. Musculoskeletal manifestations of scurvy. *Joint Bone Spine*. 2005;72:124–128. https://doi.org/10.1016/j.jbspin.2004.01.007
111. Gayen SK, Abdelrahman AA, Preston IR, Petit RD, Hill NS. Vitamin C deficiency-induced pulmonary arterial hypertension. *Chest*. 2020;157:e21–e23. https://doi.org/10.1016/j.chest.2019.06.043
112. Wandzilak TR, D'Andre SD, Davis PA, Williams HE. Effect of high dose vitamin C on urinary oxalate levels. *J Urol.* 1994;151:834–837. https://doi.org/10.1016/s0022-5347(17)35100-5
113. Gogel HK, Tandberg D, Strickland RG. Substances that interfere with guaiac card tests: implications for gastric aspirate testing. *Am J Emerg Med*. 1989;7:474–480. https://doi.org/10.1016/0735-6757(89)90248-9
114. Fry PC, Fox HM, Tao HG. Metabolic response to a pantothenic acid deficient diet in humans. *J Nutr Sci Vitaminol (Tokyo).* 1976;22:339–346. https://doi.org/10.3177/jnsv.22.339
115. Hodges RE, Bean WB, Ohlson MA, Bleiler R. Human pantothenic acid deficiency produced by omega-methyl pantothenic acid. *J Clin Invest*. 1959;38:1421–1425. https://doi.org/10.1172/jci103918
116. Glusman M. The syndrome of "burning feet" (nutritional melagia) as a manifestation of nutritional deficiency. *Am J Med*. 1947;3:211–223.
117. Xu J, Patassini S, Begley P, et al. Cerebral deficiency of vitamin B5 (d-pantothenic acid; pantothenate) as a potentially reversible cause of neurodegeneration and dementia in sporadic Alzheimer's disease. *Biochem Res Commun.* 2020;527:676–681. https://doi.org/10.1016/j.bbrc.2020.05.015
118. Jungert A, Ellinger S, Watzl B, Richter M; German Nutrition Society (DGE). Revised D-A-CH reference values for the intake of biotin. *Eur*

J Nutr. 2022;61:1779–1787. https://doi.org/10.1007/s00394-021-02756-0
119. Baugh CM, Malone JH, Butterworth CE Jr. Human biotin deficiency. A case history of biotin deficiency induced by raw egg consumption in a cirrhotic patient. *Am J Clin Nutr*. 1968;21:173–182. https://doi.org/10.1093/ajcn/21.2.173
120. Mock DM, Baswell DL, Baker H, Holman RT, Sweetman L. Biotin deficiency complicating parenteral alimentation: diagnosis, metabolic repercussions, and treatment. J Pediatr 1985;106:762–769. https://doi.org/10.1016/s0022-3476(85)80350-4
121. Wolf B, Heard GS, Weissbecker KA, McVoy JR, Grier RE, Leshner RT. Biotinidase deficiency: initial clinical features and rapid diagnosis. *Ann Neurol*. 1985;18:614–617. https://doi.org/10.1002/ana.410180517
122. Mardach R, Zempleni J, Wolf B, et al. Biotin dependency due to a defect in biotin transport. *J Clin Invest.* 2002;109:1617–1623. https://doi.org/10.1172%2FJCI13138
123. Eng WK, Giraud D, Schlegel VL, Wang D, Lee BH, Zempleni J. Identification and assessment of markers of biotin status in healthy adults. *Br J Nutr.* 2013;110:321–329. https://doi.org/10.1017/s0007114512005065
124. Wolf B, Heard GS, McVoy JR, Raetz HM. Biotinidase deficiency: the possible role of biotinidase in the processing of dietary protein-bound biotin. *J Inherit Metab Dis.* 1984;7 (suppl 2):121–122. https://doi.org/10.1007/978-94-009-5612-4_35
125. Mock DM, Heird GM. Urinary biotin analogs increase in humans during chronic supplementation: the analogs are biotin metabolites. *Am J Physiol*. 1997;272:E83–E85. https://doi.org/10.1152/ajpendo.1997.272.1.e83
126. Zeisel SH. Nutritional genomics: defining the dietary requirement and effects of choline. *J Nutr*. 2011;141(3):531–534. https://doi.org/10.3945%2Fjn.110.130369
127. Irvine N, England-Mason G, Field CJ, Dewey D, Aghajafari F. Prenatal folate and choline levels and brain and cognitive development in children: a critical narrative review. *Nutrients*. 2022;14(2):364. https://doi.org/10.3390/nu14020364

128. Buchman AL, Dubin MD, Moukarzel AA, et al. Choline deficiency: a cause of hepatic steatosis during parenteral nutrition that can be reversed with intravenous choline supplementation. *Hepatology*. 1995;22:1399–140.
129. Wortmann SB, Mayr JA. Choline-related-inherited metabolic diseases—a mini review. *J Inherit Metab Dis*. 2019;42:237–242. https://doi.org/10.1002/jimd.12011
130. Bragg MG, Prado EL, Stewart CP. Choline and docosahexaenoic acid during the first 1000 days and children's health and development in low- and middle-income countries. *Nutr Rev*. 2022;80:656–676. https://doi.org/10.1093/nutrit/nuab050

Test Your Knowledge Answers

1. The correct answer is **C**. Bioavailability of WSV supplements is generally similar to that of dietary sources when tested under the same conditions. However, the bioavailability of some WSVs is usually negatively affected by high heat, prolonged cooking or storage, and light exposure.
2. The correct answer is **D**. Intact functioning of one or more of the organ systems is needed for the digestion, absorption, and transport of ingested water-soluble micronutrients. The absorption of these nutrients is usually completed before reaching the large bowel. Thus, the absence of the intact large bowel is least likely to be associated with a deficiency of WSVs.
3. The correct answer is **B**. Depending on whether the IEM interferes with the bioavailability or metabolism of the WSV, these patients generally require an intake greater than the RDA to remain symptom-free. Nutrition deficiency states can be prevented by an equivalent RDA intake for the specific WSV as long as there is a correction of nondietary predisposition to the deficient state (eg, alcohol abuse, smoking, chronic illness, and intake of some medications) that may interfere with digestion, absorption, and metabolism of the micronutrient(s). Excessive folate intake may precipitate or exacerbate neuropathy in individuals with vitamin B_{12} deficiency and has been

implicated in delaying the diagnosis of pernicious anemia until after irreversible neurological damage has occurred.

4. The correct answer is **A**. Rickets is typically a result of a mineral deficiency (calcium and/or phosphorus) and/or the fat-soluble vitamin D. Rickets can also result from defects in vitamin D metabolism. Clinical manifestations of WSV deficiency may overlap and commonly include skin disorders, anemia, diarrhea, and impaired neurologic function.
5. The correct answer is **A**. In patients with a suspected IEM, the collection of plasma, cerebrospinal fluid, and urine before and after empiric therapy with pharmacological doses of a specific vitamin is useful to monitor the concentration of the vitamin, its metabolites, and other biochemical markers to aid in diagnosis and therapy. Additional genetic testing may be warranted. Nail samples are unlikely to have any use in this situation.
6. The correct answer is **C**. Vitamin B_{12} absorption occurs primarily at the distal ileum.

8

Fat-Soluble Vitamins

Winston Koo, MBBS, FACN, CNS; May Saba, PharmD, BCNSP; Mirjana Lulic-Botica, PharmD, BCPS; and Judith Christie, RN, MSN

Learning Objectives

1. Understand the physiological basis for the functions of and nutritional requirements for fat-soluble vitamins.
2. Identify the common risk factors for fat-soluble vitamin deficiency.
3. Identify the common manifestations of deficiency states for fat-soluble vitamins.
4. Articulate the potential risks associated with excessive intake of fat-soluble vitamins.

Introduction

Achieving adequate status of fat-soluble vitamins (FSVs; eg, A, D, E, K) depends on adequate intake, intestinal digestion and absorption, cellular uptake, and metabolism. Vitamins D and K are produced endogenously in substantial but variable amounts. Fortification of some vitamins (eg, vitamin D) is widely practiced because of their limited distribution in commonly consumed natural foods. In the normal population, a varied dietary intake typically meets the dietary reference intake (DRI) for fat-soluble vitamins (see Table 8-1).[1–5]

TABLE 8-1. Dietary Reference Intake for Fat-Soluble Vitamins

Life Stage	Vitamin A, mcg RAE (1 mcg = 3.3 IU)	Vitamin D,[a] IU (1 mcg = 40 IU)	Vitamin E, mg	Vitamin K,[a] mcg
0–6 mo[a]	400 (600)	400 (1000)	4	2.0
7–12 mo[a]	500 (600)	400 (1500)	5	2.5
1–3 y[b]	300 (600)	600 (2500)	6 (200)	30
4–8 y[b]	400 (900)	600 (3000)	7 (300)	55
9–13 y[b]	600 (1700)	600 (4000)	11 (600)	60
Males				
14–18 y[b]	900 (2800)	600 (4000)	15 (800)	75
Females				
14–18 y[b]	700 (2800)	600 (4000)	15 (800)	75
Pregnancy[c]				
14–18 y[b]	750 (2800)	600 (4000)	15 (800)	75
Lactation[c]				
14–18 y[b]	1200 (2800)	600 (4000)	19 (800)	75
UL	[d]	[d]	[d]	NA

Data from the Institute of Medicine,[1,2] the American Academy of Pediatrics,[3] and the U.S. Department of Agriculture and U.S. Department of Health and Human Services.[4]

Abbreviations: AI, adequate intake; EAR, estimated average requirement; NA, not available; RAE, retinol activity equivalent, 1 RAE = 1 µg retinol, 12 µg β-carotene, 24 µg α-carotene, or 24 µg β-cryptoxanthin; RDA, recommended dietary allowance; UL, upper limit.

[a] AI is the observed or experimentally determined estimate of nutrient intake by a group or groups of healthy people. It is applicable for all ages for vitamins D and K.

[b] RDA is the average daily dietary intake sufficient to meet the requirement of 97% to 98% of healthy individuals in a life stage based on sex. RDA = EAR + $2SD_{EAR}$ or 1.2 EAR or 1.3 EAR. EAR is the daily intake of a nutrient estimated to meet the nutrient requirement of half of the healthy individuals in a life stage based on sex.

[c] RDA during pregnancy and lactation for other ages.

[d] Numbers in parentheses indicate the upper limit of intake.

Nutrient requirements and biological actions of FSVs must be considered as part of total nutrition support because these vitamins have metabolic interactions with other nutrients. For example, zinc, energy, and protein metabolism affect vitamin A status through their roles in the production of retinol-binding protein (RBP) and transthyretin; novel ligands (eg, secondary bile acids and long-chain polyunsaturated fatty acids) can activate vitamin D receptors, leading to additional potential biological functions for vitamin D. Additionally, antioxidants such as vitamin C, glutathione, and ubiquinols can affect the regeneration of α-tocopherol (which is itself an antioxidant) and influence the requirement for vitamin E.

Specific clinical disorders, gastrointestinal surgical procedures, and medical therapies also may impact FSV status. Individuals with any disease state that impairs biliary and pancreatic secretions, intestinal mucosal function, micelle formation, and uptake into enterocytes are at risk for deficiency of one or more FSV. Additionally, impaired chylomicron secretion can negatively affect the distribution of FSVs to peripheral tissues. Increasing documentation shows that inherited defects in the absorption or metabolism of various vitamins contribute to deficiency states in individuals.

Individuals who have undergone bariatric surgery, especially those with severe dietary restrictions, have decreased intake and absorption of many nutrients including FSVs. In adjunct therapy for hypercholesterolemia, hepatobiliary disorders, or extreme obesity, using bile salt or fat sequestrants (eg, cholestyramine and orlistat) can interfere with FSV absorption. The same is true for mineral oil and other nonabsorbable lipids. Vitamin D metabolism is adversely affected by chronic glucocorticoid and

phenobarbital therapy. Vitamin K metabolism is adversely affected by coumarin anticoagulant therapy.[1–3]

In the general population, deficiency states from limited intake are more common for vitamins A and D than for vitamins E and K. Deficiency risk increases with the absence or inadequate endogenous production of FSVs. For example, exclusively breastfed infants living at high latitudes are predisposed to vitamin D deficiency because of low vitamin D content in human milk and low sunlight exposure, which lowers vitamin D synthesis. Restricted food variety, which may occur because of limited financial resources or the adoption of fad diets, for example, can contribute to FSV deficiencies. Concomitant deficit in other nutrients is also common in these circumstances.

Except for vitamins A and E, the recommended dietary allowance (RDA) for FSVs is uniform across different ages, despite the increased nutritional requirements imposed by pregnancy and lactation. Increasing vitamin A intake is recommended during pregnancy (by ~7%) and lactation (~70%). Increasing vitamin E during lactation (~25%) is also recommended.[1–3,6]

Table 8-2 lists the fat-soluble multivitamin preparations for parenteral nutrition (PN). Patients who require prolonged total PN may face an increased risk of morbidity and mortality. This risk is exacerbated by an ongoing shortage of various vitamin preparations necessary for PN. Unfortunately, adult and pediatric intravenous products are not interchangeable because of differing FSV content per unit of volume and the presence of greater quantities of potentially toxic excipients in the adult preparations. The U.S. Food and Drug Administration (FDA), the American Society of Health-System Pharmacists (ASHP), and the American Society for Parenteral and Enteral Nutrition (ASPEN) provide guidance on managing these shortages.[7]

TABLE 8-2. Fat-Soluble Vitamins Content per Unit Dose of Multivitamin Preparations for Parenteral Nutrition

Ingredient	Infuvite Pediatric	Infuvite Adult
Unit dose volume, mL	5[a]	10[b]
Vitamin A (retinol), mg	0.7	1
Vitamin D (cholecalciferol), mcg	10[e]	5[e]
Vitamin E (DL-α- to- copheryl acetate), mg	7	10
Vitamin K (phytonadione), mcg	200	150

Data from manufacturer product insert: Baxter Inc. for Infuvite Pediatric and Infuvite Adult. Manufacturers, products, and product information can change frequently, so always check the manufacturer's website for the most current information.

Conversion for Vitamin A: 1 mg = 3300 USP units; Vitamin D: 10 mcg = 400 USP units; Vitamin E 10 mg = 10 USP units.

[a] Two single-dose vials: vial 2 (1 mL) contains folic acid, biotin, and vitamin B, and vial 1 (4 mL) contains all the other vitamins. The daily dose for infants and children weighing 3 kg or more up to age 11 years is 5 mL, for infants weighing 1–3 kg is 3.25 mL (65% of daily dose), and for infants weighing <1 kg is 1.5 mL (30% of daily dose).

[b] Supplied as unit vials or dual vials. The unit vial is a 2-chambered single-dose vial that must be mixed just before use and will provide 1 10-mL dose. Dual vials contain 2 vials labeled vial 1 (5 mL) and vial 2 (5 mL), with both vials to be used for a single 10-mL dose.

Multiple product shortages are an ongoing issue. The American Society for Parenteral and Enteral Nutrition (ASPEN) provides guidelines on the use of pediatric intravenous multivitamins when there is a shortage or nonavailability as follows:

- Shortage: Prioritize use for neonates <2.5kg or <36 weeks post-menstrual age due to the presence of propylene glycol and a higher content of polysorbate and aluminum in adult preparations.
- Non-availability:
  - For infants <2.5 kg or <36 weeks post-menstrual age. An adult intravenous multivitamin at a daily dose of 1 mL/kg and up to a maximum of 2.5 mL/d may be used. Additional vitamin K also needs to be added.
  - For infants >2.5 kg or >36 weeks gestation, add 5 mL of adult preparation plus vitamin K to make a total of 200 mcg/d.

For updates, consult the U.S. Food and Drug Administration and professional organizations, including the American Society of Health-System Pharmacists and ASPEN.

Prolonged storage or infusion times for PN infusate may interfere with complete delivery of certain parenteral nutrients. For example, vitamin A has been known to bind to intravenous bags and tubing, while other nutrients (eg, riboflavin, vitamin K1) may undergo photo-oxidation and lipid peroxidation. Thus, PN infusate (including lipid emulsion) for preterm infants should be photoprotected.[8] Furthermore, any patient on chronic parenteral or specific enteral nutrition support requires monitoring of FSVs and overall nutritional status.

Bioavailability of the enteral supplement may be improved with the water-miscible form or with alteration in the physical form, although parenteral supplementation may still be needed in patients with diseases that impair the absorption of FSVs.

Ingestion of FSVs, often in some combination of multiple vitamins, is a common practice among healthy adults and children. With the exception of vitamin A during infancy, the upper DRI limit for FSVs is 2 to >50 times the RDA[1–3] thus, supplementation is unlikely to result in adverse effects if it is similar to daily requirements. However, no consistent health benefits have been reported for these supplements, particularly for individuals without a documented nutrient deficiency. [9–12]

Chronic excess intake of vitamin A and vitamin D is widely known to have toxic effects on various organ systems. In some cases, a single exposure to a large dose of some FSVs may be toxic or even lethal. Certain individuals (eg, those with chronic alcohol abuse and liver dysfunction) may face a higher risk of adverse effects resulting from either excessive intake or deficiency in FSVs and other essential nutrients. Cigarette consumption increases the demand for antioxidants in addition to its other adverse effects. Any patient on pharmacological doses of FSVs should be under medical supervision.

Vitamin A

Biochemistry and Physiology

Vitamin A (or retinoids) refers to retinol and its derivatives; these include synthetic analogs that carry out similar biological activities and share the same β-ionone ring structure. They also include provitamin A carotenoids

that are the dietary precursor of retinol. The principal vitamin A compounds —retinol, retinal (retinaldehyde), retinoic acid, and retinyl esters—differ in the terminal C-15 group at the end of the side chain. The all-trans-isomer is the most common and stable form, although many cis-isomers also exist.

Retinoids play a pivotal role in facilitating cell differentiation and upholding the integrity of epithelial cells throughout the body. They promote the normal differentiation of the cornea and conjunctival membranes and ensure that retinal photoreceptor rod and cone cells function properly. Beyond these functions, they also maintain immune function and express diverse genes. Specifically, these genes encode for structural and extracellular matrix proteins, enzymes, retinol-binding proteins (RBPs). They also encode fornuclear hormone receptors such as retinoic acid receptor and retinoid X receptor, which are involved in mediated signaling and embryonic development of the hindbrain, eyes, ears, heart, and limbs.[1,13] The role of vitamin A as an antioxidant, along with its other potential biological effects, is likely influenced by its capacity to regulate gene expression related to the body's standard antioxidant responses. This mechanism is more responsible for these effects than the direct activity of vitamin A itself.[14]

The main biologically active retinoids in humans are the oxidized derivatives 11-cis-retinal and all-trans-retinoid acid (ATRA). ATRA is the final product of vitamin A and takes an acidic form. It binds to cellular retinoic acid-binding proteins (CRABP) or fatty-acid-binding protein (FABP), then is transported to the nucleus for gene-regulation activities. ATRA cannot be reduced back to retinal or retinol, nor can it be stored. Provitamin A carotenoids must be converted to retinoids to exert vitamin A function.[1,13,15]

Sources

Animal products (eg, liver/fish liver oils, dairy products, eggs) are rich sources of vitamin A primarily as retinyl esters, whereas provitamin A carotenoids (mainly β-carotene) are distributed widely in green and yellow vegetables, oils, and fruits.[16,17] Ripe-colored fruits and cooked yellow tuber vegetables are more efficiently converted to vitamin A compared with dark green leafy vegetables.

Most of the vitamin A found in human milk is in the form of retinyl palmitate, and it is primarily present in the milk fat. The highest concentration of this vitamin A occurs in colostrum and transition milk. The vitamin A content of human milk is generally lower in populations deficient in vitamin A, but is still sufficient to prevent subclinical deficiency in exclusively breastfed infants during the first 6 months.[18] Cow's milk contains less Vitamin A compared to human milk.[19] The FDA encourages dairy producers to fortify reduced-fat milk to 2000 IU/L.[20] Infant formulas are fortified with vitamin A at 250 to 750 IU/100 kcal.[20] High-temperature sterilization of milk increases isomerization of trans-retinol to cis-retinol by as much as 34%, thus reducing the stability and possibly the bioavailability of vitamin A.[1,13]

Consumption of preformed vitamin A is greater in high-income countries, while provitamin A is the main form consumed in low-income countries where diets include more plant-based foods. Enriched and fortified foods are widely available in low-income and middle-income countries as part of the effort to prevent vitamin A deficiency. They account for 34% to 40% of vitamin A intake among US children and adolescents.[5,21,22]

Vitamin A supplements are available in various forms, including retinol, retinyl esters (eg, palmitate, acetate, N-formyl aspartamate), retinaldehyde, and β-carotene. These can be found either as standalone supplements or as part of multivitamin formulations, and they come in both oral and parenteral forms.[23] Because vitamin A insufficiency and deficiency are common and excessive vitamin A doses can be toxic, the World Health Organization has provided guidelines for the quality of vitamin A supplements and regulations regarding their use. These guidelines apply to infants, young children, and pregnant or lactating individuals within public health programs.[24,25]

Vitamin A activity is expressed as retinol activity equivalent (RAE). The bioconversion of dietary provitamin carotenoids to RAE is estimated to be 12:1 (micrograms) based on the relative absorption efficiency of β-carotene from food and the functional carotene-to-retinol equivalency ratio. The RAE for dietary provitamin A carotenoids other than β-carotene is lower and set at 24 mcg. The use of micrograms of RAE is preferred to

micrograms of retinol equivalent (RE) or International Units (IUs) when calculating and reporting the amount of total vitamin A in foods or supplements.[1] Vitamin A activity of 1 mcg RAE is equivalent to 1 mcg all-trans-retinol, 2 mcg supplemental all-trans-β-carotene, 12 mcg dietary all-trans-β-carotene, 24 mcg other dietary provitamin A carotenoids, and 3.3 IU of vitamin A activity.

Absorption and Metabolism

The absorption efficiency of preformed vitamin A is about 70% to 90%. Vitamin A supplements, particularly β-carotene, are generally better absorbed than dietary vitamin sources.

A water-miscible preparation of a vitamin A supplement is available for use in patients with fat malabsorption. Preterm infants may lag in their ability to absorb vitamin A; elevating plasma retinol concentrations in this population requires parenteral administration.[28]

Dietary retinyl esters are freed by acidic digestion and emulsified by bile salts to form micelles. These micelles are transported to intestinal cells, where the retinyl ester crosses the mucosal membrane and is transformed into retinol after being hydrolyzed and re-esterified. The new form, retinol, is incorporated into intracell chylomicrons and secreted into the lymph. At physiological concentrations, the uptake and efflux of unesterified retinol by enterocytes are saturable processes mediated by lipid transporters. However, at high pharmacological doses, retinol absorption becomes unsaturable.[13,28,30]

Retinyl esters and carotenoids are transported to the liver in chylomicron remnants. Apoprotein E and several specific hepatic membrane receptors are required for the uptake of chylomicron remnants by the liver. Retinyl esters are hydrolyzed to retinol and then bound to RBP for release into the circulation.

In the blood, holo-RBP associates with transthyretin to form a trimolecular complex with retinol in a 1:1:1 molar ratio for delivery to peripheral tissues. Certain proteins are necessary for cellular function. These include cellular retinol-binding proteins and retinoic-acid-binding proteins I and II. Additionally, several families of nuclear receptors are

vital, which include retinoic acid receptors α, β, and γ (abbreviated as RARα, RARβ, RARγ), along with retinoid X receptors (RXR).[31]

Retinoids, generally in the form of retinyl esters, are stored in the liver and other tissues including adipose tissue, bone marrow, lung, eye, kidney, adrenal gland, testes, and other organs. When vitamin A intake is adequate, >90% of total body vitamin A is present in the liver. Vitamin A concentration of at least 20 mcg/g of liver in adults is suggested as the minimal acceptable reserve.[18]

The kidney is the main route of excretion of vitamin A and its metabolites. Typically, most vitamin A metabolites are excreted in the urine and are biologically inactive. However, elevated plasma concentrations of retinol, RBP, and transthyretin can occur in chronic renal disease. Some retinoid metabolites are conjugated with glucuronic acid or taurine in the liver for excretion in bile.

Carotenoid metabolizing enzymes, transporters, and binding proteins are critical to the absorption and bioconversion to support its function as vitamin A.[15,32,33] Carotenoids are absorbed into duodenal mucosal cells by passive diffusion and by a facilitated process that requires membrane proteins. The absorption efficiency of β-carotene has wide interindividual variation and is usually <20%.[1,34] Its absorption is higher in the presence of dietary fat. Additionally, processing methods such as homogenization, juicing, or cooking vegetables can facilitate the release of carotenoids. Carotenoid absorption also tends to increase during poor vitamin A status. Carotenoid absorption is lower in the presence of intestinal infections or infestations and during high dietary carotenoid intake. Furthermore, β-Carotene significantly reduces lutein absorption when both are consumed simultaneously.[1]

Carotenoids are transported to the liver in chylomicron remnants. They are incorporated into very low-density lipoproteins and exported from the liver into the blood. Receptor uptake brings these lipoproteins into peripheral tissues, where they metabolize further. The enzyme β,β-carotene 15,15’ is found in the intestine, liver, and lungs, as well as in adipose and other tissues. This enzyme allows central cleavage of β-carotene, forming two retinal molecules, which convert further to other retinoids that facilitate

essential biological functions. Eccentric cleavage of carotenoids by other enzymes is also possible.[1,13,15]

Genomewide association studies and candidate gene association studies have identified single nucleotide polymorphisms associated with blood concentrations of retinol and β-carotene as well as with β-carotene bioavailability. These genetic variations likely explain, at least in part, interindividual variability in vitamin A bioavailability and status.[36]

Deficiency

Vitamin A deficiency is an endemic nutrition problem throughout much of the developing world and affects the health and survival of infants, young children, and pregnant and lactating women.[19] These life-stage groups represent periods when both nutrition demand is high and the diet is likely to be chronically deficient in vitamin A. Impaired vitamin A intake and its link to decreased absorption and digestion can worsen malnutrition and lead to progressive negative effects on vital processes of the human body throughout the life cycle.[18,37]

Other risk factors for vitamin A deficiency include fat malabsorption conditions, strict vegan diets, fad diets, and severely restricted intake of preformed vitamin A or provitamin A. Ethanol decreases liver vitamin A stores by increasing the release of hepatic retinol independent of dietary intake and decreasing the conversion of β-carotene to retinol, thus promoting vitamin A deficiency.[1,13] For any patient being treated for vitamin A deficiency, determining the presence of deficiencies in other nutrients and appropriate treatment is prudent because they may also detrimentally affect vitamin A status. For example, zinc deficiency decreases the synthesis and secretion of RBP and transthyretin and the synthesis of rhodopsin.

Numerous clinical effects of vitamin A deficiency have been reported (see Exhibit 8-1). The most specific manifestation of vitamin A deficiency is xerophthalmia, which manifests as impaired dark adaptation, dryness (xerosis) of the conjunctiva and cornea, and may progress to corneal ulceration and necrosis (keratomalacia leading to irreversible blindness).[38]

EXHIBIT 8-1. Clinical Effects of Vitamin A Deficiency

- Xerophthalmia[a]
  - XN: Impaired dark adaptation (from the slowed regeneration of rhodopsin) to night blindness
  - XCj: Conjunctival dryness (xerosis); XB: keratinization (Bitot's spot)
  - XCo: Corneal xerosis; XU/K: Corneal ulceration and/or keratomalacia of any part; XSc: Corneal scar in central part; XSp: Corneal scar in peripheral part
  - XF: Xerophthalmia fundus
- Generalized dysfunction of cellular and humoral immunity with increased morbidity and mortality, especially from measles and diarrhea
- Impaired iron mobilization from stores
- Defective lung function
- Follicular hyperkeratosis

[a] Classification according to Singh.[39]

The level of retinol in the blood is under homeostatic control over a broad range of body stores and reflects body stores only when these are very low or very high.[1,13,18,25] Additionally, low plasma retinol concentration can stem from an inadequate supply of dietary protein, energy, or zinc. This can happen when the synthesis rate of RBP decreases. Alternatively, low plasma retinol concentration may arise from acute or chronic infections, which can lower concentrations of negative acute phase proteins (ie, RBP, transthyretin) even with adequate liver retinol. In situations that may alter plasma vitamin A concentrations, simultaneous measurement of plasma RBP can be helpful for a more accurate assessment of true vitamin A status. Changes over time in plasma retinol concentration distributions within a population can be helpful to determine vitamin A status. Sufficient plasma retinol concentration in adults and children is 1 to 3 μmol/L (1 μmol/L = 28.6 mcg/dL). Plasma retinol at <0.70 μmol/L reflects vitamin A inadequacy and at <0.35 μmol/L indicates vitamin A deficiency.[1,13,18]

Other measures of vitamin A status that show abnormalities in cases of clinical vitamin A deficiency include the following:

- Relative dose response
- Modified relative dose response
- Immune function tests
- Conjunctival impression cytology
- Dark adaptation test
- Pupillary response test
- Total liver reserve by isotope dilution

However, none of these measures have sufficient data related to the usual dietary intakes of individuals or populations. As a result, it can be challenging to adequately determine vitamin A status. Some of these tests (eg, relative dose response, modified relative dose response) may be influenced by other factors, such as RBP production, that can influence their outcomes.[1,13,18]

For infants and young children with vitamin A insufficiency, the risk of mortality associated with diarrhea is reduced, and night blindness and other morbidities are significantly improved with vitamin A supplementation.[39,40] For preterm very low birth weight (<1500 g) infants, elective vitamin A supplementation by intramuscular route did not achieve a statistically significant reduction in death or chronic lung disease.[28] Oral vitamin A supplementation decreased noninvasive ventilatory support by a mean of 0.96 days.[41] Poor nutritional status is well known to impair wound healing. However, numerous nutrients, including proteins, vitamin A, vitamin C, vitamin B complex, arginine, glutamine, iron, zinc, and selenium, can have significant beneficial effects on wound healing and optimization of the immune system.

No evidence exists for a certain percentage of provitamin A carotenoids to meet the vitamin A requirement. However, adherence to the recommended dietary guidelines on fruit and vegetable consumption is likely to provide a significant amount of provitamin A to the RDA for vitamin A.[1,5]

Adverse Effects

Adverse effects of high vitamin A intake exist although there are wide interspecies and interindividual differences.[13,42] Individuals with

preexisting liver disease, hyperlipidemia, severe protein malnutrition, or high alcohol intake may be distinctly susceptible to the adverse effects of preformed vitamin A intake.

Acute toxicity occurs when children and adults ingest >20 to 100 times the RDA for vitamin A, respectively.[13,42] Acute toxicity is characterized by nausea, vomiting, headache, vertigo, blurred vision, muscular incoordination, and increased intracranial pressure.[13,42–44] Animal studies demonstrated that a similarly large single dose of vitamin A can be lethal.[45]

Infants with prolonged exposure to high-dose vitamin A may have varied and nonspecific manifestations, including irritability, anorexia, skin desquamation, and liver abnormalities including elevated liver enzymes, fibrosis, and cirrhosis. Laboratory findings of cortical hyperostosis, hypercalcemia, hyperphosphatemia, and metastatic calcifications may occur at an intake between 5500 and 6750 mcg/d for 1 to 3 months.[1,43] During a period of 1−6 months, infants who consume a moderately high daily dose of vitamin A (>600 mcg, a tolerable upper limit of intake), both from fortified foods and varying quantities of OTC low-dose vitamin A supplements, present with elevated total body and liver vitamin A (>1 μmol/g liver). However, clinical or biochemical indications of vitamin A toxicity have not been reported (eg, bone turnover, liver enzyme activity).[46]

In adults, vitamin A supplementation at or above 2000 mcg/d is associated with lower bone mineral density and hip fractures.[42] Retinoid supplementation enhances the activation of replication-competent viral reservoirs from individuals on suppressive antiretroviral therapy, although this might be a strategy for latent viral infection treatment.[47]

From the population perspective, chronic “hypervitaminosis A” from high dietary intake and self-administrated vitamin A supplementation may be of greater importance than a single high dose of vitamin A in the development of vitamin A toxicity.

Ethanol, while it promotes a deficiency of vitamin A, also enhances vitamin A hepatotoxicity.[13,42,48] Caution should be exercised when administering vitamin A supplementation to patients with renal dysfunction. This is because the kidney is the main route for excretion of vitamin A and its metabolites. Plasma retinol and RBP concentrations may not always provide reliable indicators of vitamin A toxicity. Instead, the presence of

plasma retinyl esters, which are typically absent, can serve as a marker for vitamin A toxicity.

Teratogenic effects in humans are extensively documented, particularly neural crest defects arising from naturally occurring metabolites of vitamin A (eg, trans-retinoic acid, 13-cis-retinoic acid, and their oxo-derivatives). These effects are observed primarily in pregnant women exposed during the first trimester. Data linking teratogenic effects to high-dose preformed vitamin A (ie, retinol and retinyl esters) are limited, as are data which might determine toxic nonteratogenic developmental effects.[1,13,24,42,49] Adolescents using vitamin A or derivatives for the treatment of acne must be informed of the potential teratogenic effects and counseled on the need to avoid pregnancy during this therapy.

High β-carotene intake has not been shown to cause hypervitaminosis A presumably because the absorption and conversion of provitamin A are limited by negative feedback mechanisms.[1,15,25,50] However, carotenoderma (a yellowish discoloration of the skin from hypercarotenemia) has been reported. Discontinuing intake reverses this condition. Biochemical vitamin A toxicity may occur in children who consume biofortified maize, although overt clinical toxicity has not been reported. Biochemical toxicity in this scenario is based on retinol isotope dilution studies showing a high total body vitamin store along with RBP saturation and elevated serum concentrations of α-carotene, β-carotene, lutein, and retinyl ester.[50]

The use of β-carotene supplement with or without retinoid shows little or no benefit in preventing cancer, cardiovascular disease, or death.[12] This and other antioxidants also will not delay the onset of age-related macular degeneration.[9] Excessive intake of the provitamin A carotenoids may have unintended consequences on the complex and intricately balanced natural antioxidant defense system.[51] Beta carotene was associated with an increased risk of lung cancer and other harmful outcomes in persons at high risk of lung cancer.[12,48] Also, the combination of excess β-carotene and ethanol may result in hepatotoxicity.[1,48]

Vitamin D

Biochemistry and Physiology

Vitamin D (calciferol) refers to 2 fat-soluble seco-sterols: cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2). Vitamin D_3 is photosynthesized by ultraviolet light, with the most effective wavelengths between 290 and 315 nm. This process occurs on a cholesterol precursor in the skin of vertebrates, whereas Vitamin D_2 is sourced from yeast and plant sterols. The term "vitamin D" without the subscript is frequently used generically to describe vitamins D_2 and D_3 and, correspondingly, their metabolites. The parent vitamin D compounds are biologically inert and are regarded as prohormones. These prohormones undergo 2 obligatory hydroxylation steps to form 25 hydroxyvitamin D (25 (OH)D) in the liver and 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) in the kidneys.

Quantitatively, 25(OH)D is the major circulating metabolite. It reflects the cumulative effects of exposure to sunlight and dietary intake of vitamin D and is a good marker of vitamin D status. However, improving the diagnosis and management of abnormal vitamin D status will require standardizing laboratory assays for 25(OH)D and other potential vitamin D biomarkers (eg, other metabolites of vitamin D, vitamin D–binding protein, free or bioavailable 25(OH)D, and parathyroid hormone [PTH]).[52] At physiological concentrations, $1,25(OH)_2$_D is the metabolite that mediates most of the biological functions of vitamin D.[53] However, plasma $1,25(OH)_2D$ is not a good marker of vitamin D status. This is because of its short half-life. Its concentration also fluctuates in response to changes to plasma calcium and phosphorus and is under the control of multiple hormones.

The classic actions of vitamin D include the maintenance of calcium homeostasis and bone mineralization in the prevention of rickets in children and osteomalacia in adults. The receptor-mediated action occurs in various feedback loops involving PTH, fibroblast growth factor-23 (FGF-23), and a calcitonin response to changes in plasma calcium and phosphorus. There is also $1,25(OH)_2$_D_3-mediated gene regulation for several bone anabolic and resorbing factors. VDR is widely distributed in numerous organ systems, and $1,25(OH)_2$_D_3-VDR effects include immunomodulation, antimicrobial

action, detoxification, cell proliferation, apoptosis regulation, insulin secretion, skin integrity, and β-oxidation.[53–55]

The actions of the VDR pathway in different tissues and cell types are mediated through various pathways, including endocrine, paracrine, and autocrine processes. These actions are regulated by a combination of genomic, nongenomic, and epigenomic effects. In addition to the well-known ligand $1,25(OH)_2D_3$, other compounds like lithocholic acid, curcumin, γ-tocotrienol, and derivatives of essential fatty acids may also have specific roles in physiological functions and potential therapeutic applications for various diseases.[54,55]

Disturbances in vitamin D pathways are associated with major human diseases, including cancer, infections, autoimmune diseases, cardiovascular issues, metabolic diseases, muscle function disorders, reproductive problems, and neurocognitive issues. Thus, it is crucial to prevent or correct severe vitamin D deficiency. However, supplementation of vitamin D–replete individuals does not provide demonstrable health benefits.[10–12]

Biological activity of vitamin D is expressed in Ius based on bioassays using cholecalciferol. The biological activity of 1 mcg of vitamin D is 40 IU while 1 mcg of 25(OH)D is 200 IU (ie, 5 times more potent than cholecalciferol).[2] Both forms of vitamin D undergo the same metabolic fate, although the efficacy of the best form of vitamin D to raise serum 25(OH)D concentration remains in dispute.[56,57] However, both forms of vitamin D have similar functions, particularly in the classic actions related to the clinical prevention and treatment of rickets and osteomalacia. The ubiquitous presence of the VDR in numerous cell systems is associated with a wide range of potential roles for vitamin D in clinical disorders. However, apart from its critical role in the maintenance of bone and mineral metabolism, its cause-and-effect relationship with other clinical disorders remains to be defined.[10–12]

Sources

Endogenous synthesis of vitamin D_3 requires exposure to sunlight or irradiation in the ultraviolet B range. It is extremely efficient, and a 10-minute to 15-minute whole-body exposure to peak summer sun will

generate and release up to 500 mcg (20,000 IU) of vitamin D_3 into the circulation.[58,59] Cutaneous production of vitamin D_3 is substantially diminished by decreased exposure to sunlight from seasonal changes or time of day, clouds, aerosols, thick ozone, higher latitude, aging, clothing, sunscreen use, and melanin pigmentation.[59] In dark-skinned individuals, endogenous synthesis of vitamin D is possible, although the rate of production is lower than in less-pigmented individuals. Concerns regarding the hazards of ultraviolet radiation exposure have led to revised recommendations for sunlight exposure.[60] Consequently, ensuring adequate vitamin D status, especially in the presence of factors that affect its endogenous synthesis, requires attention to dietary vitamin D supplementation.

Foods naturally rich in vitamin D are limited to the flesh of fatty fish and fish liver oil and the liver and fat from aquatic mammals (eg, seals and polar bears). Thus, dietary intake of vitamin D from foods comes primarily from fortified milk products and other fortified foods such as breakfast cereals.[5,16,17] In the United States and Canada, the average intake of vitamin D is about 5 to 10 mcg (200–400 IU) per day, with children tending to have greater intake than adults.[5] Human milk and cow's milk have very low vitamin D content (<1.25 mcg/L or 50 IU/L). In the United States, a vast majority of natural milk and all infant formulas are fortified with vitamin D_3 at 10 mcg/L (400 IU/L)[19] and 1 to 2.5 mcg/100 kcal (40–100 IU/100 kcal),[20] respectively. The amounts of vitamin D added to milk products were erratic during the early 1990s, but vitamin D fortification has been more uniform subsequently.[19]

Vitamin D is available primarily as vitamin D_3 in the form of standalone supplements, multivitamin formulations, and fortified food. The parent vitamin D compound is available in parenteral form only as part of multivitamins. The more potent vitamin D analog or hydroxylated vitamin D metabolites are available in oral and parenteral forms. These forms are frequently employed to address specific medical conditions and should not be regarded as nutrients.[61] For example, 25(OH)D is used as a supplement for patients with hepatic disease, and vitamin D analogs with minimal or no

calcemic effects are used for their antiproliferative and prodifferentiation actions.

Absorption and Metabolism

Intestinal absorption of vitamin D and its metabolites requires normal bile and pancreatic secretions. Once absorbed from the intestine, it is incorporated into chylomicrons and transported through the lymphatic system. Both endogenously synthesized vitamin D and dietary vitamin D, along with their metabolites, are transported in the bloodstream. This transport primarily occurs through a specific vitamin D binding protein and albumin to various tissues in the body. Structural differences in vitamin D_3, vitamin D_2, and their metabolites alter both their binding to the carrier protein and their metabolism. The bioavailability of vitamin D_3 compared to D_2 is a topic of controversy regarding the maintenance of circulating 25(OH)D concentrations.[56,57]

Cytochrome P450 enzyme CYP2R1 (vitamin D 25 hydroxylase) hydroxylates vitamin D to 25(OH)D in hepatic mitochondria, and subsequent hydroxylation occurs at the 1-carbon position to the most active metabolite, $1,25(OH)_2D$, with CYP27B1 (1α-hydroxylase) in the kidney. The major catabolic enzyme (CYP24A1, 24 hydroxylase) results in hydroxylation at the 24-carbon of 25(OH)D and $1,25(OH)_2D$. Further metabolic degradation is through C23 lactone and C24 oxidation pathways and results in the urinary excretion of 26,23 lactone and calcitroic acid, respectively.[54,55]

Excessive unregulated production of $1,25(OH)_2D$ by activated macrophages and lymphoma and other cells may exert paracrine or autocrine actions and even hypercalciuria and hypercalcemia. Additionally, there are at least 8 genes reported to genetically predispose individuals to higher or lower concentrations of vitamin D metabolites.[54,55] For example, the absence or mutation of the gene for the 24-hydroxylase enzyme results in the accumulation of $1,25(OH)_2D$. This can lead to neonatal hypercalcemia as well as nephrocalcinosis or the development of multiple kidney stones in adulthood.[63,64] Enterohepatic circulation of vitamin D and

its metabolites is present but probably has a limited role in their conservation.[65]

Circulating parent vitamin D is short-lived because it is either stored in the fat or metabolized in the liver. The half-life of circulating 25(OH)D is 10 days to 3 weeks. The half-life of $1,25(OH)_2D$ is approximately 4 to 6 hours.[66–68] Individuals with obesity have significantly greater total vitamin D stores than normal weight controls, although the concentration of vitamin D in omental and subcutaneous fat are similar between groups. Additionally, serum 25(OH)D was directly related to adipose vitamin D.[69] The lower circulating 25(OH)D levels in individuals with obesity may have multiple causes. One possible reason is that these individuals may require a larger amount of vitamin D to saturate their adipose tissue reservoir. An additionalcontributing factor could be altered vitamin D metabolism in adipose tissue and other target organs could be a contributing factor. This altered metabolism may play a role in modulating inflammation, adipogenesis, adipocyte differentiation, and cytokine secretion.[54,69–71]

Deficiency

Clinical deficiency states of vitamin D can result from different factors. These include a lack of vitamin D_3 production in the skin, insufficient dietary intake, problems with the absorption or metabolism of vitamin D into its active form, $1,25(OH)_2D$, or difficulties with the recognition of $1,25(OH)_2D$ by its receptor. Drugs such as glucocorticoids inhibit vitamin D–dependent calcium absorption. Phenobarbital and phenytoin can alter the metabolism and circulating half-life of vitamin D metabolites. Chronic therapy with these and other medications predisposes patients to vitamin D deficiency.

Rickets is characterized by widening at the ends of long bones, rachitic rosary, deformations including bowed legs and knock knees, and frontal bossing of the skull. Abnormal calcification of enamel and dentin of developing teeth increases susceptibility to caries. Additionally, secondary hyperparathyroidism occurs as a homeostatic response; it counteracts the decline in circulating ionized calcium concentrations resulting from vitamin D deficiency. PTH has the dual role of mobilizing calcium from the

skeleton, which can lead to the development of porotic bones. Simultaneously, it conserves renal calcium while increasing phosphorus excretion, resulting in low or absent urine calcium and elevated urine phosphorus concentrations.

Thus, vitamin D deficiency is characterized by a low circulating concentration of 25(OH)D, normal fasting circulating calcium with low or low normal phosphorus, and elevated PTH. Hypocalcemia can occur late in chronic vitamin D deficiency when there is significant depletion of skeletal calcium. Vitamin D deficiency leads to increased bone turnover, which is indicated by higher concentrations of specific markers in the circulation and/or urine. These markers include bone alkaline phosphatase, collagenous bone proteins (eg, hydroxyproline, pyridinoline, deoxypyridinoline), as well as N-teleopeptides and C-teleopeptides (amino- and carboxyl-terminal collagen crosslinks). Additionally, noncollagenous bone proteins, such as osteocalcin, may also be elevated.[72]

Based on genetic, molecular, cellular, and animal studies, it is possible that vitamin D signaling has many extraskeletal effects, including regulation of cell proliferation, immune and muscle function, skin differentiation, and reproduction, as well as vascular and metabolic properties. From observational studies in human participants, poor vitamin D status is associated with nearly all diseases predicted by these extraskeletal actions.[53,55,73] However results from randomized controlled trials and Mendelian randomization studies are mixed.[10,53] Supplementation in individuals who are vitamin D–replete does not provide demonstrable health benefits, and in some situations, may have detrimental effects on the underlying disease.[74] In any case, it remains true that severe vitamin D deficiency should be prevented or corrected.

Based on the traditional Gaussian distribution, the lower limit of serum or plasma 25(OH)D is in the range of 10 to 15 ng/mL (1 nmol/L = 0.4 ng/mL). In the development of dietary reference intakes (DRIs), the Institute of Medicine committee considered integrated bone health outcomes and vitamin D exposure. They recommended the following concentrations of plasma or serum 25(OH)-D[2]:

- <30 nmol/L as indicative of deficiency

- 30 to 49 nmol/L as indicative of inadequacy
- 50 to 125 nmol/L as sufficient
- 125 nmol/L (1 nmol/L = 0.4 ng/mL) as possibly harmful

Multiple publications have assessed vitamin D deficiency based on circulating 25(OH)D concentrations, often using it as the sole criterion. Sometimes, higher cutoff points for defining vitamin D deficiency are applied. These variations in approach have led to controversies regarding the prevalence of vitamin D deficiency and have resulted in conflicting recommendations for vitamin D intake.[75] Widespread occurrence of low circulating 25(OH)D concentrations exists in children and adults, and a target of ≥ 50 nmol/L (20 ng/mL) is generally accepted to represent an adequate vitamin D status. The occasional clinical manifestation of rickets in nonsupplemented infants and children has raised the recommended daily vitamin D intake to 10 mcg (400 IU) in infants and 15 mcg (600 IU) in children.[4] However, serum 25(OH)D concentrations above 75 nmol/L (30 ng/mL) are not associated with increased benefit,[76,77] and vitamin D supplement does not reduce all-cause mortality, cardiovascular disease, or cancer outcomes.[10–12]

Adverse Effects

Vitamin D toxicity from prolonged exposure to natural sunlight has not been reported. Increased sunlight exposure leads to a decrease in endogenous production of vitamin D_3 by conversion of previtamin D_3 to inactive metabolites. Inhibition of the 25-hydroxylase enzyme results in decreased production of 25(OH)D_3. Simultaneously, stimulation of the 24-hydroxylase enzyme increases the metabolic degradation of vitamin D metabolites. These mechanisms collectively contribute to the prevention of hypervitaminosis D and vitamin D toxicity.

Excessive vitamin D intake from supplements can result in hypervitaminosis D and is characterized by a considerable increase in plasma 25(OH)D in the range of 400 to 1250 µmol/L (160–500 ng/mL).[78,79] Other vitamin D metabolites are also elevated.[79] Clinical toxicity is manifested through hypercalcemia, and its multiple debilitating effects include polyuria, polydipsia, depression, and metastatic calcification of soft

tissues including the kidney, blood vessels, heart, and lung. These effects are generally seen with chronic supplementation of over 500 mcg (20,000 IU) daily, although toxicity can occur at lower doses.[80] Toxicity from chronic intake of ergocalciferol appears to require significantly higher doses.[81] It is possible that this lower toxicity may be a result of its relatively low bioactivity compared to cholecalciferol.

High doses of vitamin D or its metabolites or analogs are often used for the treatment and prevention of deficiency states.[61,82] However, the potential for vitamin D toxicity under these circumstances exists, and practitioners should consult the current recommendations of vitamin D dosing for specific conditions.

Vitamin E

Biochemistry and Physiology

Vitamin E has 8 naturally occurring forms: 4 tocopherols (α, β, γ, and δ) and 4 tocotrienols (α, β, γ, and δ), all in the RRR form. The RRR form of α-tocopherol is maintained in human plasma and occurs naturally in foods. Eight different stereoisomers in equal amounts are found in synthetic vitamin E (all rac-α-tocopherol): RRR, RSR, RRS, RSS, SRR, SSR, SRS, and SSS forms with structural differences at the side chain and the ring and tail junction. The various forms of vitamin E are not interconvertible in the human body, and α-tocopherol is the only vitamin E molecule that prevents the human deficiency condition of ataxia with vitamin E deficiency (AVED).[83]

Vitamin E serves as an essential physiological antioxidant. It achieves this by scavenging reactive oxygen species and related compounds, thereby inhibiting the oxidation of lipids, proteins, and DNA bases. These actions protect cell membrane polyunsaturated fatty acids, as well as thiol-rich proteins and nucleic acids.

Vitamin E may play an important role in the modulation of signal transduction and gene expression pathways.[84–86] Opposing regulatory effects of vitamin E isomers such as the anti-inflammatory effect of α-tocopherol and the proinflammatory effect of γ-tocopherol might be responsible for the seemingly conflicting clinical outcomes.[87]

The mechanism of vitamin E biologic activity is different from its antioxidant activity. The plasma concentration and biological activity of different forms of vitamin E are dependent primarily on the affinity of α-tocopherol transfer protein (α-TTP) for them. RRR α-tocopherol has the highest affinity for α-TTP. Other forms of vitamin E stereoisomers have much lower binding affinity to α-TTP.[3,88] They may have some biological functions, and their intakes are reported as α-tocopherol equivalents.[3,83,84]

Current recommendations for vitamin E intake include only the 2R-stereoisomeric forms of α-tocopherol (ie, RRR, RSR, RRS, SRR) because they are maintained in human plasma or tissue. Data on intakes from current surveys and nutrient content in foods are presented as α-tocopherol equivalents (α-Tes). This presentation includes all 8 naturally occurring forms of vitamin E. Additionally, the data are adjusted for bioavailability using previously determined equivalencies. For example, γ-tocopherol is estimated to have only 10% of the bioactivity of α-tocopherol.

About 80% of the α-TE from foods is contributed by foods containing α-tocopherol. Thus, the intake of α-TE is usually greater than the intake of α-tocopherol alone.[3,5,86] The milligrams of α-tocopherol in a meal including fortified food or multivitamin are based on the following conversion factors:

= 0.8 × mg α-TE in a meal
= 0.67 × IUs of the RRR-α-tocopherol compound
= 0.45 × IUs of all rac-α-tocopherol compound

If diets vary considerably from what might be considered typical in the United States or Canada, a conversion factor other than 0.8 might be more appropriate. All forms of supplemental α-tocopherol are used to establish the tolerable upper intake level for vitamin E because all forms of vitamin E are absorbed.[3]

Sources

The main dietary sources of vitamin E are edible vegetable oils. All of the α-tocopherol present in natural foods is in the RRR-α-tocopherol form. Oils from wheat germ, sunflower, safflower, canola, olive, and cottonseed

contain >50% of the tocopherol as α-tocopherol. Soybean and corn oils contain approximately 10 times as much γ-tocopherol as α-tocopherol. Palm and rice bran oils contain high proportions of α-tocopherol, as well as various tocotrienols. Meat, poultry, fish, dairy products, nuts, grains, and fruit, especially the oils or fatty portions, are other sources of α-tocopherol.[3,16,17] Colostrum and human milk are rich sources of vitamin E.[89] Infant formulas are fortified with a minimum of 0.7 IU/100 kcal.[20] Infant formulas fortified with the natural form of α-tocopherol have better bioavailability compared with those using the synthetic forms.[90]

Estimating dietary intake of vitamin E is difficult because the source of oil is not always certain and most nutrient databases and nutrition labels do not distinguish among the different tocopherols in food. Food preparation, such as deep-frying using vegetable oil, leads to chemical structure modification and may result in functional discrepancy. Vitamin E esters such as acetate, phosphate, and succinate from natural RRR or the synthetic mixture (all-rac) of α-tocopherol can serve as water-soluble precursors of vitamin E. They are commonly used in food fortification, supplements, and pharmacological agents.[91]

Vitamin E supplements are available alone or as multivitamins in oral preparation. Vitamin E is available in parenteral form only as part of a multivitamin.[23] A water-miscible formulation of vitamin E, tocopheryl polyethylene glycol succinate 1000 (TPGS), is approved by the FDA as a safe adjuvant and is used in drug delivery systems (stabilizer, solubilizer, bioavailability enhancer of hydrophobic drugs).[92] Nanoformulations have been used in the delivery of lipophilic drugs because their small size and large surface area can facilitate drug absorption. Nanoformulation of vitamin E, especially tocotrienols, is attractive due to the latter's poor bioavailability.[93]

Absorption and Metabolism

Reports of vitamin E absorption from the intestinal lumen vary widely from 21% to 86%. In healthy humans, the esters are hydrolyzed and absorbed as efficiently as α-tocopherol. The absorption of various forms of vitamin E is independent and shows similar apparent efficiency. Absorption efficiency depends upon biliary and pancreatic secretions, micelle formation, uptake

into enterocytes, and chylomicron secretion.[3,86] Vitamin E absorption is facilitated by dietary fat, bile salts, and pancreatic enzymes, and is lowered following vitamin E supplementation.[94] The RRR stereoisomer has roughly twice the availability of the synthetic all-rac forms.

Newly absorbed vitamin E binds to chylomicron. During chylomicron catabolism, vitamin E is distributed to circulating lipoproteins reaching various tissues. Chylomicron remnants, containing newly absorbed vitamin E, are taken up by the liver. Vitamin E rapidly transfers among lipoproteins and between lipoproteins and cell membranes, which may enrich cell membranes with vitamin E. The human plasma phospholipid transfer protein accelerates this process.[95]

The high affinity of hepatic α-TTP to α-tocopherol over all other vitamin E isomers supports the key role of the liver in the uptake, storage, and re-release of α-tocopherol. These processes can be dysregulated with excess liver fat accumulation and subsequently drive liver disease.[96] Adipose tissue and muscle are other major storage sites for vitamin E.[86,88,97,98] Circulating α-tocopherol has a relatively rapid turnover, although the flux of α-tocopherol from stores is slower. This supports the body's ability to maintain normal vitamin E status for extended periods, except during extreme oxidative stresses (see "Vitamin E Deficiency" section).

Peak plasma concentration (Tmax) of tocopherols is 6 hours, while Tmax for tocotrienols is about 3 to 4 hours. Plasma concentration (Cmax) is higher with tocopherols than tocotrienols. The plasma elimination half-life ($t_{1/2}$) for α-tocopherol is about 20 hours, while it is 2.3 to 4.4 hours for tocotrienols.[93,99]

The 4 tocopherols are ultimately degraded by ω-oxidation and subsequent β-oxidation, followed by the elimination of the metabolites in the bile and urine.[100] Excess α-tocopherol, as well as vitamin E forms that are not preferentially used, are excreted unchanged in the stool and bile.

When vitamin E intercepts a radical, α-tocopherol is oxidized to the tocopheryl radical, a 1-electron oxidation product.[83] Tocopherol radical can be reduced (ie, to regenerate α-tocopherol) by other antioxidants including vitamin C, glutathione, and ubiquinols. The tocopherol radical can undergo further metabolism and is excreted in urine. It may also act as a pro-oxidant

in the absence of a water-soluble antioxidant and oxidize other lipids in vitro. Whether this occurs in vivo is inconclusive. Vitamin E compounds other than RRR-α-tocopherol are preferentially metabolized and excreted.[3,86]

Deficiency

Plasma α-tocopherol concentrations <12 μmol/L equivalent to <0.51 mg/L (1 μmol/L = 0.042 mg/dL) are widespread in many populations.[101] Such low concentrations have been associated with an increased risk of infection, hemolytic anemia, retinopathy, growth stunting, and adverse pregnancy outcomes for both the mother and infant. It is worth noting that overt clinical deficiency resulting from low dietary vitamin E intake is unlikely in normal individuals unless they experience significant oxidative stresses. Lower placental transfer of α- tocopherol and oxidative stress during delivery may contribute to lower plasma α-tocopherol concentrations in preterm (>34 weeks) and term neonates at ≤ 8.5 mmol/L and ≤ 14.9 mmol/L, respectively.[102]

Clinical vitamin E deficiency from inadequate intake is difficult to assess because vitamin E requirements increase with increased intake of polyunsaturated fatty acids, high-level physical activity, and cigarette smoking. However, the extent of the increased requirement and the compensatory effects of other antioxidants are not defined. Intake of plant phenolic compounds and flavonoids may add to the total antioxidant pool. Cellular redox cycling is coupled to the energy status of the organism. Thus dietary deficiencies of niacin or riboflavin might result in insufficient reducing equivalents for recycling oxidized products.[3,86]

Human vitamin E deficiency is most frequently secondary to fat malabsorption syndromes. Genetic α-TTP defects are associated with a characteristic syndrome of ataxia with vitamin E deficiency, AVED. Defects in α-TTP or abetalipoproteinemia result in low hepatic preventing protein function.[86,103]

Vitamin E deficiency causes axonal degeneration of the large myelinated axons and results in posterior column and spinocerebellar symptoms. Peripheral neuropathy is initially characterized by areflexia. It progresses to an ataxic gait and is accompanied by decreased vibration and position

sensations. Ophthalmoplegia, skeletal myopathy, and pigmented retinopathy also may occur.[3,83,86] Neurological symptoms can progress if untreated and may be reversed if treated early. Increased erythrocyte fragility in vitro and hemolytic anemia with vitamin E deficiency are reversible with adequate replacement of vitamin E.

Vitamin E adequacy cannot be assessed with plasma α-tocopherol alone because plasma α-tocopherol concentrations are elevated in the presence of hyperlipidemia. Abnormal lipoprotein metabolism with elevated plasma lipids does not necessarily increase α-tocopherol delivery to the tissues. Simultaneous measurement of circulating lipids or cholesterol should be performed, although plasma α-tocopherol level at <12 μmol/L (0.5 mg/dL) is consistent with vitamin E inadequacy.[86,101]

In individuals with elevated serum lipids, vitamin E is "trapped" in the circulation, and a ratio of serum α-tocopherol to serum total lipids of <0.6 mg/g in children and <0.8 mg/g in adults indicates vitamin E deficiency regardless of serum α-tocopherol concentrations. In individuals with normal serum lipid concentrations (328–573 mg/dL), corrections are not necessary to assess whether α-tocopherol concentrations are within the normal range.[86,104] Hydrogen peroxide–induced hemolysis and lipid peroxidation biomarkers in plasma, urine, or breath are elevated during vitamin E depletion and are normalized upon vitamin E repletion. However, these markers are nonspecific and may vary with intake of other antioxidants.

Routine supplementation of vitamin E in high doses is recommended for specific disorders such as hepatobiliary disorders and cystic fibrosis. In most malabsorptive states, plasma α-tocopherol can be elevated to normal ranges, but other clinical benefits are not well documented.[104]

Vitamin E supplementation is a subject of controversy when it comes to individuals who are not vitamin E deficient. No conclusive data support using high vitamin E intake for managing chronic illnesses.[3,9,12,86] Ingestion of supplements containing vitamin E, vitamin C, zinc, and optional beta-carotene, as well as variable amounts of manganese, selenium, copper, docosahexaenoic acid, lutein, zeaxanthin, resveratrol, and hydroxytyrosol, may have a beneficial effect. This effect includes improving the proinflammatory and proangiogenic profiles of patients with age-related macular degeneration. However, there was no significant

differential effect on visual acuity compared to the control group.[105] Vitamin E supplement does not reduce all-cause mortality, cardiovascular disease events, or cancer incidence.[12]

Adverse Effects

All forms of vitamin E are absorbed and could contribute to vitamin E toxicity, although not all forms are maintained in plasma. Normal adults appear to tolerate oral tocopherol intake of 100 to 800 mg/d,[106] but adverse effects from the consumption of vitamin E as a supplement or pharmacological agent are possible. Vitamin E supplementation may be associated with hemorrhagic stroke.[12] Individuals deficient in vitamin K or those on anticoagulant therapy may be at an increased risk for coagulation defects from high vitamin E intake.[3,86] Preterm infants born at <1.5 kg with elevated plasma vitamin E at a mean of 5.1 mg/ dL have an increased incidence of sepsis and necrotizing enterocolitis.[107] Plasma α-tocopherol concentrations are not informative for assessing adverse effects because they plateau at approximately 3 to 4 times the values for nonsupplemented individuals.[3]

Vitamin K

Biochemistry and Physiology

Vitamin K belongs to the family of 2-methyl-1,4-naphthoquinones. Two naturally occurring compounds exhibit vitamin K activity: vitamin K_1 (phylloquinone, phytomenadione, and phytonadione) and vitamin K_2 (menaquinone). Vitamin K_1 is derived from plants, while vitamin K_2 originates from animals or is synthesized by intestinal bacteria. Different strains of bacteria can produce various forms of menaquinones. These forms can differ in the number of 5-carbon prenyl units they contain. The number of prenyl units, in turn, plays a role in governing processes such as transport, target tissue uptake, and subsequent excretion. Menadione (vitamin K_3) is chemically synthesized and contains only the 2-methyl-1,4-naphthoquinone core. Other synthetic forms of vitamin K, also known as vitamin K_4, may include a reduced form of vitamin K_3 (menadiol) or its

ester forms (eg, diacetate vitamin K_3). In contrast to the natural forms of vitamin K, synthetic forms of vitamin K are hydrophilic and have greater bioavailability. Long-chain menaquinones have about 60% of the activity of phylloquinone.[1,108]

Vitamin K, in its reduced form, serves as a cofactor for γ-glutamyl carboxylase enzymes. These enzymes are responsible for the posttranslational carboxylation of glutamic acid (Glu) residues, transforming them into γ-carboxyglutamyl (Gla) residues. This process occurs in a subclass of proteins known as vitamin K–dependent proteins, also referred to as γ-carboxylated proteins or Gla-proteins. The major Gla-proteins include procoagulatory and anticoagulatory. Procoagulatory proteins include prothrombin (coagulation factor II) and factors VII, IX, and X; and the anticoagulatory proteins include C, S, and Z. GLA-proteins expressed in connective tissues with osteocalcin (bone Gla protein) increase bone mineralization, whereas matrix Gla-proteins block mineralization in other tissues such as blood vessels, where it would be pathological. Other putative noncofactor functions of vitamin K include suppression of inflammation, prevention of brain oxidative damage, and involvement in sphingolipid synthesis.[1,108,109]

Sources

Vitamin K content in most foods is very low (<10 mcg/100 g), and the majority is obtained from a few leafy green vegetables.[110] Hydrogenation of plant oils to form solid shortenings results in some conversion of phylloquinone to 2′,3′-dihydrophylloquinone, but it is uncertain whether these forms are metabolically and functionally identical. These forms of vitamin K are most prevalent in margarines, infant formulas, and prepared foods.[1,16,17,111–113]

Phylloquinone exhibits relatively stable properties when heated but is highly sensitive to natural and fluorescent light. When subjected to heating, its content decreases by <20%. However, exposure to light can result in a reduction of up to 80%.

Menaquinones are produced from bacterial fermentation during the production of cheese and fermented vegetables such as sauerkraut, and in Japan, natto.[111,112] They are endogenously produced in the human intestine

but are probably insufficient to meet the daily requirement for vitamin K.[114] The type of vitamin K produced endogenously is dependent on which species of bacteria is present.

Vitamin K is present in low concentrations in human milk (<5 mcg/L).[4] Commercial infant formulas are fortified with vitamin K (50–100 mcg/L) based on a minimum of 4 mcg/100 kcal.[20] Intravenous fat emulsions are another source of vitamin K, although the content varies with composition of the fat emulsion and manufacturing process.[115]

Vitamin K_1 is the most common form of synthetic vitamin K. Vitamin K supplements are available alone or as part of many multivitamin preparations in oral and parenteral forms.[23]

Absorption and Metabolism

Vitamin K absorption occurs primarily in the jejunum. It depends on the presence of bile and pancreatic secretions and is enhanced by dietary fat. Free phylloquinone is almost completely absorbed. In contrast, absorption of vitamin K from food sources is much lower, generally less than 20%, and varies substantially among individuals.[1,117] Absorbed phylloquinone is secreted into the lymph and enters the circulation. In the postprandial state, vitamin K is transported to peripheral tissue mainly by chylomicron. Long-chain menaquinones are also transported by low-density and very low-density lipoproteins. Liver uptake and turnover of phylloquinone is rapid. Cellular uptake of vitamin K is managed by lipoprotein receptors.[108]

Both phylloquinone and menaquinones activate the steroid and xenobiotic receptors that initiate their catabolism. Vitamin K is excreted primarily in bile and urine after oxidative degradation of the phytyl side chain followed by glucuronide conjugation. The liver has the highest concentration of phylloquinone, and significant amounts are also present in the heart and other tissues. Hepatic reserves are rapidly depleted from restricted dietary intake. Because of limited storage capacity, the body recycles vitamin K in the vitamin K oxidation–reduction cycle, allowing it to be reused multiple times.[118]

Deficiency

Individuals at risk for vitamin K deficiency include those with severe fat malabsorption conditions (eg, hepatobiliary disorders) or those who have had bariatric surgery, especially with severe diet restriction. Prolonged use of broad-spectrum antibiotics may decrease vitamin K synthesis by intestinal bacteria. Long-term differences in dietary vitamin K intake modulate the response to coumarin anticoagulants, which act by blocking vitamin K recycling.

The classic sign of vitamin K deficiency is an increase in prothrombin time, and in severe cases, a hemorrhagic event. Both abnormalities are responsive to vitamin K. However, achieving this level of deficiency through simple restriction of vitamin K intake is nearly impossible for nutritionally adequate, healthy individuals. The exception to this is exclusively breastfed infants who have not received vitamin K prophylaxis therapy at birth.[118] The role of vitamin K in matrix-Gla formation would support its physiological activity in the metabolism of multiple organ systems, but to date, its role in chronic diseases such as osteoporosis and atherosclerosis remains to be defined. Vitamin E supplementation might worsen the manifestation of vitamin K deficiency.[86]

Multiple biochemical measurements respond to alterations in dietary vitamin K intake and may help assess relative changes in vitamin K status. These include prothrombin time; vitamin K–dependent factors II, VII, IX, and X; plasma phylloquinone and menaquinone concentrations; and proteins induced in vitamin K deficiency such as un(der)-γ-carboxylated prothrombin (PIVKA-II) and osteocalcin (ucOC). However, prothrombin time is the only indicator of vitamin K status associated with acute adverse clinical effects. Urinary menadione (vitamin K_3) excretion also changes in response to vitamin K depletion or repletion.[108,120] Vitamin K prophylaxis is recommended in newborn infants[119] and in conditions that predispose patients to fat-soluble vitamin deficiency states.

Adverse Effects

Vitamin K toxicity is rare. Parenteral administration of a large amount of water-soluble synthetic vitamin K (vitamin K_3) has been associated with hemolytic anemia, hyperbilirubinemia, kernicterus, and with liver damage

and anaphylactic reaction.[1,4] No adverse effects associated with other vitamin K supplements or from food have been reported in healthy individuals, although high dietary intake or supplemental vitamin K can inhibit the anticoagulation effect of vitamin K antagonists. Elevated intake of vitamin E antagonizes vitamin K action, probably through its effect on vitamin K absorption and metabolism.

Conclusion

Collectively, FSVs are nutrients critical to all physiologic functions. They are also critical to normal growth and development as well as reproductive health. Deficiency in one or more FSVs, as with excessive intake, can result in dire consequences and even death. Risk factors for deficiency include those individuals with situations or diseases that affect digestion, absorption, cellular uptake, and metabolism of FSVs. For example, patients who underwent bariatric surgery, especially those on severely restricted diets, are predisposed to deficiency states from limited intake, and interference with digestion, absorption, and metabolism associated with FSVs. Endogenous synthesis and regeneration of select FSVs cannot replace the need for dietary intake. FSVs also have metabolic interactions with other nutrients. For example, zinc, energy, and protein metabolism can affect vitamin A status. Thus, nutrient requirements and biological actions of FSVs must be part of total nutrition support in health and disease."

Test Your Knowledge Questions

1. Human milk is a good source of which fat-soluble vitamins?
   A. A and E
   B. D and A
   C. E and D
   D. K and A
2. Which of the following statements about vitamin A is correct?
   A. Carotenoids are found primarily in animal products.
   B. Absorption decreases with the presence of dietary fat.
   C. Biological activity is mediated directly as carotenoids.

D. Retinoids have higher bioactivity potency than carotenoids.

3. Which of the following statements on endogenous synthesis of vitamin D is correct?
   A. Individuals with dark skin cannot produce vitamin D.
   B. Chronic exposure to sunlight results in vitamin D toxicity.
   C. A brief period of sunlight exposure can generate a large amount of vitamin D.
   D. Sunscreen, clothing, and winter do not decrease the endogenous synthesis of vitamin D.
4. Which of the following statements concerning vitamin E is correct?
   A. Natural RRR-α-tocopherol has similar biopotency to all other naturally occurring vitamin E stereoisomers.
   B. Vegetable oils are poor sources of vitamin E.
   C. Soybean and corn oils have a much higher content of α-tocopherol than γ-tocopherol.
   D. Anemia can be a manifestation of vitamin E deficiency.
5. Which of the following does not interfere with vitamin K action?
   A. Cholestyramine
   B. Chloroquine
   C. Orilstat
   D. Coumarin-type anticoagulants
6. A teratogenic effect may be a manifestation of the metabolites of which of the following vitamins?
   A. K
   B. D
   C. A
   D. E

References

1. Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary intake for Reference Intakes. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium,*

and Zinc. National Academies Press; 2001. https://doi.org/10.17226/10026

2. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. *Dietary Reference Intakes for Vitamin D and Calcium*. National Academies Press; 2011. https://doi.org/10.17226/13050
3. Institute of Medicine (US) Panel on Dietary Antioxidants and Related Compounds. *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*. National Academies Press; 2000. https://doi.org/10.17226/9810
4. Committee on Nutrition, American Academy of Pediatrics. Fat soluble vitamins. In: Kleinman RE, Greer FR, eds. *Pediatric Nutrition*. 8th ed. American Academy of Pediatrics 2019:639–654. https://doi.org/10.1542/9781610023610
5. U.S. Department of Agriculture and U.S. Department of Health and U.S. Department of Health and Human Services. Dietary guidelines for Americans 2020–2025. 9th ed. U.S. Department of Agriculture and U.S. Department of Health and Human Services; 2020.
6. Jouanne M, Oddoux S, Noel A, Voisin-Chiret AS. Nutrient Requirements during Pregnancy and Lactation. Nutrients 2021;13:692–709. https://doi.org/10.3390/nu13020692
7. ASPEN guidelines and clinical resources, 2021 Parenteral nutrition multivitamin product shortage considerations. American Society for Parenteral and Enteral Nutrition. Accessed September 1, 2022. https://www.nutritioncare.org/Guidelines_and_Clinical_Resources/Product_Shortages/
8. Robinson DT, Ayers,P, et al. Recommendations for photoprotection of parenteral nutrition for premature infants: an ASPEN position paper. *Nutr Clin Pract*. 2021;1–15. https://doi.org/10.1002/ncp.10747
9. Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. *Cochrane Database Syst Rev*. 2017;7(7):CD000253. https://doi.org/10.1002/14651858.CD000253.pub4
10. Michos ED, Cainzos-Achirica M, Heravi AS, Appel LJ. Vitamin D, calcium supplements, and implications for cardiovascular health:

JACC focus aeminar. *J Am Coll Cardiol*. 2021;77:437–449. https://doi.org/10.1016/j.jacc.2020.09.617
11. Bouillon R, Manousaki D, Rosen C, Trajanoska K, Rivadeneira F, Richards JB. The health effects of vitamin D supplementation: evidence from human studies. *Nat Rev Endocrinol*. 2022;18:96–110. https://doi.org/10.1038/s41574-021-00593-z
12. U.S. Preventive Services Task Force, Mangione CM, Barry MJ, Nicholson WK, et al. Vitamin, mineral, and multivitamin aupplementation to prevent cardiovascular disease and cancer: US Preventive Services Task Force recommendation statement. JAMA 2022;327:2326–2333. https://doi.org/10.1001/jama.2022.8970
13. Carazo A, Macáková K, Matoušová K, Krčmová LK, Protti M, Mladeˇnka P. Vitamin A update: forms, sources, kinetics, detection, function, deficiency, therapeutic use and toxicity. *Nutrients*. 2021;13:1703. https://doi.org/10.3390/nu13051703
14. Blaner WS, Shmarakov IO, Traber MG. Vitamin A and vitamin E: will the real antioxidant please stand up? *Annu Rev Nutr*. 2021;41:105–131. https://doi.org/10.1146/annurev-nutr-082018-124228
15. Bohn T, Desmarchelier C, El SN, et al. β-Carotene in the human body: metabolic bioactivation pathways—from digestion to tissue distribution and excretion. *Proc Nutr Soc*. 2019;78:68–87. https://doi.org/10.1017/S0029665118002641
16. Pennington JAT, Douglass JS. *Bowes & Church's Food Values of Portions Commonly Used*. 20th ed. Lippincott Williams & Wilkins; 2014.
17. FoodData Central. National nutrient database for standard reference - 2018. U.S. Department of Agriculture, Agricultural Research Service. Accessed September 21, 2022. https://fdc.nal.usda.gov/fdc-app.html#/
18. World Health Organization. *Indicators for Assessing Vitamin A Deficiency and Their Application in Monitoring and Evaluating Intervention Programmes*. World Health Organization. Accessed September 11, 2022. https://www.who.int/publications/i/item/WHO-NUT-96.10
19. Murphy SC, Whited LJ, Rosenberry LC, Hammond BH, Bandler DK, Boor KJ. Fluid milk vitamin fortification compliance in New York

state. *J Dairy Sci*. 2001;84:2813–2820. https://doi.org/10.3168/jds.S0022-0302(01)74737-6
20. Code of Federal Regulations Title 21. Nutrient specifications for infant formula. 21 CFR Part 107.100 Subpart D. National Archives and Records Administration. Accessed October 19, 2022. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-B/part-107/subpart-D/section-107.100
21. Berner LA, Keast DR, Bailey RL, Dwyer JT. Fortified foods are major contributors to nutrient intakes in diets of US children and adolescents. *J Acad Nutr Diet*. 2014;114:1009–1022.e8. https://doi.org/10.1016/j.jand.2013.10.012
22. Van Loo-Bouwman CA, Naber TH, Schaafsma G. A review of vitamin A equivalency of beta-carotene in various food matrices for human consumption. *Br J Nutr*. 2014;111:2153–2166. https://doi.org/10.1017/S0007114514000166
23. Dietary supplement label database. National Institutes of Health, Office of Dietary Supplements. Accessed September 21, 2022. https://dsld.od.nih.gov/
24. World Health Organization. *The Micronutrient Initiative. Safe Vitamin A Dosage During Pregnancy and Lactation.* World Health Organization; 1998.
25. World Health Organization. *Technical Note: Quality and Regulatory Considerations for the Use of Vitamin A Supplements in Public Health Programmes for Infants and Children Aged 6–59 months*. World Health Organization; 2019. https://www.who.int/publications/i/item/9789241516303
26. Koo WWK, Krug-Wispe S, Succop P, Tsang RC, Neylan M. Effect of different vitamin A intakes in very low birth weight infants. *Am J Clin Nutr*. 1995;62:1216–1220. https://doi.org/10.1093/ajcn/62.6.1216
27. Carlson SE, Peeples JM, Werkman SH, Koo WW. Plasma retinol and retinol binding protein concentrations in premature infants fed preterm formula past hospital discharge. *Eur J Clin Nutr*. 1995;49:134–6
28. Darlow BA, Graham PJ, Rojas-Reyes MX. Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants. *Cochrane Database Syst*

Rev. 2016;(8):CD000501. https://doi.org/10.1002/14651858.CD000501.pub4
29. Blaner WS, Li Y, Brun PJ, Yuen JJ, Lee SA, Clugston RD. Vitamin A absorption, storage and mobilization. *Subcell Biochem*. 2016;81:95–125. https://doi.org/10.1007/978-94-024-0945-1_4
30. Gudas LJ. Retinoid metabolism: new insights. *J Mol Endocrinol*. 2022;69:T37–T49. https://doi.org/10.1530/JME-22-0082
31. Petkovich M, Chambon P. Retinoic acid receptors at 35 years. *J Mol Endocrinol*. 2022;69:T13–T24. https://doi.org/10.1530/JME-22-0097
32. von Lintig J, Moon J, Lee J, Ramkumar S. Carotenoid metabolism at the intestinal barrier. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2020;1865(11):158580. https://doi.org/10.1016/j.bbalip.2019.158580
33. Geng T, Bao S, Sun X, Ma D, Zhang H, Ge Q, et al. A clarification of concepts related to the digestion and absorption of carotenoids and a new standardized carotenoids bioavailability evaluation system. *Food Chem*. 2023;400:134060. https://doi.org/10.1016/j.foodchem.2022.134060
34. Tang G, Qin J, Dolnikowski GG, Russell RM. Vitamin A equivalence of beta-carotene in a woman as determined by a stable isotope reference method. *Eur J Nutr*. 2000;39:7–11. https://doi.org/10.1007/s003940050070
35. Olsen JA. Adverse effects of large doses of vitamin A and retinoids. *Semin Oncol*. 1983;10:290–293.
36. Borel P, Desmarchelier C. Genetic variations associated with vitamin A status and vitamin A bioavailability. *Nutrients*. 2017;9(3):246. https://doi.org/10.3390/nu9030246
37. Wiseman EM, Bar-El Dadon S, Reifen R. The vicious cycle of vitamin A deficiency: a review. *Crit Rev Food Sci Nutr*. 2017;57:3703–3714. https://doi.org/10.1080/10408398.2016.1160362
38. Singh K. Modified classification of xerophthalmia. *Indian J Ophthalmol*. 1991;39:105–107.
39. World Health Organization. Guideline: Vitamin A Supplementation in Infants and Children 6 to 59 Months of Age. World Health Organization; 2011. https://www.who.int/publications/i/item/9789241501767

40. Imdad A, Mayo-Wilson E, Haykal MR, et al. Vitamin A supplementation for preventing morbidity and mortality in children from six months to five years of age. *Cochrane Database Syst Rev*. 2022;3(3):CD008524. https://doi.org/10.1002/14651858.CD008524.pub4
41. Phattraprayoon N, Ungtrakul T, Soonklang K, Susantitaphong P. Oral vitamin A supplementation in preterm infants to improve health outcomes: a systematic review and meta-analysis. *PLoS ONE*. 2022;17: e0265876. https://doi.org/10.1371/journal.pone.0265876
42. Penniston KL, Tanumihardjo SA. The acute and chronic toxic effects of vitamin A. *Am J Clin Nutr*. 2006;83:191–201. https://doi.org/10.1093/ajcn/83.2.191
43. Persson B, Tunell R, Ekengren K. Chronic vitamin A intoxication during the first half year of life; description of 5 cases. *Acta Paediatr Scand*. 1965;54:49–60. https://doi.org/10.1111/j.1651-2227.1965.tb06345.x
44. Mahoney CP, Margolis MT, Knauss TA, Labbe RF. Chronic vitamin A intoxication in infants fed chicken liver. *Pediatrics*. 1980;65:893–897.
45. Macapinlac MP, Olson JA. A lethal hypervitaminosis A syndrome in young monkeys (Macacus fascicularis) following a single intramuscular dose of a water-miscible preparation containing vitamins A, D2 and E. *Int J Vitam Nutr Res*. 1981;51:331–341.
46. Engle-Stone R, Miller JC, Reario MFD, Arnold CD, Stormer A, Lafuente E, et al. Filipino children with high usual vitamin A intakes and exposure to multiple sources of vitamin A have elevated total body stores of vitamin A but do not show clear evidence of vitamin A toxicity. *Curr Dev Nutr*. 2022;6(8):nzac115. https://doi.org/10.1093/cdn/nzac115
47. Sidell N, Kane MA. Actions of retinoic acid in the pathophysiology of HIV infection. *Nutrients*. 2022;14(8):1611. https://doi.org/10.3390/nu14081611
48. Leo MA, Lieber CS. Alcohol, vitamin A, and beta-carotene: adverse interactions, including hepatotoxicity and carcinogenicity. *Clin Nutr*. 1999;69:1071–1085. https://doi.org/10.1093/ajcn/69.6.1071
49. Azais-Braesco V, Pascal G. Vitamin A in pregnancy: requirements and safety limits. *Am J Clin Nutr*. 2000;71:1325S-33S.

https://doi.org/10.1093/ajcn/71.5.1325s
50. Mondloch S, Gannon BM, Davis CR, et al. High provitamin A carotenoid serum concentrations, elevated retinyl esters, and saturated retinol-binding protein in Zambian preschool children are consistent with the presence of high liver vitamin A stores. *Am J Clin Nutr*. 2015;102:497–504. https://doi.org/10.3945/ajcn.115.112383
51. Black HS. Reassessment of a free radical theory of cancer with emphasis on ultraviolet carcinogenesis. *Integr Cancer Ther*. 2004;3:279–293. https://doi.org/10.1177/1534735404270612
52. Sempos CT, Heijboer AC, Bikle DD, et al. Vitamin D assays and the definition of hypovitaminosis D: results from the First International Conference on Controversies in Vitamin D. *Br J Clin Pharmacol*. 2018;84:2194–2207. https://doi.org/10.1111/bcp.13652
53. Bouillon R, Marcocci C, Carmeliet G, et al. Skeletal and extraskeletal actions of vitamin D: current evidence and outstanding questions. *Endocr Rev*. 2019;40(4):1109–1151. https://doi.org/10.1210/er.2018-00126
54. Bouillon R, Bikle D. Vitamin D metabolism revised: fall of dogmas. *J Bone Miner Res*. 2019;34:1985–1992. https://doi.org/10.1002/jbmr.3884
55. Saponaro F, Saba A, Zucchi R. An update on vitamin D metabolism. *Int J Mol Sci*. 2020;21:6573. https://doi.org/10.3390/ijms21186573
56. Holick MF, Biancuzzo RM, Chen TC, et al. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. *J Clin Endocrinol Metab*. 2008;93:677–681. https://doi.org/10.1210/jc.2007-2308
57. Tripkovic L, Lambert H, Hart K, et al. Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. *Am J Clin Nutr*. 2012;95:1357–64. https://doi.org/10.3945/ajcn.111.031070
58. Lehmann B. The vitamin D3 pathway in human skin and its role for regulation of biological processes. *Photochem Photobiol*. 2005;81:1246–1251. https://doi.org/10.1562/2005-02-02-IR-430
59. Engelsen O, Brustad M, Aksnes L, Lund E. Daily duration of vitamin D synthesis in human skin with relation to latitude, total ozone, altitude, ground cover, aerosols and cloud thickness. *Photochem*

Photobiol. 2005;81:1287–1290. https://doi.org/10.1562/2004-11-19-RN-375
60. Balk SJ; the Council on Environmental Health and Section on Dermatology. Ultraviolet radiation: a hazard to children and adolescents. *Pediatrics*. 2011;127(3):e791–e817. Reaffirmed Pediatrics 2017;139(3):e20164205. https://doi.org/10.1542/peds.2010-3501
61. Vieth R. Vitamin D supplementation: cholecalciferol, calcifediol, and calcitriol. *Eur J Clin Nutr*. 2020;74:1493–1497. https://doi.org/10.1038/s41430-020-0697-1
62. Schlingmann KP, Kaufmann M, Weber S, Irwin A, Goos C, John U, et al. Mutations in CYP24A1 and idiopathic infantile hypercalcemia. *N Engl J Med*. 2011;365:410–21.https://doi.org/10.1056/NEJMoa1103864
63. Tebben PJ, Milliner DS, Horst RL, Harris PC, Singh RJ, Wu Y, et al. Hypercalcemia, hypercalciuria, and elevated calcitriol concentrations with autosomal dominant transmission due to CYP24A1 mutations: effects of ketoconazole therapy. *J Clin Endocrinol Metab*. 2012;97:E423–7. https://doi.org/10.1210/jc.2011-1935
64. Cools M, Goemaere S, Baetens D, Raes A, Desloovere A, Kaufman JM, et al. Calcium and bone homeostasis in heterozygous carriers of CYP24A1 mutations: a cross-sectional study. *Bone*. 2015;81:89–96. https://doi.org/10.1016/j.bone.2015.06.018
65. Clements MR, Chalmers TM, Fraser DR. Enterohepatic circulation of vitamin D: a reappraisal of the hypothesis. *Lancet*. 1984;1:1376–1379. https://doi.org/10.1016/S0140-6736(84)91874-9
66. Mawer EB, Backhouse J, Holman CA, Lumb GA, Stanbury SW. The distribution and storage of vitamin D and its metabolites in human tissues. *Clin Sci*. 1972;43:413–431. https://doi.org/10.1042/cs0430413
67. Mawer EB, Schaefer K, Lumb GA, Stanbury SW. The metabolism of isotopically labeled vitamin D3 in man: the influence of the state of vitamin D nutrition. *Clin Sci*. 1971;40:39–53. https://doi.org/10.1042/cs0400039
68. Kumar R. The metabolism and mechanism of action of 1,25-dihydroxyvitamin D3. *Kidney Int*. 1986;30:793–803. https://doi.org/10.1038/ki.1986.258

69. Carrelli A, Bucovsky M, Horst R, et al. Vitamin D storage in adipose tissue of obese and normal weight women. *J Bone Miner Res*. 2017;32:237–242. https://doi.org/10.1002/jbmr.2979
70. Mutt SJ, Hyppönen E, Saarnio J, Järvelin MR, Herzig KH. Vitamin D and adipose tissue-more than storage. *Front Physiol*. 2014;5:228. https://doi.org/10.3389/fphys.2014.00228
71. Bonnet L, Hachemi MA, Karkeni E, et al. Diet induced obesity modifies vitamin D metabolism and adipose tissue storage in mice. *J Steroid Biochem Mol Biol*. 2019;185:39–46. https://doi.org/10.1016/j.jsbmb.2018.07.006
72. Koo WWK, Tsang RC. Calcium and magnesium homeostasis. In: MacDonald MG, Seshia MMK, eds. *Avery's Neonatology—Pathophysiology and Management of the Newborn*. 7th ed. Lippincott-Williams and Wilkins 2016:646–669.
73. Sun J, Zhang YG. Vitamin D receptor influences intestinal barriers in health and disease. *Cells*. 2022;11:1129. https://doi.org/10.3390/cells11071129
74. Nevado J, Tenbaum SP, Castillo AI, Sánchez-Pacheco A, Aranda A. Activation of the human immunodeficiency virus type I long terminal repeat by 1 alpha, 25-dihydroxyvitamin D3. *J Mol Endocrinol.* 2007;38:587–601. https://doi.org/10.1677/JME-06-0065
75. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96:1911–1930. https://doi.org/10.1210/jc.2011-0385
76. Rosen CJ, Abrams SA, Aloia JF, et al. IOM committee members respond to endocrine society vitamin D guideline. *J Clin Endocrinol Metab*. 2011;97:1146–1152. https://doi.org/10.1210/jc.2011-2218
77. Koo W, Walyat N. Vitamin D and skeletal growth and development. *Curr Osteoporos Rep*. 2013;11:188–193. https://doi.org/10.1007/s11914-013-0156-1
78. Jacobus CH, Holick MF, Shao Q , et al. Hypervitaminosis D associated with drinking milk. *N Engl J Med*. 1992;326:1173–1177. https://doi.org/10.1056/NEJM199204303261801
79. Jones G. Pharmacokinetics of vitamin D toxicity. *Am J Clin Nutr*. 2008;88:582S-586S. https://doi.org/10.1093/ajcn/88.2.582S

80. Rizzoli R. Vitamin D supplementation: upper limit for safety revisited? *Aging Clin Exp Res*. 2021;33:19–24. https://doi.org/10.1007/s40520-020-01678-x
81. Stephenson DW, Peiris AN. The lack of vitamin D toxicity with megadose of daily ergocalciferol (D2) therapy: a case report and literature review. *South Med J*. 2009;102:765–768. https://doi.org/10.1097/SMJ.0b013e3181a8d1e4
82. Bilezikian JP, Formenti AM, Adler RA, et al. Vitamin D: Dosing, levels, form, and route of administration: does one approach fit all? *Rev Endocr Metab Disord*. 2021;22:1201–1218. https://doi.org/10.1007/s11154-021-09693-7
83. Azzi A. Reflections on a century of vitamin E research. Looking at the past with an eye on the future. *Free Radic BiolMed*. 2021;175:155–160. https://doi.org/10.1016/j.freeradbiomed.2021.07.042
84. Traber MG. Vitamin E. *Adv Nutr*. 2021;12:1047–1048. https://doi.org/10.1093/advances/nmab019
85. Khadangi F, Azzi A. Vitamin E—The next 100 years. *IUBMB Life*. 2019;71:411–415. https://doi.org/10.1002/iub.1990
86. Traber MG, Head B. Vitamin E: how much is enough, too much and why! *Free Radic Biol Med*. 2021;177:212–225. https://doi.org/10.1016/j.freeradbiomed.2021.10.028
87. Cook-Mills JM, Abdala-Valencia H, Hartert T. Two faces of vitamin E in the lung. *Am J Respir Crit Care Med*. 2013;188:279–284. https://doi.org/10.1164/rccm.201303-0503ED
88. Arai H, Kono N. α-Tocopherol transfer protein (α-TTP). *Free Radic Biol Med*. 2021;176:162–175. https://doi.org/10.1016/j.freeradbiomed.2021.09.021
89. Debier C. Vitamin E during pre- and postnatal periods. *Vitam Horm*. 2007;76:357–373. https://doi.org/10.1016/S0083-6729(07)76013-2
90. Stone WL, LeClair I, Ponder T, Baggs G, Barrett Reis B. Infants discriminate between natural and synthetic vitamin E. *Am J Clin Nutr*. 2003;77:899–906. https://doi.org/10.1093/ajcn/77.4.899
91. Zingg JM. Water-soluble vitamin E-tocopheryl phosphate. *Adv Food Nutr Res*. 2018;83:311–363. https://doi.org/10.1016/bs.afnr.2017.12.007

92. Yang C, Wu T, Qi Y, Zhang Z. Recent advances in the application of vitamin E TPGS for drug delivery. *Theranostics*. 2018;8:464–485. https://doi.org/10.7150/thno.22711
93. Mohd Zaffarin AS, Ng SF, Ng MH, Hassan H, Alias E. Pharmacology and pharmacokinetics of vitamin E: nanoformulations to enhance bioavailability. *Int J Nanomedicine*. 2020:15:9961–9974. https://doi.org/10.2147/IJN.S276355
94. Lodge JK, Hall WL, Jeanes YM, Proteggente AR. Physiological factors influencing vitamin E biokinetics. *Ann N Y Acad Sci*. 2004;1031:60–73. https://doi.org/10.1196/annals.1331.006
95. Kostner GM, Oettl K, Jauhiainen M, Ehnholm C, Esterbauer H, Dieplinger H. Human plasma phospholipid transfer protein accelerates exchange/transfer of alpha-tocopherol between lipoproteins and cells. *Biochem J*. 1995;305:659–667. https://doi.org/10.1042/bj3050659
96. Violet PC, Ebenuwa IC, Wang Y, et al. Vitamin E sequestration by liver fat in humans. *JCI Insight*. 2020;5:e133309. https://doi.org/10.1172/jci.insight.133309
97. Kono N, Arai H. Intracellular transport of fat soluble vitamins A and E. *Traffic*. 2015;16:19–34. https://doi.org/10.1111/tra.12231
98. Burton GW, Traber MG, Acuff RV, et al. Human plasma and tissue alpha-tocopherol concentrations in response to supplementation with deuterated natural and synthetic vitamin E. *Am J Clin Nutr*. 1998; 67:669–684. https://doi.org/10.1093/ajcn/67.4.669
99. Traber MG, Ramakrishnan R, Kayden HJ. Human plasma vitamin E kinetics demonstrate rapid recycling of plasma RRR-alpha-tocopherol. *Proc Natl Acad Sci*. 1994;91:10005–10008. https://doi.org/10.1073/pnas.91.21.10005
100. Schultz M, Leist M, Petrizika M, Gassmann B, Brigelius-Flohe R. A novel urinary metabolite of α-tocopherol, 2,5,7,8-tetramethyl-2(2′ carboxyethyl)-6-hydroxychroman, as an indicator of adequate vitamin E supply? *Am J Clin Nutr*. 1995;62:1527S-1534S. https://doi.org/10.1093/ajcn/62.6.1527S
101. Peter S, Friedel A, Roos FF, Wyss A, Eggersdorfer M, Hoffmann, K, Weber P. A systematic review of global alpha-tocopherol status as assessed by nutritional intake levels and blood serum concentrations.

Int J Vitam Nutr Res. 2015;85:261–281. https://doi.org/10.1024/0300-9831/a000281
102. Assunção AGF, da Silva LTP, Camargo JDDAS, Cobucci RN, Ribeiro KDDS. Vitamin E levels in preterm and full-term infants: a systematic review. *Nutrients*. 2022;14:2257. https://doi.org/10.3390/nu14112257
103. DiDonato I, Bianchi S, Federico A. Ataxia with vitamin E deficiency: update of molecular diagnosis. *Neurol Sci*. 2010;31:511–515. https://doi.org/10.1007/s10072-010-0261-1
104. Okebukola PO, Kansra S, Barret J. Vitamin E supplementation in people with cystic fibrosis. *Cochrane Database Syst Rev*. 2020;9:CD009422. https://doi.org/10.1002/14651858.CD009422.pub4
105. Garcia-Layana A, Recalde S, Hernandez M, et al. A randomized study of nutritional supplementation in patients with unilateral wet age-relted macular degeneration. *Nutrients*. 2021;13:1253. https://doi.org/10.3390/nu13041253
106. Farrell PM, Bieri JG. Megavitamin E supplementation in man. *Am J Clin Nutr*. 1975;28:1381–1386. https://doi.org/10.1093/ajcn/28.12.1381
107. Johnson L, Bowen FW Jr, Abbasi S, et al. Relationship of prolonged pharmacologic serum levels of vitamin E to incidence of sepsis and necrotizing enterocolitis in infants with birth weight 1,500 grams or less. *Pediatrics*. 1985;75:619–638. https://doi.org/10.1542/peds.75.4.619
108. Mladěnka P, Macáková K, Krčmová LK, et al. Vitamin K— sources, physiological role, kinetics, deficiency, detection, therapeutic use, and toxicity. *Nutr Rev*. 2022;80:677–698. https://doi.org/10.1093/nutrit/nuab061
109. Benzakour O. Vitamin K dependent proteins: functions in blood coagulation and beyond. *Thromb Haemost*. 2008;100:527–529. https://doi.org/10.1160/TH08-07-0497
110. Bügel S, Spagner C, Poulsen SK, et al. Phylloquinone content from wild green vegetables may contribute substantially to dietary intake. *Can J Agric Crops*. 2016;1:83–88. https://doi.org/10.20448/803.1.2.83.88
111. Fu X, Harshman SG, Shen X, et al. Multiple vitamin K forms exist in dairy foods. *Curr Dev Nutr*. 2017;1:e000638.

https://doi.org/10.3945/cdn.117.000638
112. Walther B, Chollet M. Menaquinones, bacteria, and foods: vitamin K2 in the diet. In: Gordeladze JO, ed. *Vitamin K2—Vital for Health and Wellbeing*. IntechOpen Limited (eBook); 2017:63–84. https://doi.org/10.5772/63712
113. Tarento TDC, McClure DD, Talbot AM, et al. A potential biotechnological process for the sustainable production of vitamin K1. *Crit Rev Biotechnol*. 2019;39:1–19. https://doi.org/10.1080/07388551.2018.1474168
114. Booth SL, Suttie JW. Dietary intake and adequacy of vitamin K. *J Nutr*. 1998;128:785–788. https://doi.org/10.1093/jn/128.5.785
115. Chambrier C, Bannier E, Lauverjat M, Drai J, Bryssine S, Boulétreau P. Replacement of long-chain triglyceride with medium-chain triglyceride/long-chain triglyceride lipid emulsion in patients receiving long-term parenteral nutrition: effects on essential fatty acid status and plasma vitamin K1 levels. *J Parenter Enteral Nutr*. 2004;28:7–12. https://doi.org/10.1177/014860710402800107
116. Ferland G, Sadowski JA. Vitamin K1 (phylloquinone) content of edible oils: effects of heating and light exposure. *J Agric Food Chem*. 1992;40:1869–1873. https://doi.org/10.1021/jf00022a028
117. Jones KS, Bluck LJ, Wang LY, et al. The effect of different meals on the absorption of stable isotope-labelled phylloquinone. *Br J Nutr*. 2009;102:1195–1202. https://doi.org/10.1017/S0007114509371688
118. Shearer M, Newman P. Recent trends in the metabolism and cell biology of vitamin K with special reference to vitamin K cycling and MK-4 biosynthesis. *J Lipid Res*. 2014;55:345–362. https://doi.org/10.1194/jlr.R045559
119. Hand I, Noble L, Abrams SA; AAP Committee on Fetus and Newborn, Section on Breastfeeding, Committee on Nutrition. Vitamin K and the newborn infant. *Pediatrics*. 2022;149(3):e2021056036. https://doi.org/10.1542/peds.2021-056036
120. Shea MK, Booth SL. Concepts and controversies in evaluating vitamin K status in population-based studies. *Nutrients*. 2016;8(1):8. https://doi.org/10.3390/nu8010008

Test Your Knowledge Answers

1. The correct answer is **A**. In healthy, exclusively breastfed babies, human milk provides adequate vitamins A and E during the first 6 months. Daily vitamin D supplementation is recommended for all breastfed babies. Vitamin K content is low in human milk, and it is recommended that all babies receive a single intramuscular dose immediately after birth to prevent hemorrhagic disease. No supplementation is needed thereafter. All infant formulas in the United States are fortified with fat-soluble vitamins, and no supplements are needed except for the first dose of vitamin K.
2. The correct answer is **D**. Vitamin A is present in the diet as retinyl esters derived almost exclusively from animal sources. The intestinal absorption of vitamin A and provitamin A is enhanced in the presence of dietary fat. Provitamin A carotenoids must be converted to retinoids to exert vitamin A function. The bioconversion of dietary provitamin carotenoids to RAE is estimated to be 12:1 (mcg:mcg), based on the relative absorption efficiency of β-carotene from food and the functional carotene-to-retinol equivalency ratio. One RAE for dietary provitamin A carotenoids other than β-carotene is lower and set at 24 mcg.
3. The correct answer is **C**. The endogenous synthesis of vitamin D_3 requires exposure to sunlight or irradiation in the ultraviolet B range. It is extremely effective and 10 to 15 minutes of whole-body exposure to peak summer sun will generate and release up to 20,000 IU of vitamin D_3 into the circulation. However, prolonged sunlight exposure increases the conversion of previtamin D_3 to inactive metabolites and prevents the risk of vitamin D toxicity. The cutaneous production of vitamin D_3 is substantially diminished by decreased exposure to sunlight from seasonal changes, time of day, clouds, aerosols, thick ozone, higher latitude, aging, clothing, sunscreen use, and melanin pigmentation. In individuals with dark skin, the endogenous synthesis of vitamin D is possible, although the rate of production is lower than less-pigmented individuals.

4. The correct answer is **D**. Vitamin E is available in 8 isomers as tocopherols and tocotrienols. In humans, the function of vitamin E depends on its affinity to α-tocopherol transfer protein (α-TTP), which is greatest for RRR α-tocopherol compared to other isomers. The main dietary sources of vitamin E are edible vegetable oils. Oils from wheat germ, sunflower, safflower, canola, olive, and cottonseed contain >50% of the tocopherol as α-tocopherol. Soybean and corn oils contain approximately 10 times as much γ-tocopherol as α-tocopherol. Vitamin E deficiency can have multiple clinical manifestations including neuropathy and anemia.
5. The correct answer is **B**. Chronic antibiotic use may decrease the bacteria synthesis of vitamin K, although the antimalarial chloroquine has not been reported to interfere with vitamin K action. Cholestyramine, orlistat, and coumarin-type anticoagulants can interfere with the absorption or action of vitamin K.
6. The correct answer is **C**. In humans, teratogenic effects, particularly neural crest defects, from naturally occurring metabolites of vitamin A (trans-retinoic acid, 13-cis-retinoic acid, and their oxo-derivatives) are well documented in women exposed during the first trimester. Limited data link teratogenic effects to high-dose preformed vitamin A (retinol and retinyl esters), and data are insufficient to determine the presence of toxic nonteratogenic developmental effects. Adolescents using vitamin A or derivatives acne treatment must be informed of the potential teratogenic effects and counseled on the need to avoid pregnancy during this therapy.

9

Fluids and Electrolytes

Gerald L. Schmidt, PharmD, BCNSP

Learning Objectives

1. Understand the effects of age on total body water.
2. Identify factors that influence the movement of fluid and electrolytes between the intracellular and extracellular fluid compartments.
3. Differentiate between acute and chronic electrolyte abnormalities and recommend the appropriate treatment.
4. Explain how to replace fluid deficits in pediatric patients who are mildly, moderately, or severely dehydrated.

Introduction

Water is the most abundant and probably the most important substance in the body. It is essential for digesting, absorbing, transporting, and utilizing nutrients as well as excreting waste products. The regulation of fluids and electrolyte balance is maintained by an elaborate system of interrelated regulatory systems to ensure proper cell function. Unfortunately, fluid and electrolyte imbalances are common, and severe imbalances can have a detrimental effect on major organ systems. This chapter will focus on fluid and electrolyte homeostasis, commonly encountered fluid and electrolyte abnormalities, and the treatment of these disorders.

Fluid Distribution

Adipose tissue is the least hydrated body tissue; therefore, patients with obesity will have a lower percentage of total body water (TBW) content. TBW volume varies depending on age, weight, sex, percent body fat, and health status. Water accounts for about 80% of total body weight in preterm infants and 75% of total body weight in term infants.[1–4] TBW continues to decrease to 55%–60% of total body weight by 18 years of age.[5,6] TBW is divided into separate compartments:

- intracellular fluid (ICF; 32%–52% of total body weight)
- transcellular fluid (1.5%–2.5% of total body weight)
- extracellular fluid (ECF; 16%–26% of total body weight)

The ECF is further divided into interstitial space (12%–19% of total body weight) and intravascular space (4%–6% of total body weight).[6–10] Relative percentages in each compartment at various ages are presented in Table 9-1.

TABLE 9-1. Distribution of Total Body Water as a Percentage of Total Body Weight

Age/Life Stage	Total Body Water	Intracellular	Extracellular		Transcellular
Preterm infant	80%	52%	26%	Intravascular 6% Interstitial 19%	2.5%
3-month-old infant	70%	46%	22%	Intravascular 5.5% Interstitial 16.5%	2%
6-month-old infant	60%	39%	19%	Intravascular 5% Interstitial 14%	1.8%
10- to 18-year-old child/adolescent	Male 59% Female 57%	38% 36%	18%	Intravascular 4.5% Interstitial 13.5%	1.7%
Elderly patient	50%	32%	16%	Intravascular 4% Interstitial 12%	1.5%

The primary factor that determines water distribution between the ICF and ECF compartments is osmotic pressure. Sodium is the predominant extracellular osmotic agent, and potassium is the predominant intracellular osmotic agent. The sodium-potassium-adenosine triphosphatase (Na+-K+-ATPase) pump maintains the sodium and potassium gradient in normal conditions by pumping 3 sodium ions extracellularly for every 2 potassium

ions it pumps intracellularly. A disruption in the function of the Na+-K+-ATPase pump can have a significant effect on fluid distribution between the compartments.[9,11,12]

The composition of intravenously administered fluid also plays an important role in fluid dynamics between the ICF and ECF. For example, when 100 mL of 5% dextrose (a solute-free solution) is administered intravenously to a patient, the dextrose is metabolized and the resultant water is proportionally distributed to all compartments. Approximately 65% of the fluid volume (65 mL) would go into the ICF, 32% (32 mL) would remain in the ECF, and 3% (3 mL) would go into the transcellular fluid compartment. Of the 32 mL remaining in the ECF, 25% (8 mL) would stay in the intravascular space, and 75% (24 mL) would be in the interstitial space (see Figure 9-1). If 100 mL of 0.9% sodium chloride was given, all 100 mL would stay in the ECF: 25% (25 mL) in the intravascular space and 75% (75 mL) in the interstitial space (see Figure 9-2).[13,14]

FIGURE 9-1. Fluid Distribution of 100 mL Dextrose 5% in Water

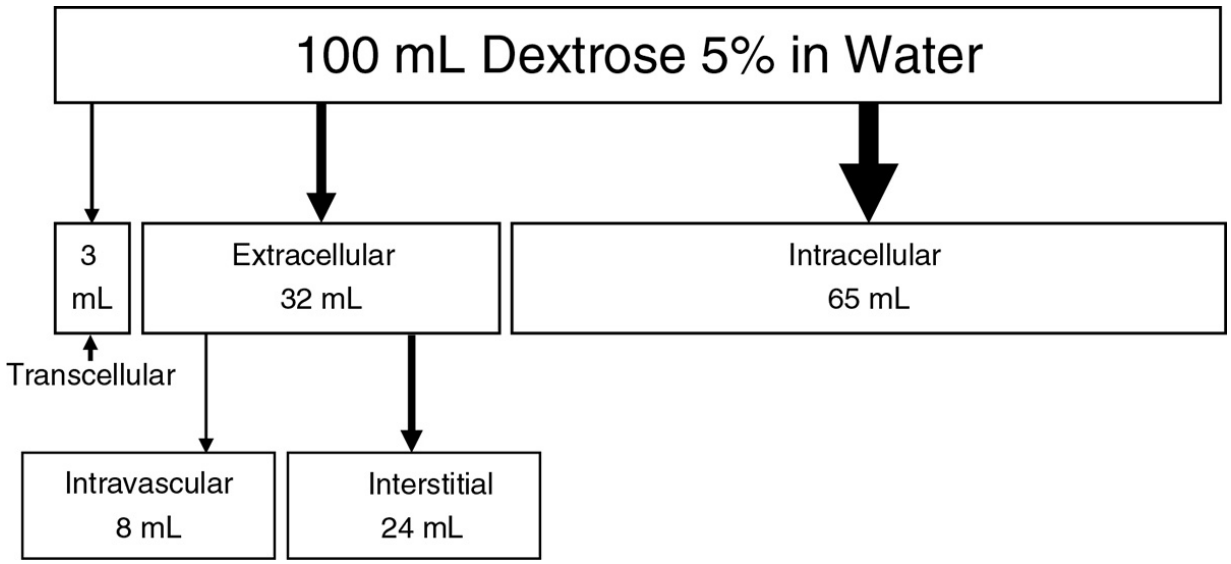
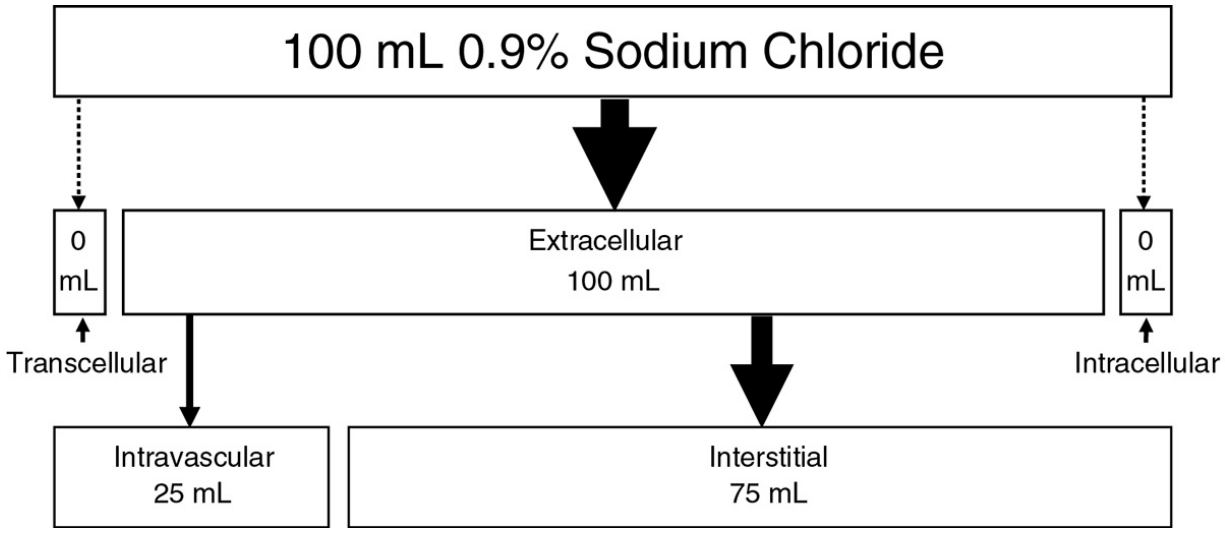


FIGURE 9-2. Fluid Distribution of 100 mL of 0.9% Sodium Chloride



The administration of a hypertonic solution (eg, 3% sodium chloride) has a different effect on fluid distribution. The increased tonicity of the 3% sodium chloride would create an osmotic gradient, pulling fluid into the ECF from the ICF. Thus, the ECF volume would increase as would the ECF and ICF osmolality. However, the ICF volume would decrease due to the fluid shift caused by the hypertonic fluid. The volume of the ECF increase would be determined by the volume of the hypertonic solution given.[13]

The balance between the ECF and ICF is important in fluid homeostasis, but these are not the only compartments that must be maintained. The ECF components, the intravascular space, and the interstitial space are maintained by Starling forces, which consist of plasma oncotic pressure and hydrostatic pressure. As vascular permeability increases, albumin leaks from the plasma to the interstitial space. When fluid moves from the plasma to the interstitial space, edema occurs.[15] This capillary leak reduces plasma oncotic pressure, which in turn causes fluid to move from the plasma to the interstitial space. If this happens quickly, and the plasma volume is not replaced, intravascular volume depletion can occur, resulting in hypotension and poor perfusion.[9,12,13]

Fluid Regulation

The primary source of fluid is through ingestion, although some water will be generated from the oxidation of carbohydrates, proteins, and fat.[16] The majority of fluid losses are through urinary output but also via the skin and the respiratory and gastrointestinal (GI) tracts.[1,2,17] Sodium and fluid balance are closely linked. Disturbances of water balance lead to changes in plasma osmolarity and sodium balance, and changes in sodium balance result in changes in plasma osmolarity and fluid volume. To maintain a relatively normal serum osmolarity (290 ± 5 mOsm/L), the total body sodium-to-TBW ratio must be maintained in a relatively narrow range.

When a fluid imbalance occurs, physiological feedback mechanisms are activated to either increase or decrease renal water excretion or to increase or decrease thirst, thereby influencing fluid intake.[13,17,18] An abnormality in either of these 2 mechanisms, or excessive losses via the skin or GI tract can have a significant effect on water and sodium balance.[1,2,4,17,18] The treatment of a fluid imbalance requires the identification of the condition that caused the abnormality and the timeframe during which the abnormality occurred. Acute disturbances— changes occurring in 48 hours or less—are more frequently associated with significant signs and symptoms and should be corrected acutely. Chronic disturbances developing over a longer period are typically asymptomatic and should be corrected less aggressively.[6,10]

Fluid Considerations and Requirements in Children

Normal daily fluid requirements can be estimated in several ways. One of the most common methods is the weight-based Holliday-Segar formula (see Table 9-2).[6,19] For example, using this method, a child weighing 27 kg would require a minimum of 1640 mL of fluid per day.

TABLE 9-2. Calculating Estimated Fluid Requirements (Holliday-Segar Formula/4:2:1 Shortcut)

Body Weight	Daily Fluid Requirement (Holliday-Segar)	Fluid Requirements (4:2:1 Shortcut)
≤ 10 kg	100 mL/kg	4 mL/kg/h[a]
>10 kg to ≤ 20 kg	1000 mL + 50 mL/kg for wt >10 kg	40 mL/h + 2 mL/kg/h >10 kg
>20 kg	1500 mL + 20 mL/kg for wt >20 kg	60 mL/h + 1 mL/kg >20 kg

[a] This may underestimate fluid requirements by about 5% in young children. 5 mL/kg/hr is often used to avoid this.

$$\begin{aligned}
&100\ \text{mL/kg for first 10 kg} = 100 \times 10 &&= 1000\ \text{mL}\\
&50\ \text{mL/kg for next 10 kg} = 50 \times 10 &&= \ 500\ \text{mL}\\
&20\ \text{mL/kg for weight} > 20\ \text{kg}\ 20 \times 7 &&= \ 140\ \text{mL}\\
&\text{TOTAL} &&1640\ \text{mL}
\end{aligned}$$

Another method for calculating fluid requirements is the 4:2:1 shortcut method (see Table 9-2). For example, using this method, a child weighing 27 kg would require a minimum of 67 mL/h or 1608 mL of fluid per day.

$$\begin{aligned}
60\ \text{mL/h} + 1\ \text{mL/kg}\left(7\ \text{mL/h}\right) &= 67\ \text{mL/h} - 24\ \text{h}\\
&= 1608\ \text{mL}
\end{aligned}$$

Both methods are commonly used to estimate fluid requirements; however, they do not address fluid requirements in abnormal circumstances, such as kidney failure or congestive heart failure, obesity, or very low birth weight (VLBW). In VLBW patients, additional losses are partially because of the large skin-to-body surface area ratio and partially the immaturity of the skin's barrier function, which leads to increased evaporative fluid loss.[1,2,17]

Phototherapy and radiant warmers also add to insensible water losses; however, humidified incubators reduce fluid requirements by decreasing insensible losses.[4,18] In VLBW patients, requirements are approximately 100 mL/kg plus insensible losses. Approximate insensible losses from radiant warmers and humidified incubators can be found in Table 9-3.[18]

TABLE 9-3. Estimated Insensible Water Losses in Preterm Infants in Different Environments in the First 24 to 48 Hours

	Insensible Water Losses (mL/kg/d)	
Weight (g)	Radiant Warmer	Humidified Incubator
<750	125–200	80–140
751–1000	100–150	60–80
1001–1250	75–100	45–60
1251–1500	60–75	30–45
1501–2000	50–60	20–30
>2000	35–50	15–20

Several conditions require adjustments in fluid intake to provide optimal care. After birth, a contraction of the ECF compartment takes place due to the loss of interstitial fluid, which results in a 5%−10% weight loss in term infants and 10%−15% weight loss in preterm infants. These losses are normal and should not be replaced at the risk of fluid overload.[2,4,17] In VLBW patients, daily insensible fluid losses are highest during the first few weeks of life and decrease over time, mainly because of maturation and thickening of the skin shortly after birth. Antenatal corticosteroids that help lung maturation will also affect skin thickening, which reduces fluid losses via the skin.[18] Therefore, VLBW infants whose mothers did not receive antenatal corticosteroids before birth may have excessive fluid losses for an extended period compared with those whose mothers received antenatal corticosteroids.[2] Other conditions that increase insensible water loss include phototherapy, omphalocele, gastroschisis, tachypnea, and the administration of nonhumidified oxygen.[20] Conditions that may require fluid restriction

because of decreased fluid losses include kidney and lung dysfunction and heart failure.[1,2]

One simple way to assess fluid balance in infants and neonates is daily weights. It is important to use the same scale and ensure that the patient has the same equipment attached for accurate assessment. Rapid weight changes typically reflect changes in water balance. Another useful indicator for assessing fluid status is serum sodium concentrations. Increased serum sodium concentration with little weight gain or loss typically indicates dehydration, whereas low serum sodium concentration along with weight gain typically indicates fluid overload.[1,6,18]

Treatment of Fluid Imbalances

When assessing and/or treating fluid and electrolyte imbalances, the patient's volume status must be assessed to determine if the patient is euvolemic, hypervolemic, or hypovolemic. Euvolemic patients can usually self-regulate fluid status and require little more than maintenance fluids and electrolyte supplementation.[21] Patients who are either hypervolemic or hypovolemic require additional assessment and possibly additional treatment. Conditions that affect fluid balance will also affect serum sodium concentration. When addressing fluid issues, assessing trends in serum sodium concentration is essential to making the appropriate adjustment. Whenever possible, treat the underlying cause of the electrolyte disturbance rather than just treating the serum sodium concentration.

Dilutional hyponatremia (one form of hypervolemia) can occur from conditions in which fluid accumulates, such as sepsis or kidney or liver dysfunction, especially when ascites is present. In general, chronic fluid disturbances take longer than 48 hours to develop, and patients typically do not exhibit signs and symptoms unless the fluid overload is severe, resulting in very low serum sodium concentration (typically <120 mEq/L). Overzealous diuresis or administration of hypertonic saline can result in osmotic demyelination syndrome (ODS). Serum sodium should not be increased faster than 0.5 mEq/L/h or by no more than 10 mEq/L in 24 hours to prevent ODS.[10,22]

Hypovolemia

Hypovolemia is a condition in which TBW is decreased significantly enough to cause symptoms. The body can correct the problem by stimulating the thirst response, increasing antidiuretic hormone (ADH) release, or both. When the plasma osmolarity is increased or when the blood volume or pressure is reduced, the thirst response is stimulated. In hypovolemia, the serum osmolarity increases and the blood volume decreases, which results in the release of ADH. This release increases the permeability of water in the collecting tubule, resulting in water reabsorption (ie, water retention).

The resultant water retention will result in more concentrated urine.[2] Signs and symptoms of hypovolemia include the following:

- thirst
- tachycardia
- altered mental status
- weakness
- fatigue
- neuromuscular irritability
- agitation
- seizures
- coma[13]

Other conditions that may lead to hypovolemia include GI hemorrhage, vomiting, diarrhea, excessive sweating, burns, diabetes insipidus, and excessive diuresis. Various methods are used for correcting volume depletion, but 3 principles always apply:

1. The fluid deficit must be replaced with an appropriate fluid.
2. Maintenance fluids must be provided on an ongoing basis.
3. If there are continued ongoing losses (eg, gastric drainage, vomiting, diarrhea), these losses must be replaced on an ongoing basis to prevent further fluid deficits.

Hypovolemia can be assessed by using either capillary refill time and/or weight loss percentage. Four factors determine the percentage of dehydration:

1. capillary refill time greater than 2 seconds
2. abnormal overall appearance
3. absence of tears
4. dry mucous membranes

A capillary refill time >2 seconds plus 1 other factor would indicate a fluid deficit of <5%. A capillary refill time >2 seconds plus 2 other factors would correlate to a fluid deficit of 5%−10%. A capillary refill time >2 seconds plus 3 other factors would correlate to a fluid deficit of >10%.[23]

Fluid deficits can also be gauged using estimated weight loss (EWL; see Table 9-4).[24,25] Based on clinical symptoms, dehydration is classified as mild, moderate, or severe. Mild dehydration can be identified by the presence of dry mucous membranes with normal hemodynamic parameters. Moderate dehydration can be defined as the presence of changes in hemodynamic parameters suggesting intravascular depletion, such as tachycardia, mild hypotension, and orthostasis. Severe volume depletion is defined by the presence of more profound hemodynamic compromise, such as moderate to severe hypotension, tachycardia, and poor perfusion.

TABLE 9-4. Clinical Assessment and Treatment of Dehydration in Infants and Adolescents

Age Group	Mild Dehydration	Moderate Dehydration	Severe Dehydration
	Characterized by dry mucous membranes, oliguria	Characterized by dry mucous membranes, marked oliguria, tachycardia, poor skin turgor and sunken fontanelles (infants only)	Characterized by dry mucous membranes, marked oliguria, tachycardia, poor skin turgor and sunken fontanelles (infants only), hypotension and poor perfusion
EWL infants and children	Percent dehydration: 5% Fluid deficit: 50 mL/kg Fluid replacement: 20 mL/kg bolus; then 15 mL/kg plus regular maintenance fluids over first 8 h; then 15 mL/kg plus regular maintenance fluids over next 16 h	Percent dehydration: 10% Fluid deficit: 100 mL/kg Fluid replacement: 20 mL/kg bolus; then 40 mL/kg plus regular maintenance fluids over first 8 h; then 40 mL/kg plus regular maintenance fluids over next 16 h	Percent dehydration: 15% Fluid deficit: 150 mL/kg Fluid replacement: 20 mL/kg bolus; then 65 mL/kg plus regular maintenance fluids over first 8 hours; then 65 mL/kg plus regular maintenance fluids over next 16 h • Patient may require more than 1 bolus to resolve hypotension and tachycardia • For every additional bolus, fluid replacement would decrease by 10 mL/kg
EWL adolescents	Percent dehydration: 3% Fluid deficit: 30 mL/kg Fluid replacement: 10 mL/kg bolus; then 10 mL/kg plus	Percent dehydration: 5%−6% Fluid deficit: 50−60 mL/kg Fluid replacement: 10 mL/kg bolus; then 20 mL/kg plus regular maintenance fluids over first 8 h; then 20	Percent dehydration: 7%−9% Fluid deficit: 70−90 mL/kg Fluid replacement: 10 mL/kg bolus; then 35 mL/kg plus regular maintenance fluids over first 8 h; then 35 mL/kg

Age Group	Mild Dehydration	Moderate Dehydration	Severe Dehydration
	regular maintenance fluids over first 8 h; then 10 mL/kg plus regular maintenance fluids over next 16 h	mL/kg plus regular maintenance fluids over next 16 h	plus regular maintenance fluids over next 16 h • Patient may require more than 1 bolus to resolve hypotension and tachycardia • For every additional bolus, fluid replacement would decrease by 5 mL/kg

Abbreviation: EWL, estimated weight loss.

Clinical symptoms of mild, moderate, and severe hypovolemia generally correspond to a 5%, 10%, and 15% weight loss in infants, respectively, which can be detected if prehypovolemia and posthypovolemia weights are available. In teenagers, mild, moderate, and severe hypovolemia correspond to a 3%, 5%, and 7% loss in body weight, respectively. Fluid therapy must include replacement of the volume deficit as well as provision of maintenance fluids and ongoing losses as stated above.

Once the weight loss is estimated, dehydration status (mild, moderate, or severe) is determined and the appropriate amount of fluid to be administered (in mL/kg) is then determined based on the dehydration severity. An initial bolus of 20 mL/kg of an isotonic fluid (usually 0.9% sodium chloride) is given in infants and children, and 10 mL/kg is given in adolescents. Then 50% of the remaining volume deficit is given over the next 8 to 16 hours in addition to regular maintenance fluids. The remaining deficit is then administered over the next 16 to 24 hours in addition to regular maintenance fluids. Serum sodium should be decreased no faster than 0.5 mEq/L/h or by no more than 10 mEq/L in 24 hours to prevent cerebral edema.

For example, an infant weighing 5 kg has a 500 mL (10%) fluid deficit. Given the degree of fluid deficit (10% or more), an isotonic fluid bolus (20 mL/kg or 2% of the patient's body weight = 100 mL) would be indicated initially. After this bolus, the remaining deficit (8% or 400 mL) would be

replaced as follows: 50% (200 mL) over the next 8 hours and 50% (200 mL) over the subsequent 16 hours. In addition to the deficit replacement, usual maintenance fluids (see Table 9-2, column 3) must be administered.

If the patient is severely volume depleted, they will generally require more than one 20-mL/kg fluid bolus to resolve the tachycardia, hypotension, and other symptoms. Once the tachycardia and hypotension have resolved, the fluid deficit and maintenance requirements can be calculated. In teenagers, the fluid deficit associated with mild, moderate, and severe dehydration is generally about 50% of that seen in infants; therefore, the initial bolus is generally 10 mL/kg rather than 20 mL/kg. Alternatively, as in adults, a fluid bolus of 500 mL to 1000 mL may be given initially and repeated based on hemodynamic response.

Hypertonic dehydration (hypernatremia) must be managed differently. In hypertonic dehydration, the fluid from the ICF compartment is drawn into the intravascular space. Rapid administration of fluid, as described previously, may cause rapid fluid shifts that can result in cerebral edema and intracranial bleeding. In hypertonic dehydration, the fluid volume deficit is calculated and gradually replaced (usually over 48 h).[25] However, the need for a fluid bolus as described earlier is based on hemodynamic parameters. If the patient is hemodynamically compromised (hypotension, severe tachycardia), then a 10−20 mL/kg bolus of an isotonic fluid is imperative to restore perfusion and normalize hemodynamic parameters. When correcting severe symptomatic hypovolemic hypernatremia, the underlying cause of the hypernatremia should be treated. When treating hypovolemia, it is important to avoid overhydration. Studies have shown poorer outcomes in patients who are over-resuscitated.[26]

Hypervolemia

Hypervolemia, or increased TBW, causes a decreased serum osmolarity resulting in dilute urine by suppressing ADH secretion. The precise mechanism by which plasma osmolarity suppresses ADH release is unclear, but it is probably related to specialized cells that sense osmolarity changes and send messages to the neuroendocrine cells located in the hypothalamus or the organum vasculosum. In most cases, the thirst response will be

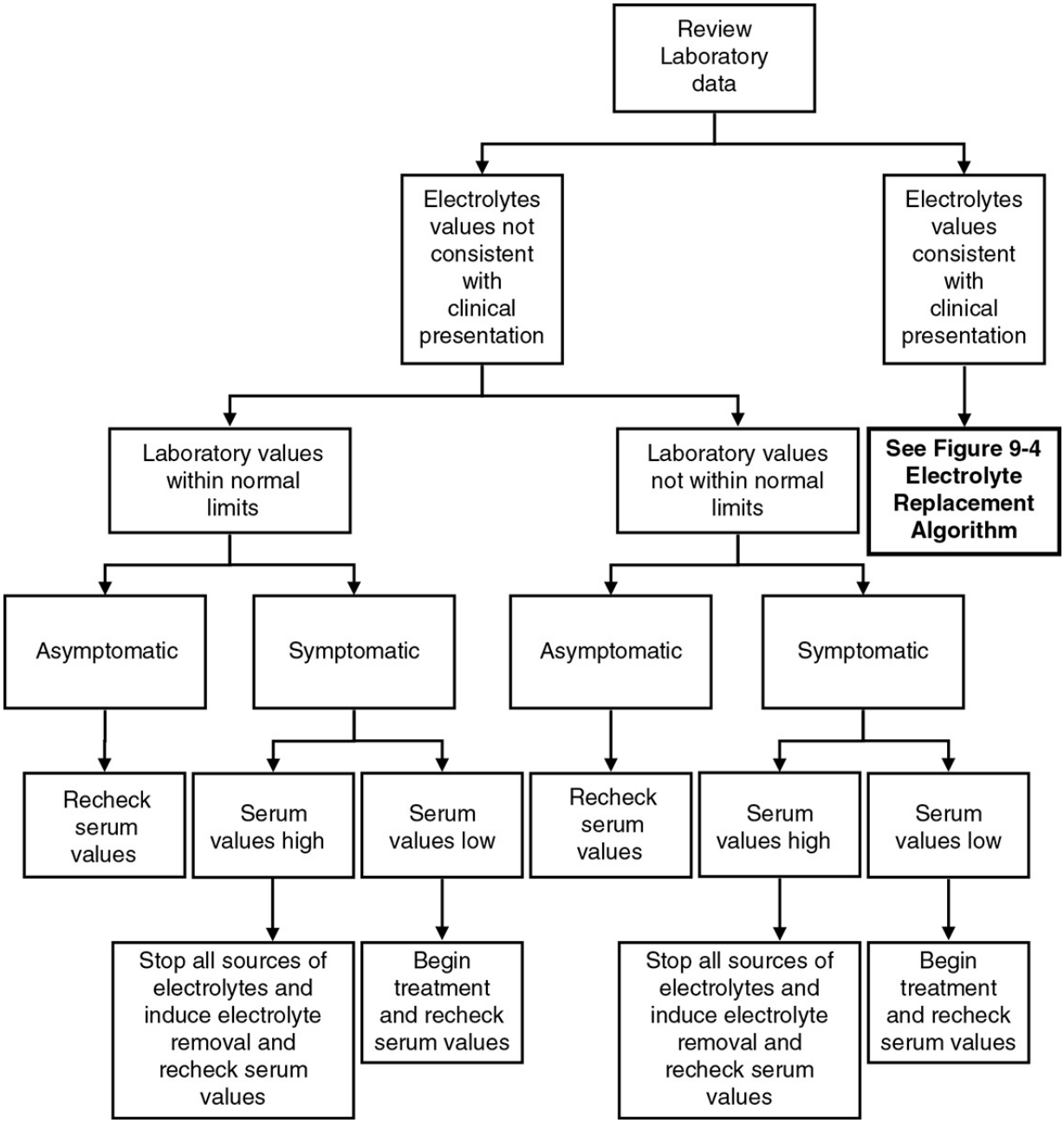
suppressed, ADH will be suppressed, and the excess water will be excreted by the kidneys.

However, conditions in which the low plasma osmolarity fails to inhibit ADH secretion (such as in severe low-output congestive heart failure), cell expansion, hypervolemia, and hyponatremia continue to progress. Symptoms include headache, nausea, vomiting, muscle twitching, disorientation, depressed reflexes, and, if severe, seizures and coma. Other conditions that may result in hypervolemia include kidney or liver failure with ascites, sepsis, cardiac failure, and syndrome of inappropriate antidiuretic hormone (SIADH).[13,22,27,28]

Electrolyte Assessment

Changes in the ECF compartment are responsible for the signs and symptoms associated with fluid and electrolyte imbalances. Therefore, it is the ECF compartment that must be corrected to alleviate those signs and symptoms. Before any fluid or electrolyte treatment, laboratory values must be validated as treatment based on inaccurate laboratory values can have serious consequences. An algorithm for assessing the validity of electrolyte laboratory values can be found in Figure 9-3.

FIGURE 9-3. Laboratory Assessment



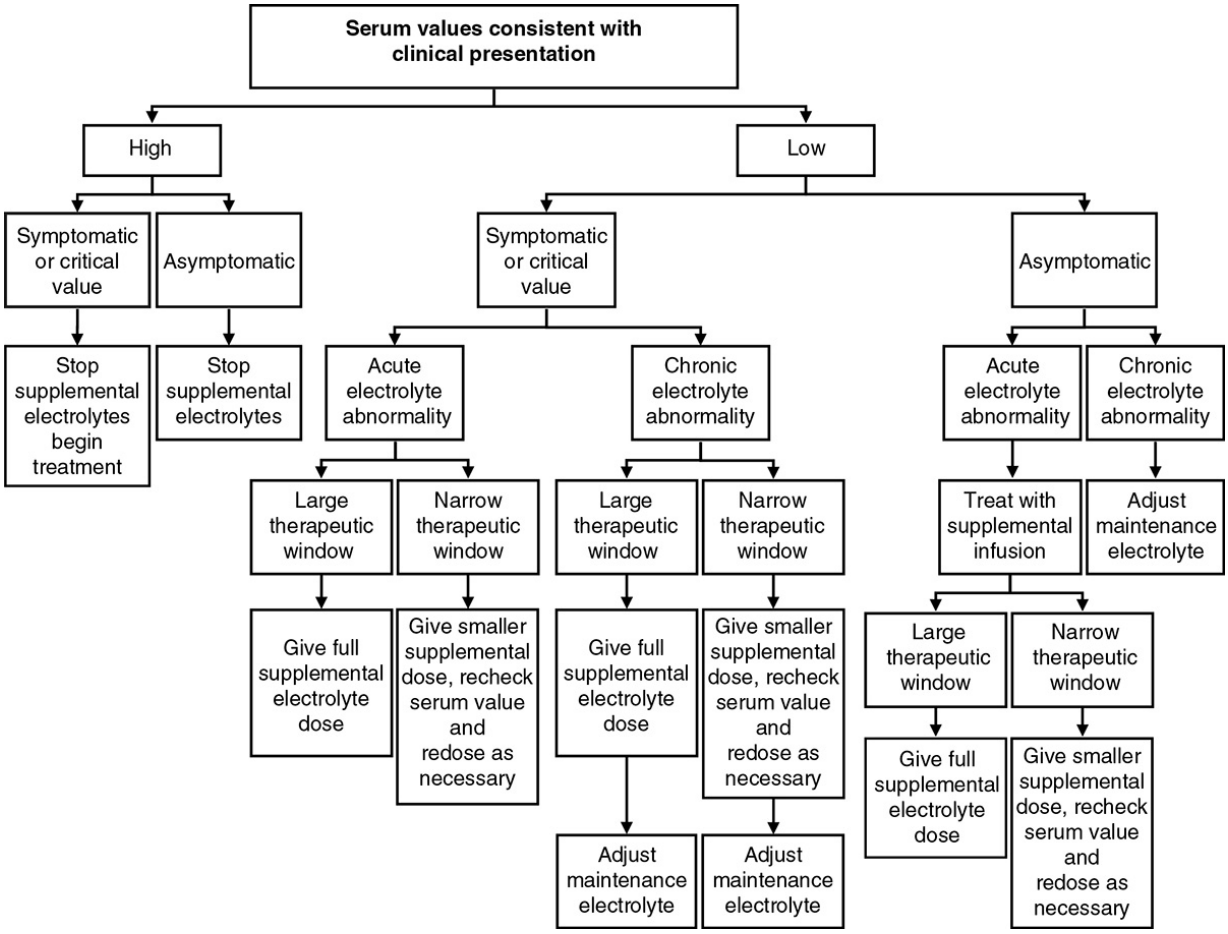
When assessing and treating fluid imbalances, the first step is to determine the cause of the electrolyte imbalance. For example, is hypokalemia a result of chronic diuretic therapy or the result of an intracellular shift secondary to a large dextrose infusion? Once the cause has been identified, the next step is to classify the event as either acute or

chronic. The prescriber can then determine whether a supplemental infusion or a change in the maintenance solution is a more appropriate intervention to correct the abnormality. Acute problems should usually be treated with supplemental infusions, whereas chronic problems should be treated with maintenance solutions.

The next step is to determine the relative safety range of the electrolyte to be corrected. If treating severe hypokalemia, it is typically safer to administer a relatively moderate potassium infusion and then recheck the serum potassium concentration before repeating the dose, rather than giving one large potassium supplemental infusion. If the deficit was inappropriately assessed and the single supplementation was too high, the patient could develop hyperkalemia and its associated consequences. In a patient with severe hypomagnesemia, overestimating the magnesium supplementation will have little clinical impact. Therefore, the prescriber can be more aggressive with magnesium supplementation compared to potassium supplementation.

The final step is to assess the acuity of the electrolyte imbalance. If the serum electrolyte concentration is critical or life-threatening, the problem should be treated acutely. After initial treatment, the maintenance solution can be adjusted, if necessary. An algorithm for the evaluation and treatment of electrolyte abnormalities can be found in Figure 9-4.

FIGURE 9-4. Electrolyte Replacement Assessment Algorithm



Reference values for normal serum electrolyte concentrations based on age appear at the beginning of each electrolyte section that follows. These values are included to illustrate the differences in electrolyte concentrations for various age groups. Laboratory reference values vary among institutions, so practitioners should use the appropriate reference values for adjusting serum electrolytes at their respective institutions.

Sodium

Preterm neonates: 130–140 mEq/L

Term neonates/infants: 133–146 mEq/L

Children/adolescents: 135–145 mEq/L

Sodium is the most abundant extracellular cation in the body. It has 2 primary functions: fluid balance and maintenance of membrane potential. The body maintains sodium homeostasis primarily by the renin-angiotensin-aldosterone system and ADH secretion.[2,10,19,27] Other systems involved in sodium maintenance include the sympathetic nervous system, atrial natriuretic peptide, the kallikrein-kinin system, various intrarenal mechanisms, and other factors that regulate kidney and medullary blood flow. The body maintains cell membrane potential by the Na+-K+-ATPase pump. Three sodium ions are pumped out of the cell for every 2 potassium ions that are pumped into the cell, which produces the negative charge in the cells necessary for the normal functioning of nerves and muscle cells and the active transport of nutrients, such as glucose and amino acids.[11,12]

In normal situations, the body's sodium losses match the body's sodium intake. The kidney can reabsorb up to 99% of the sodium presented to the renal tubules, so in times of a sodium intake deficit, serum sodium concentrations can be maintained. Daily sodium losses in these instances may be only a few milliequivalents (mEq). Medications can also affect sodium balance. Lactulose, 0.9% sodium chloride, and hypertonic saline can cause hypernatremia, and medications such as chlorpropamide, demeclocycline, and loop diuretics can cause hyponatremia. Diuretics can also cause sodium imbalances. Loop diuretics cause hypovolemic hypernatremia due to increased water loss relative to sodium loss, and the overzealous use of thiazide diuretics causes hypovolemic hyponatremia.

Sodium requirements vary among patients depending on age group. In general, daily parenteral requirements for sodium are about 2 to 5 mEq/kg in term infants, children, and adolescents. In preterm infants, as little as 1 mEq/kg/d of sodium may maintain sodium concentrations, but in general, 3

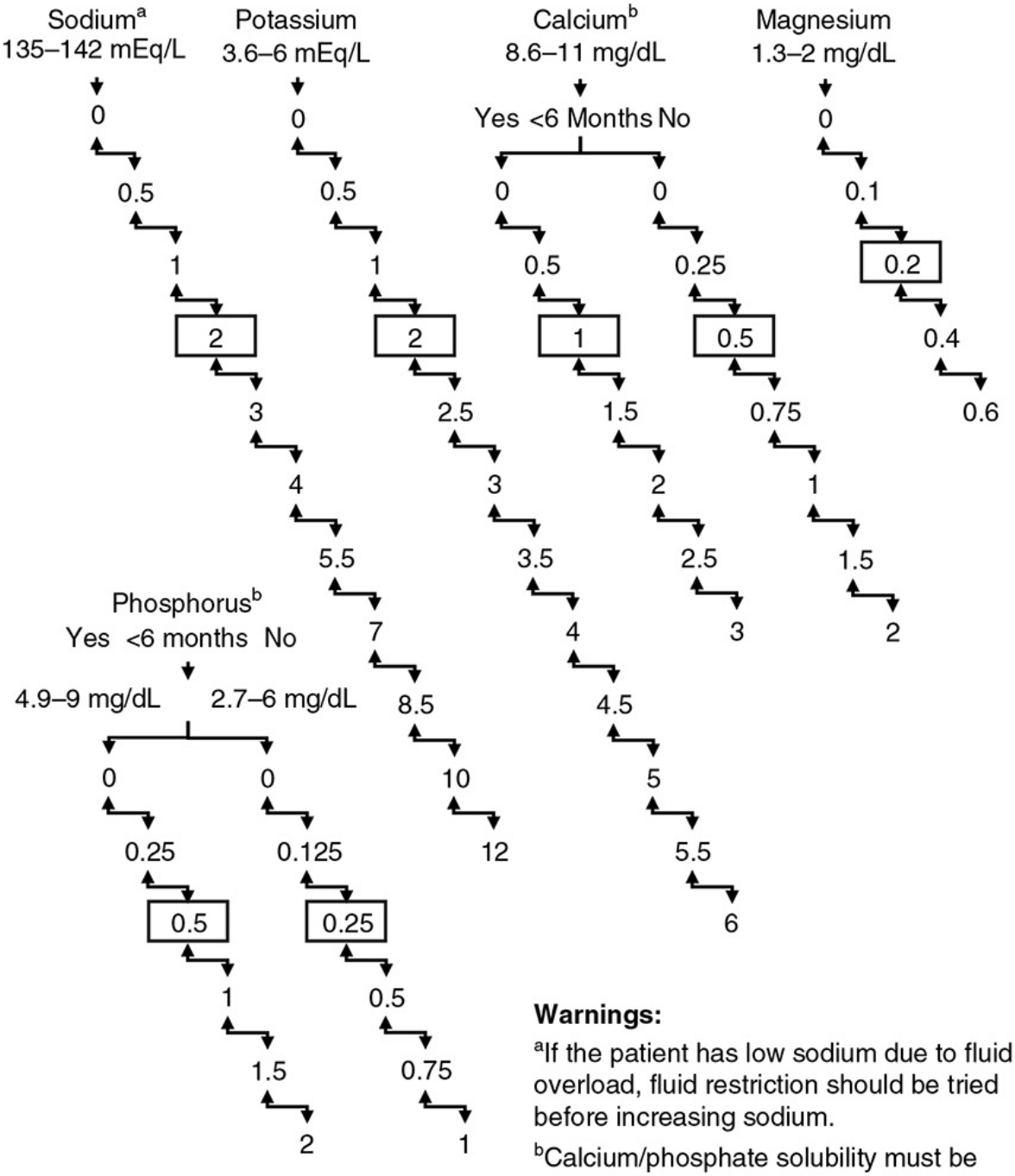
to 4 mEq/kg/d is recommended for the first week of life and then 3 to 6 mEq/kg/d in preterm infants <28 weeks gestation.[1,2,4,18,29] Oral sodium requirements vary with age (see Table 9-5).[30] An algorithm for the adjustment of maintenance electrolytes in intravenous fluids can be found in Figure 9-5.

TABLE 9-5. Oral Electrolyte Requirements by Age

	Sodium		Potassium		Magnesium		Calcium		Phosphorus	
Age	Mg	mEq	Mg	mEq	Mg	mEq	Mg	mEq	Mg	mmol
0 to < 0.5 y	110	5	400	21	302	2.5	210	10.5	100	3
0.5 to < 1 y	370	16	860	45	76	6	270	13.5	275	9
1 to < 2 y	800	34	2000	105	80	7	500	25	460	15
2 to < 3 y										
3 to < 4 y										
4 to < 5 y	1000	43	2300	121	130	11	800	40	500	16
5 to < 6 y										
6 to < 7 y										
7 to < 8 y										
8 to < 9 y										
9 to < 10 y	1200	52	2500	132	240	20	1300	65	1250	40
10 to < 11 y										
11 to < 12 y										
12 to < 14 y										
≥ 14 y (M)	1500	65	3000	158	340	28				
≥ 14 y (F)	1500	65			300	25				

FIGURE 9-5. Maintenance Electrolyte Replacement Flow Chart

Directions: This flow chart is for the adjustment of maintenance electrolytes only. The number in the box is the starting dose of electrolyte in mEq/kg or mmol/kg. If the serum concentration is high, move up the arrow 1 step, if the serum concentration is low, move down the arrow 1 step. For phosphorus, potassium, or magnesium, if the serum creatinine is >1.5 mg/dL, move up the arrow 1 step.



Warnings:

[a]If the patient has low sodium due to fluid overload, fluid restriction should be tried before increasing sodium.

[b]Calcium/phosphate solubility must be checked before compounding IV fluids.

Hyponatremia

In adults, *hyponatremia* is defined as a serum sodium concentration of <135 mEq/L. In neonates, hyponatremia is anywhere from 130 to 136 mEq/L. In this chapter, hyponatremia will be defined as a serum sodium of <135 mEq/L.[29] Hyponatremia is one of the most common electrolyte disturbances found in hospitalized patients. Signs and symptoms include headache, nausea, vomiting, muscle cramps, lethargy, restlessness, disorientation, and depressed reflexes. These signs and symptoms are more common with an acute decrease in the serum sodium concentration typically below 125 mEq/L. Severe acute hyponatremia is life-threatening; fortunately, most cases of hyponatremia in hospitalized patients develop slowly and are less severe. Hyponatremia can be divided into 3 categories:

1. *Hyperosmolar* hyponatremia is distinguished by a serum osmolality of more than 295 mOsm/L. It is typically caused by the excessive presence and/or the administration of osmotically active agents, such as mannitol and glucose. If hyponatremia is secondary to hyperglycemia, you may underestimate the fluid needed for resuscitation. This would be important in a patient with diabetic ketoacidosis. For every 100 g/dL increase in serum glucose concentration, there is a 1.6 mEq/L decrease in the serum sodium concentration, although newer literature shows the correction factor may be as low as 1 mEq/L.[31,32] The correction of serum sodium due to hyperglycemia can be estimated with the following equation:

$$\text{Corrected } Na^{+}\left(mEq/L\right) = \text{Serum } Na^{+}\left(mEq/L\right) + \left[0.016 \times \left\{\text{Serum Glucose}\left(mg/dL\right)\right\} - 100\right]$$

2. *Isoosmolar* hyponatremia is a less common condition in which the serum osmolality is within the normal range. It can be caused by an excess of plasma proteins or lipids. If the hyponatremia is a result of hypertriglyceridemia, a closer approximation of the effective serum sodium concentration can be calculated using the following equation:[33]

$$\text{Corrected } Na^{+}\left(mEq/L\right) = \text{Measure } Na^{+}\left(mEq/L\right) + \left[0.002 \times \text{triglycerides}\left(mmol/L\right)\right]^{34}$$

3. *Hypoosmolar* hyponatremia is defined as a serum osmolality of <280 mOsm/L.

There are 3 types of hypoosmolar hyponatremia:

- *Hypovolemic* is a loss of both TBW and a larger loss of total body sodium. Signs and symptoms include low blood pressure, nausea, vomiting, and tachycardia. Causes include extrarenal losses; gastrointestinal losses, third spacing due to burns, effusions, peritonitis ascites, and pancreatitis or renal losses; and overzealous diuresis, osmotic diuresis, salt wasting nephropathy, and mineralocorticoid deficiency.
- *Hypervolemic* is an increase in total body sodium but a larger increase in TBW. Symptoms include peripheral edema, ascites, and pulmonary edema. Causes include renal failure, nephrotic syndrome, congestive heart failure, and hepatic failure. Treatment is sodium and water restriction; however, hypertonic saline may be indicated if the serum sodium concentration is below 125 mEq/L or if the patient is symptomatic. The sodium deficit can be estimated by using the following equation:

$$\text{Sodium deficit}\left(mEq\right) = *TBW \times \text{wt.}\left(kg\right) \times \left(Na_{\text{desired}}\left[mEq/L\right] - Na_{\text{actual}}\left[mEq/L\right]\right)$$

*TBW = 0.8 in preterm infants; 0.7 in term infants to infants ≤ 6 months of age; and 0.6 in infants >6 months of age

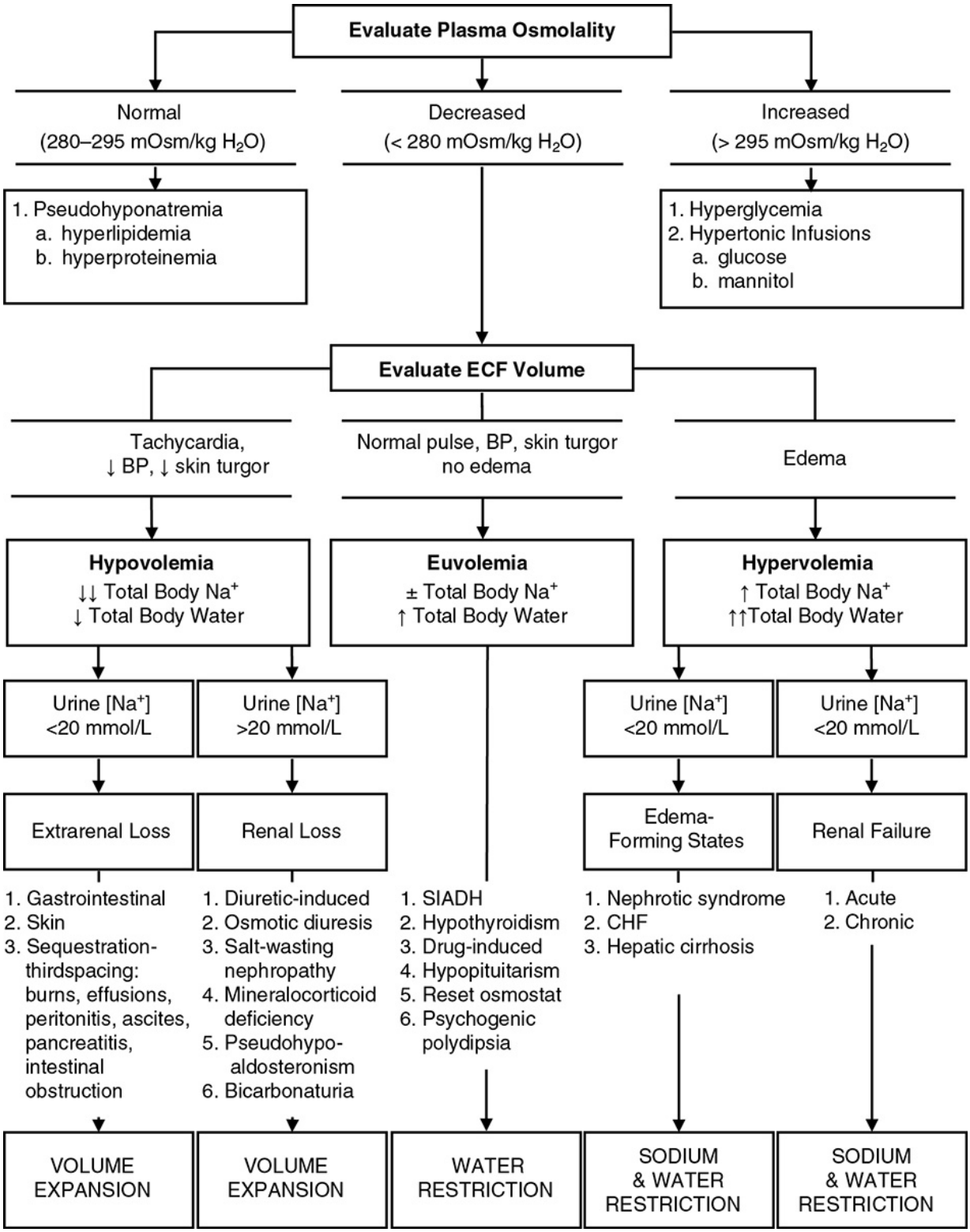
For example, a 7 kg neonate with a serum sodium of 127 and a desired serum sodium of 140 mEq/L would have a sodium deficit of 54.6 mEq.

$$\left(140 - 127\right) \times 7\left(kg\right) \times 0.6 = 54.6\,mEq$$

Typically, no more than 30% to 50% of the sodium deficit should be replaced over 6 to 12 hours.[10,22]

- *Euvolemic* is an increase in TBW and normal total body sodium. It can be caused by hypothyroidism, hypopituitarism, psychogenic polydipsia, and (most commonly) SIADH.[10,35] Refer to Figure 9-6 for an algorithm for the evaluation and treatment of hyponatremia.

FIGURE 9-6. Evaluating Hyponatremia



Adapted with permission from Matarese and Gottschlich.[35]

Hypernatremia

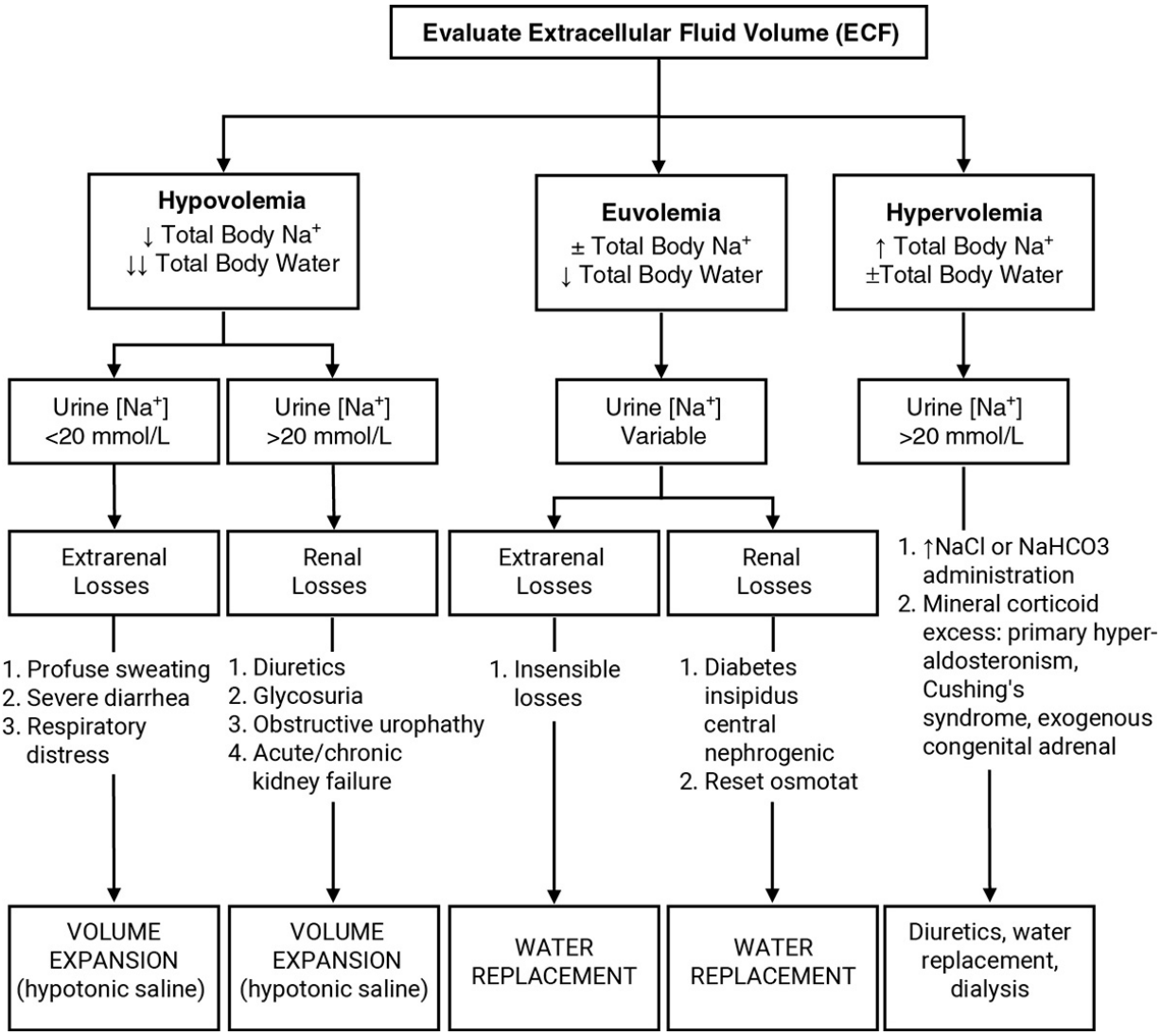
Hypernatremia is defined as serum sodium concentration greater than 145 mEq/L. It can be life-threatening if not managed appropriately. Hypernatremia usually develops under conditions of low or normal total body sodium, but it can also develop with an increase in total body sodium. Hypernatremia is typically a result of net water loss. Causes of hypernatremia include lack of oral hydration, diarrhea, vomiting, overzealous diuresis, fever, and the inability to express a need for water (eg, infants, children, or patients who have altered mental status). Assessing a patient with hypernatremia requires evaluating fluid status. Hypernatremia can be divided into 3 categories:

1. *Hypovolemic* hypernatremia is a condition in which there are excessive sodium losses but an even larger TBW loss. These fluid losses can be due to either renal or nonrenal losses. Renal losses may be due to diuretic use or increased solute diuresis from conditions such as glycosuria or azotemia. Excessive nonrenal fluid losses include diarrhea and excessive sweating (eg, from phototherapy or open bed warmers). Treatment includes volume expansion with hypotonic saline. Keep in mind that correcting serum sodium faster than 10 mEq/L over 24 hours can lead to cerebral edema.
2. *Euvolemic* hypernatremia is usually caused by high renal water losses with relative normal total body sodium. Diabetes insipidus is the most common renal cause, and insensible loss is the most common extrarenal cause. Treatment involves water replacement.
3. *Hypervolemic* hypernatremia is characterized by an increase in total body sodium with normal TBW. It can be caused by excessive administration of isotonic or hypertonic saline or mineralocorticoid excess, Cushing's syndrome, or adrenal malignancy. Management involves treating the underlying disorder, diuresis, and free water replacement.

An algorithm for the evaluation and treatment of hypernatremia is shown in Figure 9-7. If hypernatremia is due to sodium intake, then sodium intake must be decreased. If hypernatremia is associated with hypovolemia, then rehydration should be started immediately. If the hypovolemia is mild and asymptomatic, then rehydration can be addressed by simply altering the oral

fluid intake. If the hypovolemia is moderate to severe or if the patient is symptomatic, corrective treatment with an appropriate solution should begin immediately to stabilize the patient. Approximately half of the deficit should be given over the first 12 to 24 hours, and the remaining amount given over the next 24 hours.[10]

FIGURE 9-7. Evaluation of Hypernatremia



Adapted with permission from Matarese and Gottschlich.[35]

Potassium

Newborns: 3.7–5.9 mEq/L

Infants: 4.1–5.3 mEq/L

Children/adolescents: 3.4–4.7 mEq/L

Potassium is the primary ICF cation. Potassium is essential for cell metabolism and the maintenance of resting membrane potential. Intracellular potassium concentration is approximately 140 mEq/L (ICF potassium concentration equals the ECF sodium concentrations due to the action of the Na+-K+-ATPase pump).[11,36] Other factors that affect potassium distribution include those affecting the Na+-K+-ATPase pump, such as insulin, catecholamines, and ECF pH; exercise; and cell breakdown.[37,38] Potassium is primarily excreted via the kidneys. Potassium excretion varies based on serum potassium concentrations and the release of aldosterone and angiotensin II. A lack of aldosterone causes potassium retention, whereas an excess causes potassium depletion.[39,40]

In times of a potassium deficit, urinary excretion drops significantly but not entirely. If potassium intake increases significantly, urinary potassium excretion will increase as well as potassium excretion via nonrenal mechanisms (GI tract), a process known as potassium adaptation. In chronic kidney insufficiency, GI potassium losses may increase to 30% to 50% of the ingested potassium.[41–43] Medications that affect potassium concentrations can be found in Table 9-6. Supplementation in parenteral nutrition (PN) solutions or maintenance intravenous fluids should start at about 2 to 4 mEq/kg and may increase or decrease depending on kidney function, GI losses, and medication use.[1,2,18] Oral potassium requirements vary with age (see Table 9-5). An algorithm for the adjustment of maintenance electrolytes in intravenous fluids can be found in Figure 9-5.

TABLE 9-6. Medications Affecting Potassium and Magnesium

	Medication
Hyperkalemia	Potassium-sparing diuretics Nonsteroidal anti-inflammatory drugs Angiotensin-converting enzyme inhibitors Angiotensin-II receptor blockers Trimethoprim Pentamidine Cyclosporine Tacrolimus Heparin Penicillin G potassium β-blockers Succinylcholine Aliskiren Everolimus Apriprazole Canagliflozin
Hypokalemia	Loop diuretics Thiazide diuretics Fludrocortisones High-dose glucocorticoids High-dose penicillins Phenolphthalein Sodium polystyrene sulfonate Sorbitol β_2–adrenergic agonists Tocolytic agents Theophylline Caffeine Insulin/dextrose
Hypermagnesemia	Tocolytic agents Magnesium-containing antacids Magnesium-containing enemas
Hypomagnesemia	Cisplatinum Foscarnet Amphotericin B Aminoglycosides Thiazide diuretics Loop Diuretics Capreomycin

	Medication
	Pentamidine Panitumab Matozumab Cetuximab

Hypokalemia

Hypokalemia is usually defined as a serum potassium concentration less than 3.4 mEq/L. It is a common electrolyte abnormality seen in clinical practice. The most common causes of hypokalemia are abnormal kidney function or GI losses. Hypokalemia can also be observed in hyperaldosteronism, which is frequently seen in short bowel syndrome and severe liver failure. Other causes of hypokalemia include medications, metabolic alkalosis, hypomagnesemia, catecholamines, and inadequate intake. Signs and symptoms are nonspecific but include muscle weakness and cramping, dysrhythmias, paralysis, muscle necrosis, and possibly death.[42,44]

The treatment of hypokalemia depends on both the severity and the cause. Oral potassium supplements are available as a variety of salts, and the choice of agent depends on other concomitant electrolyte imbalances, cost, and patient preference. In an asymptomatic patient with mild to moderate hypokalemia, oral supplementation is preferred because of safety reasons (eg, no risk for potassium extravasation). Oral supplementation also reduces the risk of overcorrection causing hyperkalemia and too-rapid correction causing dysrhythmias. Oral potassium liquid preparations often have an unpleasant taste, and all potassium supplements can be irritating to the GI tract, causing nausea, vomiting, and/or diarrhea. The optimal oral potassium supplementation for mild to moderate potassium depletion is 1 to 5 mmol/kg/d divided into 4 daily doses, not to exceed 1 to 2 mEq/kg as a single dose, taken with plenty of fluid.[42,45]

The use of intravenous potassium supplementation should be reserved for symptomatic patients, those who have severe hypokalemia (<3 mEq/L), or when administration via the GI tract is contraindicated. Recommended doses range from 0.5 to 1 mEq/kg, depending on the severity of the hypokalemia and kidney function.[46] Generally, infusion rates should not

exceed 0.5 mEq/kg/h unless continuous cardiac monitoring is available. Serum concentrations should be evaluated 1 to 2 hours after completion of the infusion and repeated as needed based on serum potassium levels.[45]

Potassium can be caustic to the vein, so to minimize irritation, the concentration for administration through a peripheral vein should not exceed 4 mEq/100 mL. When administering intravenous potassium supplementation, co-administration with dextrose may worsen hypokalemia by stimulating insulin release, which promotes the intracellular shift of potassium via stimulation of the Na+-K+-ATPase pump. Concurrent hypomagnesemia may result in refractory hypokalemia due to increased renal potassium losses due to the kidney's attempt to conserve magnesium and the impairment of the Na+-K+-ATPase pump. As such, it is important to correct a low magnesium concentration while treating hypokalemia.[42]

Hyperkalemia

Hyperkalemia is defined as a serum potassium concentration greater than 4.5 mEq/L. Higher serum concentrations may be clinically acceptable depending on the patient's age. Signs and symptoms of hyperkalemia include the following:

- muscle twitching
- cramping
- weakness
- ascending paralysis
- electrocardiogram changes (eg, peaked T-waves, prolonged PR interval)
- dysrhythmias (eg, bradyarrhythmias, ventricular fibrillation, and asystole)

Hyperkalemia is one of the most dangerous electrolyte imbalances that develops in preterm infants. The immaturity of the kidneys results in a reduced glomerular filtration rate, urinary potassium excretion, acidosis, and immature renal tubular response to aldosterone.[47]

Hyperkalemia can occur from excessive potassium intake in the presence of altered kidney excretion or metabolic acidosis caused by conditions such as diabetic ketoacidosis and renal tubular acidosis. Metabolic acidosis causes hyperkalemia by causing a shift of potassium

from the ECF to the ICF to balance the excess hydrogen ions that are moving into the ICF. Clinically significant hyperkalemia can also develop because of cell lysis (hemolysis) or tissue injury and death (eg, burns, rhabdomyolysis) in vivo because of the release of the ICF potassium into the serum.

Treatment of hyperkalemia depends on both the severity and the cause. All sources of potassium intake should be discontinued immediately, and if feasible, any medication that may contribute to hyperkalemia should be stopped or the dose reduced. The treatment of severe or symptomatic hyperkalemia consists of 3steps:

1. Reduce the excitability of the cardiac muscle by administering intravenous calcium gluconate.[2]
2. Shift nesemia is defined as a serum magnen/glucose, β_2-adrenergic agonists, or sodium bicarbonate will shift the potassium into the ICF by either directly or indirectly stimulating the Na+-K+-ATPase pump.[47]
3. Remove potassium from the body. Diuretics, cation exchange resins, and dialysis all reduce potassium concentrations by increasing excretion or directly removing potassium from the body. Loop and thiazide diuretics (loop to a greater extent than thiazide) reduce potassium serum levels by increasing renal excretion. Cation exchange resins, such as sodium zirconium cyclosilicate and sodium polystyrene reduce potassium serum levels by binding potassium in the GI tract. Sodium polystyrene should be used as a last resort because of the delayed onset of action and significant complications, such as intestinal necrosis.[2]

Serum potassium concentrations should be monitored frequently during treatment, especially in patients being treated with dextrose and insulin, β_2-adrenergic agonists, and sodium bicarbonate because once these therapies are discontinued, potassium will shift back to the ECF compartment. Potassium concentrations should be monitored for at least 12 hours after the hyperkalemia has resolved to ensure that the equilibration of potassium between the ICF and ECF is complete.[48]

Pseudo-hyperkalemia is common in infants and young children and can occur when red blood cells lyse during the blood-drawing process. The high

concentration of potassium released during the lysis gives a falsely high serum potassium level. This form of hyperkalemia is most detected in pediatric patients with normal kidney function. Hyperkalemia can also occur if the blood sample is contaminated with the PN solution. This occurs when the PN solution is drawn up into the blood sample due to the administration of a PN solution close to the blood sample site. If pseudo hyperkalemia is suspected, if the patient is asymptomatic and has normal kidney function, the serum potassium concentration should be repeated (avoid rapid aspiration and use of narrow gauge needles, if possible) before starting any treatment for hyperkalemia.[47]

Magnesium

All age groups: 1.6–2.3 mg/dL

Magnesium is an essential cofactor in more than 300 enzymatic reactions, including those involved in glucose metabolism, fatty acid synthesis and breakdown, and DNA and protein metabolism. Magnesium plays a critical role in the functioning of the Na+-K+-ATPase pump, thus affecting neuromuscular transmission, cardiovascular excitability, vasomotor tone, and muscle contraction. Magnesium is also an integral component of bone and parathyroid hormone (PTH) secretion. Magnesium is found primarily in the ICF, with only about 2% of total body stores found in the ECF. More than 50% of the magnesium in the body resides in bone. About 61% of serum magnesium is physiologically active in the ionized form, 33% protein bound, and 5% complexed to phosphate, citrate, and other compounds.[49,50]

Magnesium homeostasis is maintained and regulated by the GI tract, kidneys, and bone via PTH. Healthy individuals absorb between 30% and 60% of ingested magnesium. Magnesium is absorbed in the distal jejunum and ileum, and the percentage of absorption is inversely proportional to the magnesium intake. Magnesium is primarily excreted via the kidneys with about 35% of ingested magnesium excreted in the urine. In the presence of high magnesium intake, renal excretion increases to maintain normal serum

magnesium concentrations.[50] Very little magnesium (1%–2%) is excreted via the feces. If a patient becomes magnesium-depleted, the mineral leaches from the bones to maintain ECF magnesium concentrations. ECF magnesium is then sacrificed to the ICF to maintain normal metabolic functions. A more detailed description of the biochemistry, physiology, absorption, excretion, and metabolism of magnesium can be found in Chapter 6, "Minerals."

Medications that affect magnesium concentrations are listed in Table 9-6. Usual intravenous magnesium supplementation in PN solutions ranges from 0.25 mEq/kg to 0.5 mEq/kg (25–50 mg/kg) daily but may be higher in patients with abnormal magnesium losses. Oral magnesium requirements vary with age (see Table 9-5). An algorithm for the adjustment of maintenance electrolytes in intravenous fluids can be found in Figure 9-5.

Hypomagnesemia

Hypomagnesemia is defined as a serum magnesium concentration <1.6 mg/dL and is a common condition in hospitalized patients. Signs and symptoms include the following:

- apathy
- depression
- psychosis
- muscle weakness
- vertigo
- ataxia
- seizures
- confusion
- leg cramps
- hyperactive tendon reflexes
- anorexia
- nausea
- vomiting
- paresthesia
- Chvostek's and Trousseau's sign
- spontaneous carpal-pedal spasm
- cardiac complications including dysrhythmias

Hypomagnesemia can also contribute to the development of other electrolyte abnormalities and may result in refractory hypokalemia because of increased renal potassium losses due to the kidney's attempt to conserve magnesium and the impairment of the Na+-K+-ATPase pump.[49] Hypomagnesemia may also contribute to the development of hypocalcemia. Magnesium deficiency can impair parathyroid function, and hypomagnesemia accompanied by hypoparathyroidism is a common cause of neonatal hypocalcemia.[50]

Hypomagnesemia can be caused by decreased intake, increased excretion, or an intracellular shift of magnesium. Excessive renal losses may occur in patients with acute tubular necrosis, renal tubular acidosis, Bartter syndrome, or hyperaldosteronism, or they may be induced by medications such as amphotericin B, cisplatin, cyclosporine, aminoglycosides, and foscarnet.[50] Intracellular shifts can be caused by dextrose and/or insulin administration. Because only about 1% to 2% of total body magnesium is found in the ECF, serum concentrations are not a good reflection of total body magnesium stores. Therefore, the treatment of hypomagnesemia is empirical.

The intravenous route is preferred in patients with moderate-to-severe hypomagnesemia because of the GI intolerance generally seen with large oral doses. Recommended doses are 0.25 to 0.5 mEq/kg (25−50 mg/kg), up to 16 mEq (2 g) every 8 to 12 hours for 2 to 3 doses.[45,49,50] There is a renal magnesium threshold for magnesium reabsorption; thus, up to 50% of an individual magnesium dose will be eliminated via the kidneys if the magnesium is not distributed intracellularly. Suggested rates for optimal magnesium retention are 0.1 to 0.25 mEq/kg/h (10−25 mg/kg/h) with a maximum of 1 g/h (8 mEq/h). Some practitioners suggest reducing it by 50% in patients with kidney dysfunction to lessen the risk of hypermagnesemia; however, this may not be necessary when a 1-time dose is given since magnesium will not continue to accumulate once the dose is complete.[45] Serum magnesium should be rechecked approximately 1 to 2 hours after the infusion is completed, and additional boluses should be given if needed.

Hypermagnesemia

Hypermagnesemia is defined as a serum magnesium concentration >2.4 mg/dL. Hypermagnesemia is usually well tolerated but can affect neurological, neuromuscular, and cardiac function when magnesium concentrations exceed 3 mg/dL.[50] Physical findings include nausea, vomiting, diaphoresis, flushing, depressed mental function, drowsiness, muscular weakness, hypotension, and bradycardia. Hypermagnesemia occurs primarily in the setting of kidney insufficiency in combination with continued magnesium intake. In preterm infants, the most common cause of hypermagnesemia is the placental transfer of magnesium during the treatment of the mother for preterm labor contractions with magnesium sulfate.[50,51] Neonates with hypermagnesemia will have poor muscle tone, which will return to normal as the serum magnesium concentration decreases over approximately 2 to 5 days, depending on the severity of the initial hypermagnesemia and the neonate's kidney function.[52]

In patients with symptomatic hypermagnesemia, intravenous calcium should be administered immediately to counteract the cardiac effects of hypermagnesemia. Hemodialysis may be required to reduce the magnesium concentration to a safer value. Treatments for hypermagnesemia in an asymptomatic patient include dietary magnesium restriction, administration of a loop diuretic, and hemodialysis if severe kidney dysfunction is present and other methods are unsuccessful.[50,52]

Calcium

Preterm neonates: 6.2–11 mg/dL (total);

1.75–2 mmol/L (ionized [SI units])

Term neonates (< 36 h): 7.6–10.4 mg/dL (total);

1.05–1.37 mmol/L (ionized [SI units])

Term neonates (36–84 h): 7.6–10.4 mg/dL (total);

1.1–1.42 mmol/L (ionized [SI units])

Children (2–12 y): 8.8–10.8 mg/dL (total);

1.2–1.38 mmol/L (ionized [SI units])

Adolescents/Adults (>12 y): 8.6–10.8 mg/dL (total);

1.2–1.38 mmol/L (ionized [SI units])

Calcium is one of the most abundant ions in the body. It accounts for 1% to 2% of total body weight. Calcium is necessary for many physiological functions, including neuromuscular activity, preservation of the integrity of cell membranes, the regulation of endocrine secretory activities, blood coagulation, the activation of the complement system, and bone metabolism. Serum calcium concentrations are controlled by the parathyroid gland. When serum calcium is low, PTH secretion is stimulated. This increases bone resorption, augments renal calcium conservation, and activates vitamin D, which increases calcium absorption from the GI tract. When serum calcium concentration is increased, the thyroid releases calcitonin, which acts to inhibit bone resorption and increase renal calcium excretion. Generally, serum calcium concentrations are maintained by either renal excretion of excess calcium or the leaching of calcium from the bone.[53,54] A more detailed description of the biochemistry, physiology, absorption, excretion, and metabolism of calcium can be found in Chapter 6, "Minerals."

About 99% of the body's calcium is found in teeth and bone, with only 1% found in the blood, muscle, and other tissues. There are 3 forms of calcium in the body: (1) complexed, (2) protein bound, and (3) ionized. The ionized fraction of calcium is the metabolically active form of calcium, which is the most important physiologically.[55] Serum pH, phosphorus, and

albumin affect ionized calcium levels. Ionized calcium levels can be affected by pH as well. Alkalosis promotes the binding of calcium to albumin, which reduces the fraction of ionized calcium in the blood without reducing total calcium.[56]

Complexed calcium is combined with nonprotein anions such as phosphate, carbonate, and citrate and is not available for physiological activity. Slightly less than half of the serum calcium is bound to protein, primarily albumin. Therefore, hypoalbuminemia causes a falsely low serum calcium measurement because it measures calcium bound to albumin.[57] Although not completely reliable in critically ill patients, serum calcium concentrations can be corrected for the degree of hypoalbuminemia using the following equation:

$$\text{Adjusted calcium} = \text{measured total calcium}\left(\text{mg/dL}\right) + \left[0.8 \times \left(4 - \text{serum albumin}\left[\text{g/dL}\right]\right)\right]$$

Supplementation of calcium in PN solutions typically ranges from 1 to 2.5 mEq/kg depending on the patient's age, although in preterm infants requirements may be higher.[55] Oral calcium requirements also vary with age and can be found in Table 9-5. An algorithm for the adjustment of maintenance electrolytes in intravenous fluids can be found in Figure 9-5.

Hypocalcemia

Measured hypocalcemia is commonly encountered in patients with hypoalbuminemia but does not require treatment unless the corrected calcium or ionized calcium is low. Signs and symptoms of hypocalcemia include the following:

- hypotension
- decreased myocardial contractility
- prolonged QT interval

- paresthesia
- Chvostek's and Trousseau's signs
- muscle cramps
- tetany
- seizures

Hypocalcemia can be caused by the following:

- vitamin D deficiency or the inability to activate vitamin D
- hyperphosphatemia
- pseudo hypoparathyroidism
- decreased PTH activity
- sepsis
- rhabdomyolysis
- massive blood transfusions[59]

Medications can also cause hypocalcemia. Furosemide, phenobarbital, and phenytoin are particularly important to preterm infants. Sulfur-containing amino acids (eg, cysteine) also increase renal calcium excretion. The increased renal calcium excretion that occurs with cysteine supplementation in PN solutions is counterbalanced by the increased solubility of calcium and phosphorus in PN solutions that contain cysteine hydrochloride because of the lower pH of the PN solution.[60,61]

Patients with severe or acute symptomatic hypocalcemia require immediate treatment. Intravenous calcium is available commercially in 2 salt forms: chloride and gluconate. Calcium chloride contains 13.6 mEq of elemental calcium per gram; calcium gluconate contains 4.65 mEq of elemental calcium per gram. Calcium gluconate is preferred over calcium chloride because of the higher incidence of tissue necrosis associated with calcium chloride if extravasation occurs.[58] For hypocalcemic tetany, 0.5 to 1 mEq/kg of calcium gluconate infused over 5 to 10 minutes may be used; this dose may be followed up by 2.5 to 4 mEq/kg given over 24 hours.[45,46] If hypomagnesemia is present, magnesium supplementation should be given to help correct hypocalcemia. In cases of hypocalcemia secondary to hyperphosphatemia, treating with an oral phosphate binder should be considered before giving intravenous calcium to prevent calcium/phosphate precipitation in soft tissues.

Hypercalcemia

Hypercalcemia is less common in children than adults and can be classified into two categories: congenital causes and acquired causes. Congenital causes are most common in neonates, and acquired causes are more common in adolescents. Symptoms of hypercalcemia can range from asymptomatic hypercalcemia to symptoms of hypotonia, poor feeding, vomiting, constipation, abdominal pain, lethargy, malnutrition, dehydration, and seizures. Hypercalcemia can come from increased bone resorption, dehydration, increased gastrointestinal absorption of calcium (secondary to high vitamin D_3 levels), and decreased renal excretion of calcium due to thiazide diuretics.

Hypercalcemia can be further classified as parathyroid hormone (PTH) −dependent hypercalcemia or PTH-independent hypercalcemia. PTH-dependent hypercalcemia can result from an excess of vitamin D_3 production or malignancy. PTH-independent hypercalcemia is more common in children and can be genetic or acquired. Causes include hypervitaminosis A and D, chronic inflammatory disorders, infections, congenital syndromes, and inborn errors of metabolism.

Hypercalcemia has also been associated with extracorporeal membrane oxygenation (ECMO), although the mechanism is not known.[62] Treatment of hypercalcemia begins with stopping any medications that may exacerbate the hypercalcemia, such as calcium, vitamin D supplements, and thiazide diuretics. Symptomatic acute hypercalcemia may require fluid to correct the intravascular volume contraction caused by hypercalcemic diuresis. Normal saline (0.9% sodium chloride) is the fluid of choice and lowers serum calcium by diluting the serum calcium level during the rehydration and promoting urinary calcium excretion from the proximal renal tubule and the loop of Henle.

In more severe hypercalcemia, loop diuretics such as furosemide can be added to enhance the urinary excretion of calcium, but volume status should be monitored closely to prevent intravascular volume contraction. Hemodialysis may be necessary for patients with life-threatening hypercalcemia or those with kidney failure. Intravenous bisphosphonates (pamidronate, 0.5−1 mg/kg) have also been used to treat hypercalcemia of

malignancy but should not be used to treat acute hypercalcemia because of the delayed onset of action.[62,63]

Phosphorus

Newborns: 4.5–9 mg/dL

Infants/children (10 d–2 y): 4.5–6.7 mg/dL

Children (2–12 y): 4.5–5.5 mg/dL

Adolescents/adults (>12 y): 2.7–4.5 mg/dL

Phosphorus, mainly in the form of phosphate, is the primary intracellular anion in the body. Reference values for serum phosphorus levels vary with age, with normal values ranging from 4.5 to 9 mg/dL in preterm infants and newborns down to normal adult values of 2.7 to 4.5 mg/dL by 12 years of age. Phosphorus has many important functions, including bone and cell membrane composition, maintenance of normal pH, and provision of energy-rich bonds (ATP), making it integral in all cellular functions that require energy. Phosphorus is required for glucose utilization, neurological function, muscle function, DNA, and RNA.[64,65] Phosphorus is also important for 2,3-diphosphoglycerate (2,3-DPG) synthesis, and a deficiency of 2,3-DPG causes a decrease in peripheral oxygen uptake and transport.[55] Phosphorus homeostasis is maintained by GI absorption, renal excretion, PTH, and distribution between the ICF and ECF. Glucose and insulin, catecholamines, and alkalosis all cause an intracellular shift of phosphorus. Cell destruction and acidosis cause a shift to the ECF.

A more detailed description of the biochemistry, physiology, absorption, excretion, and metabolism of phosphorus can be found in Chapter 6, "Minerals." Intravenous phosphorus requirements are 1 to 3.5 mmol/kg in preterm infants and 0.7 to 1.3 mmol/kg/d in term infants and children up to 18 years of age.[55] Oral phosphorus requirements vary with age (see Table 9-5). An algorithm for the adjustment of maintenance electrolytes in intravenous fluids can be found in Figure 9-5.

Hypophosphatemia

The definition of hypophosphatemia varies with age. The normal lower range for serum phosphorus concentrations in pediatric patients up to the age of 12 is 4.5 mg/dL. For children 12 years of age or older, the normal lower range for serum phosphorus concentrations is 2.7 mg/dL. Hypophosphatemia is common in patients with critical illness, malnutrition, alkalosis, continuous renal replacement therapy, and those receiving phosphate binders (eg, aluminum-, magnesium-, and calcium-containing products; sevelamer; or sucralfate). Signs and symptoms of hypophosphatemia are nonspecific and potentially life-threatening:

- muscle weakness
- impaired myocardial contractility
- ventricular arrhythmias
- respiratory failure (2,3-DPG deficiency)
- rhabdomyolysis
- ileus
- immune dysfunction
- encephalopathy.[64]

Primary causes of hypophosphatemia include excessive phosphate binders, inadequate intake of phosphate, or the administration of large amounts of dextrose solutions in malnourished (refeeding syndrome).

Treatment of hypophosphatemia varies, depending on the serum phosphorus concentration and the presence of signs and symptoms. Mild asymptomatic hypophosphatemia can be treated with oral phosphate supplements, assuming that the GI tract is functional.[65] However, oral supplements are not well absorbed and often cause diarrhea. Currently, there are no oral liquid phosphorus supplements commercially available, but the saline enema containing monobasic and dibasic sodium phosphate (1.5 mmol of phosphate/mL) can be used if a liquid preparation is needed. Patients with symptomatic or moderate-to-severe hypophosphatemia should be treated with intravenous phosphate.

Three salt forms are available for replacing phosphate: (1) sodium phosphate, (2) potassium phosphate, and (3) sodium glycerophosphate (not available in the US). Sodium phosphate provides 4 mEq sodium for every 3

mmol phosphate, potassium phosphate provides 4.4 mEq potassium for every 3 mmol phosphate, and sodium glycerophosphate provides 2 mEq of sodium for every 1 mmol of phosphate. When ordering phosphate, the dose should be ordered in millimoles of phosphate rather than milliequivalent of the sodium or potassium component of the salt.

The following are recommendations for mild, moderate, and severe hypophosphatemia:

- Mild: Phosphorus levels from 2.3 to 3 mg/dL is 0.16 to 0.32 mmol/kg given over 4 to 6 hours
- Moderate: Phosphorus levels from 1.6 to 2.2 mg/dL is 0.32 to 0.64 mmol/kg given over 6 to 8 hours
- Severe: 1.5 mg/dL or less is 0.64 to 1 mmol/kg given over 8 to 12 hours.[45]

For patients with moderate or severe hypophosphatemia, serum phosphate concentrations should be checked 1 to 2 hours after the infusion is completed, and the patient should receive additional doses as needed. Phosphate should be replaced no faster than 0.1 to 0.2 mmol/kg/h to allow the phosphate time to move intracellularly and to prevent possible hypocalcemia. This rate usually necessitates a 4-to-6-hour infusion. If potassium phosphate is used to replace phosphate, the infusion rate should be based on the potassium rate. Electrocardiogram monitoring should accompany the infusion of doses >0.5 mEq/kg/h. Sodium phosphate is the preferred salt for phosphate supplementation.

Hyperphosphatemia

Hyperphosphatemia is defined as a serum phosphate concentration >4.5 to 9 mg/dL, depending on the patient's age. Hyperphosphatemia is most common in patients with chronic kidney disease and can lead to numerous disorders, including delayed or poor growth, bone deformities, bone fractures and vascular calcification, nausea, vomiting, and neuromuscular irritability. Other causes of hyperphosphatemia include cellular destruction from trauma or cytotoxic agents and the excessive administration of phosphate-containing laxatives.[66–68]

The biggest concern with hyperphosphatemia is soft tissue and vascular calcification from elevated serum calcium and phosphorus concentrations. Although there are several variables in the development of vascular calcifications, a calcium-phosphorus product exceeding 55 mg^2/dL^2 (total serum calcium [mg/dL] × serum phosphorus [mg/dL]) in adults, is often considered the point at which vascular calcifications can occur.[69] Although calcium-containing and aluminum-containing antacids have been used to reduce the intestinal absorption of phosphorus, lanthanum carbonate and sevelamer hydrochloride are commonly used because of their effectiveness, and they do not cause anemia and osteomalacia like aluminum-containing products.[66,67]

Test Your Knowledge Questions

1. A child weighing 12 kg is admitted to the hospital secondary to nausea, vomiting, and diarrhea. On physical exam, the patient has dry mucous membranes, tachycardia, and poor skin turgor. The parent notes that the patient is not urinating much, and the serum sodium is 158 mEq/L. How should the patient be rehydrated?
   A. Give the patient an infusion of 44 mL/h of normal saline.
   B. Give the patient a 20 mL/kg bolus; then give 40 mL/kg plus regular maintenance fluids (normal saline) over the first 8 hours; then give 40 mL/kg plus regular maintenance fluids over the next 16 hours. Make sure not to decrease the serum sodium more than 0.5 mEq/L/h.
   C. Give the patient a 20 mL/kg bolus; then give 65 mL/kg plus regular maintenance fluids over the first 8 hours; then give 65 mL/kg plus regular maintenance fluids over the next 16 hours. Make sure not to decrease the serum sodium by more than 0.5 mEq/L/h.
2. Administering 100 mL of 0.9% sodium chloride would have which of the following effects on a patient who is euvolemic and has a normal serum sodium?
   A. Increase the ICF by 65 mL and the ECF by 32 mL, with an 8-mL increase in intravascular volume.

B. Increase the ECF by 65 mL and the ICF by 32 mL, with a 25-mL increase in intravascular volume.
C. Increase the ECF by 100 mL, with a 25-mL increase in intravascular volume.
D. Increase the ICF by 100 mL, with an 8-mL increase in intravascular volume.

3. Which patient would have the highest percentage of TBW?
   A. Elderly patient
   B. 18-year-old patient
   C. 6-month-old patient
   D. Preterm infant
4. A 7-year-old child weighing 23 kg is admitted for nausea, vomiting, and malnutrition. The patient is started on maintenance fluids containing $D_{10}W$/0.2% NaCl with KCl 20 mEq/L. The following morning, the serum potassium dropped to 3.2 mEq/L, the serum magnesium dropped to 1.4 mg/dL and the serum phosphate dropped to 1.6 mg/dL. How would you correct these electrolyte abnormalities?
   A. Make no changes in the maintenance solution. The levels will slowly increase to the normal range after the electrolytes shift due to refeeding having equilibrated.
   B. Increase the potassium in the maintenance solution and add magnesium and phosphate.
   C. Keep the electrolytes in the maintenance solution the same and replace the electrolytes outside the maintenance solution with oral or intravenous supplementation depending on oral tolerance.
   D. Both B and C.

References

1. Ågren J, Segar JL, Söderström F, Bell EF. Fluid management considerations in extremely preterm infants born at 22–24 weeks of gestation. *Semin Perinatol*. 2022;46(1):151541. https://doi.org/10.1016/j.semperi.2021.151541
2. Chow JM, Douglas D. Fluid and electrolyte management in the preterm infant. *Neonatal Netw*. 2008;27(6):379–386.

https://doi.org/10.1891/0730-0832.27.6.379
3. Sartorio A, Malavolti M, Agosti F, et al. Body water distribution in severe obesity and its assessment from eight-polar bioelectrical impedance analysis. *Eur J Clin Nutr*. 2005;59(2):155–160. https://doi.org/10.1038/sj.ejcn.1602049
4. Bhatia J. Fluid and electrolyte management in the very low birth weight neonate. *J Perinatol*. 2006;26(suppl 1):S19–21. https://doi.org/10.1038/sj.jp.7211466
5. Mattoo TK, Lu H, Ayers E, Thomas R. Total body water by BIA in children and young adults with normal and excessive weight. *PLoS One*. 2020;15(10):e0239212. https://doi.org/10.1371/journal.pone.0239212
6. Friedman A. Fluid and electrolyte therapy: a primer. *Pediatr Nephrol*. 2010;25(5):843–846. https://doi.org/10.1007/s00467-009-1189-7
7. Kight BP, Waseem M. Pediatric fluid management. StatPearls. Accessed November 9, 2023. https://www.statpearls.com/nursepractitioner/ce/activity/94963
8. Collins CT, Reid J, Makrides M, et al. Prediction of body water compartments in preterm infants by bioelectrical impedance spectroscopy. *Eur J Clin Nutr*. 2013;67(suppl 1):S47–53. https://doi.org/10.1038/ejcn.2012.164
9. Hellerstein S. Fluids and electrolytes: physiology. *Pediatr Rev*. 1993;14(2):70–79. https://doi.org/10.1542/pir.14-2-70
10. Harring TR, Deal NS, Kuo DC. Disorders of sodium and water balance. *Emerg Med Clin North Am*. 2014;32(2):379–401. https://doi.org/10.1016/j.emc.2014.01.001
11. Fedosova NU, Habeck M, Nissen P. Structure and function of Na,K-ATPase—the sodium-potassium pump. *Compr Physiol*. 2021;12(1):2659–2679. https://doi.org/10.1002/cphy.c200018
12. Bennet D, Khorsandian Y, Pelusi J, Mirabella A, Pirrotte P, Zenhausern F. Molecular and physical technologies for monitoring fluid and electrolyte imbalance: a focus on cancer population. *Clin Transl Med*. 2021;11(6):e461. https://doi.org/10.1002/ctm2.461
13. Luft FC. Did you know? fluid-and-electrolyte replacement and the uncertainity principle. *Acta Physiol. (Oxf)*. 2020;230(4):e13511. https://doi.org/10.1111/apha.13511

14. Lobo DN. Fluid, electrolytes and nutrition: physiological and clinical aspects. *Proc Nutr Soc*. 2004;3:453–466.
15. Jacob M, Chappell D. Reappraising Starling: the physiology of the microcirculation. *Curr Opin Crit Care*. 2013;19(4):282–289. https://doi.org/10.1097/MCC.0b013e3283632d5e
16. Dashty M. A quick look at biochemistry: carbohydrate metabolism. *Clin Biochem*. 2013;46(15):1339–1352. https://doi.org/10.1016/j.clinbiochem.2013.04.027
17. Oh W. Fluid and electrolyte management of very low birth weight infants. *Pediatr Neonatol*. 2012;53(6):329–333. https://doi.org/10.1016/j.pedneo.2012.08.010
18. Segar JL. A physiological approach to fluid and electrolyte management of the preterm infant: review. *J Neonatal Perinatal Med*. 2020;13(1):11–19. https://doi.org/10.3233/npm-190309
19. Oh GJ, Sutherland SM. Perioperative fluid management and postoperative hyponatremia in children. *Ped Nephrol*. 2016;31(1):53–60. https://doi.org/10.1007/s00467-015-3081-y
20. Bielicki IN, Somme S, Frongia G, Holland-Cunz SG, Vuille-Dit-Bille RN. Abdominal wall defects-current treatments. *Children (Basel)*. 2021;8(2):170. https://doi.org/10.3390/children8020170
21. Kendrick JB, Kaye AD, Tong Y, et al. Goal-directed fluid therapy in the perioperative setting. *J Anaesthesiol Clin Pharmacol*. 2019;35(suppl 1):S29–S34. https://doi.org/10.4103/joacp.JOACP_26_18
22. Feld LG, Neuspiel DR, Foster BA, et al. Clinical Practice Guideline: Maintenance Intravenous Fluids in Children. *Pediatrics*. 2018;142(6) https://doi.org/10.1542/peds.2018-3083
23. Churgay CA, Aftab Z. Gastroenteritis in children: part 1. Diagnosis. *Am Fam Physician*. 2012;85(11):1059–1062.
24. Roberts KB. Fluid and electrolytes: parenteral fluid therapy. *Pediatr Rev*. 2001;22(11):380–387.
25. Santillanes G, Rose E. Evaluation and management of dehydration in children. *Emerg Med Clin North Am*. 2018;36(2):259–273. https://doi.org/10.1016/j.emc.2017.12.004
26. Malbrain ML, Marik PE, Witters I, et al. Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice. *Anaesthesiol*

Intensive Ther. 2014;46(5):361–380. https://doi.org/10.5603/ait.2014.0060
27. Kopač M. Evaluation of Hypervolemia in Children. *J Pediatr Intensive Care*. 2021;10(1):4–13. https://doi.org/10.1055/s-0040-1714703
28. Ghali JK, Tam SW. The critical link of hypervolemia and hyponatremia in heart failure and the potential role of arginine vasopressin antagonists. *J Card Fail*. 2010;16(5):419–431. https://doi.org/10.1016/j.cardfail.2009.12.021
29. Bischoff AR, Tomlinson C, Belik J. Sodium intake requirements for preterm neonates: review and recommendations. *J Pediatr Gastroenterol Nutr*. 2016;63(6):e123–e129. https://doi.org/10.1097/mpg.0000000000001294
30. Gowrishankar M, Blair B, Rieder MJ. Dietary intake of sodium by children: why it matters. *Paediatr Child Health*. 2020;25(1):47–61. https://doi.org/10.1093/pch/pxz153
31. Wolf MB. Hyperglycemia-induced hyponatremia: reevaluation of the Na(+) correction factor. *J Crit Care*. 2017;42:54–58. https://doi.org/10.1016/j.jcrc.2017.06.025
32. Katz MA. Hyperglycemia-induced hyponatremia—calculation of expected serum sodium depression. *N Engl J Med*. 1973;289(16):843–4. https://doi.org/10.1056/nejm197310182891607
33. Song L, Hanna RM, Nguyen MK, Kurtz I, Wilson J. A novel case of pseudohyponatremia caused by hypercholesterolemia. *Kidney Int Rep*. 2019;3:491–493.
34. Sodium change in hypertriglyceridemia. Merck Manual Professional Version. Accessed November 9, 2023. https://www.merckmanuals.com/professional/multimedia/clinical-calculator/sodium-change-in-hypertriglyceridemia
35. Whitmire, SJ. Fluids and electrolytes. In: Matarese LE, Gottschlisch MM, eds. *Contemporary Nutrition Support Practice: A Clinical Guide*. Saunders; 1998:129–130.
36. Horisberger JD, Lemas V, Kraehenbühl JP, Rossier BC. Structure-function relationship of Na,K-ATPase. *Annu Rev Physiol*. 1991;53:565–584. https://doi.org/10.1146/annurev.ph.53.030191.003025

37. Rodan AR. Potassium: friend or foe? *Pediatr Nephrol*. 2017;32(7):1109–1121. https://doi.org/10.1007/s00467-016-3411-8
38. Lindinger MI, Sjøgaard G. Potassium regulation during exercise and recovery. *Sports Med*. 1991;11(6):382–401. https://doi.org/10.2165/00007256-199111060-00004
39. Bravo EL. Regulation of aldosterone secretion: current concepts and newer aspects. *Adv Nephrol Necker Hosp*. 1977;7:105–120.
40. Lanham-New SA, Lambert H, Frassetto L. Potassium. *Adv Nutr*. 2012;3(6):820–821. https://doi.org/10.3945/an.112.003012
41. Leonberg-Yoo AK, Tighiouart H, Levey AS, Beck GJ, Sarnak MJ. Urine potassium excretion, kidney failure, and mortality in CKD. *Am J Kidney Dis*. 2017;69(3):341–349. https://doi.org/10.1053/j.ajkd.2016.03.431
42. Zieg J, Gonsorcikova L, Landau D. Current views on the diagnosis and management of hypokalaemia in children. *Acta Paediatr*. 2016;105(7):762–772. https://doi.org/10.1111/apa.13398
43. Klevay LM, Bogden JD, Aladjem M, et al. Renal and gastrointestinal potassium excretion in humans: new insight based on new data and review and analysis of published studies. *J Am Coll Nutr*. 2007;26(2):103–110. https://doi.org/10.1080/07315724.2007.10719591
44. Rehman Siddiqu NU, Merchant Q, Hasan BS, et al. Comparison of enteral versus intravenous potassium supplementation in hypokalaemia in paediatric patients in intensive care post cardiac surgery: open-label randomised equivalence trial (EIPS). *BMJ Open*. 2017;7(5):e011179. https://doi.org/10.1136/bmjopen-2016-011179
45. Taketomo CK, Hodding JH, Krauss DM, eds. *Lexicomp Pediatric and Neonatal Dosage Handbook*. 26th ed. Wolters Kluwer; 2019.
46. Phelps SJ, Hagemann TM, Lee KR, Thompson AJ, eds. *Pediatric Injectable Drugs*. 11th ed. American Society of Health-System Pharmacists; 2018.
47. Palmer BF, Clegg DJ. Diagnosis and treatment of hyperkalemia. *Cleve Clin J Med*. 2017;84(12):934–942. https://doi.org/10.3949/ccjm.84a.17056
48. Elliott TL, Braun M. Electrolytes: potassium disorders. *FP Essent*. 2017;459:21–28.

49. Anderson S, Farrington E. Magnesium treatment in pediatric patients. *J Pediatr Health Care*. 2021;35(5):564–571. https://doi.org/10.1016/j.pedhc.2021.03.003
50. Hansen BA, Bruserud Ø. Hypomagnesemia in critically ill patients. *J Intensive Care*. 2018;6:21. https://doi.org/10.1186/s40560-018-0291-y
51. Junqueira EO, Marba STM, Caldas JPS. Hypermagnesemia and feeding intolerance in preterm infants: a cohort study. *JPEN J Parenter Enteral Nutr*. 2022;46(5):1054–1060. https://doi.org/10.1002/jpen.2336
52. Harker HE, Majcher TA. Hypermagnesemia in a pediatric patient. *Anesth Analg*. 2000;91(5):1160–1162. https://doi.org/10.1097/00000539-200011000-00022
53. Chan GM. Calcium needs during childhood. *Pediatr Ann*. 2001;30(11):666–670. https://doi.org/10.3928/0090-4481-20011101-07
54. Chacham S, Pasi R, Chegondi M, Ahmad N, Mohanty SB. Metabolic bone disease in premature neonates: an unmet challenge. *J Clin Res Pediatr Endocrinol*. 2020;12(4):332–339. https://doi.org/10.4274/jcrpe.galenos.2019.2019.0091
55. Mihatsch W, Fewtrell M, Goulet O, Molgaard C, Picaud JC, Senterre T. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: calcium, phosphorus and magnesium. *Clin Nutr*. 2018;37(6 Pt B):2360–2365. https://doi.org/10.1016/j.clnu.2018.06.950
56. Krapf R, Jaeger P, Hulter HN. Chronic respiratory alkalosis induces renal PTH-resistance, hyperphosphatemia and hypocalcemia in humans. *Kidney Int*. 1992;42(3):727–734. https://doi.org/10.1038/ki.1992.340
57. Jassam N, Gopaul S, McShane P, et al. Calcium adjustment equations in neonates and children. *Ann Clin Biochem*. 2012;49(Pt 4):352–358. https://doi.org/10.1258/acb.2011.011060
58. Di Maio S, Soliman AT, De Sanctis V, Kattamis CC. Current treatment of hypoparathyroidism: theory versus reality waiting guidelines for children and adolescents. *Acta Biomed*. 2018;89(1):122–131. https://doi.org/10.23750/abm.v89i1.7118
59. Moe S. Disorders involving calcium, phosphorus and magnesium. *Prim Care Clin Office Pract*. 2008;35(2):215–237.
60. Maruyama H, Saito J, Nagai M, Mochizuki M, Ishikawa Y, Ito Y. Maximization of calcium and phosphate in neonatal total parenteral

nutrition. *Pediatr Int*. 2018;60(7):634–638. https://doi.org/10.1111/ped.13579
61. Schmidt G, Baumgartner T, Fischlschweiger W, Sitren H, Thakker K, Cerda J. Cost conainment using cysteine HCl acidification to increase calcium/phosphate solubility in hyperalimentation solutions. *J Parener Enteral Nutr*. 1986;10:203–207.
62. Stokes VJ, Nielsen MF, Hannan FM, Thakker RV. Hypercalcemic disorders in children. *J Bone Miner Res*. 2017;32(11):2157–2170. https://doi.org/10.1002/jbmr.3296
63. Simm PJ, Biggin A, Zacharin MR, et al. Consensus guidelines on the use of bisphosphonate therapy in children and adolescents. *J Paediatr Child Health*. 2018;54(3):223–233. https://doi.org/10.1111/jpc.13768
64. Reintam Blaser A, Gunst J, Ichai C, et al. Hypophosphatemia in critically ill adults and children—A systematic review. *Clin Nutr*. 2021;40(4):1744–1754. https://doi.org/10.1016/j.clnu.2020.09.045
65. Bitzan M, Goodyer PR. Hypophosphatemic Rickets. *Pediatr Clin North Am*. 2019;66(1):179–207. https://doi.org/10.1016/j.pcl.2018.09.004
66. Bacchetta J, Bernardor J, Garnier C, Naud C, Ranchin B. Hyperphosphatemia and chronic kidney disease: a major daily concern both in adults and in ahildren. *Calcif Tissue Int*. 2021;108(1):116–127. https://doi.org/10.1007/s00223-020-00665-8
67. Abdullah S, Diezi M, Sung L, Dupuis LL, Geary D, Abla O. Sevelamer hydrochloride: a novel treatment of hyperphosphatemia associated with tumor lysis syndrome in children. *Pediatr Blood Cancer*. 2008;51(1):59–61. https://doi.org/10.1002/pbc.21478
68. Ladenhauf HN, Stundner O, Spreitzhofer F, Deluggi S. Severe hyperphosphatemia after administration of sodium-phosphate containing laxatives in children: case series and systematic review of literature. *Pediatr Surg Int*. 2012;28(8):805–814. 10.1007/s00383-012-3124-4
69. Goodman WG, Goldin J, Kuizon BD, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med*. 2000;342(20):1478–1483. https://doi.org/10.1056/nejm200005183422003

Test Your Knowledge Answers

1. The correct answer is **B**. Based on the signs and symptoms, the patient is moderately dehydrated. A 20 mL/kg bolus with 40 mL/kg of replacement fluids plus maintenance fluids for the first 8 hours is appropriate, followed by 40 mL/kg of replacement fluids plus maintenance fluids for the next 16 hours. Serum sodium levels should be monitored to make sure serum sodium levels are not decreased faster than 0.5 mEq/L/h. The fluid replacement 65 mL/kg is for a patient that is severely dehydrated and may lead to overcorrection of the fluid status. The replacement at 100 mL/kg plus maintenance fluids is too aggressive and may result in decreasing the serum sodium more than 0.5 mEq/L/h, which results in cerebral edema.
2. The correct answer is **C**. The effect of fluid gains on body fluid compartments depends on the osmolarity of the fluid given and the osmolarity and the size of the fluid compartments. The administration of 100 mL of 0.9% sodium chloride is isotonic and will not alter the plasma osmolarity. Because there is no gradient, 100 mL of the isotonic saline will stay in ECF, and the intravascular volume will be increased 25 mL.
3. The correct answer is **D**. TBW decreases with age. TBW is about 80% of total body weight in preterm infants, 70% by 3 months of age, and about 60% by 6 months of age. It remains about 60% into adulthood.
4. The correct answer is **C**. The drop in the serum electrolytes concentration is due to the intracellular shift of the potassium, magnesium, and phosphate seen in refeeding. This is an acute issue and should be treated with supplemental electrolytes. Oral or intravenous supplementation is acceptable, depending on oral tolerance. Replacing the electrolytes in the maintenance solution is not recommended because over time, the potassium, magnesium, and phosphate will accumulate as the maintenance solution continues.

PART II

Age-Specific Nutrition for Growth and Development

10. Nutrition and Early Development

Ricardo Rueda, MD, PhD
Paula Soriano, MSc
Esther Castanys-Muñoz, PhD
José M. López-Pedrosa, PhD
Yen-Ling Low, PhD

11. Human Milk Feeding and Clinical Considerations

Christina J. Valentine, MD, MS, RD, FAAP, FASPEN
Amy Gates, PhD, RDN, LD

12. Infant Formulas and Complementary Feeding

Kelly Green Corkins, MS, RD, LDN, CNSC, FAND, FASPEN
Lindsey Lee, MS, RD, LDN, CSP

13. Enteral Formulas

Kelly Green Corkins, MS, RD, LDN, CNSC, FAND, FASPEN

14. Childhood Overweight and Obesity: Efficacy and Safety of Popular Diets and Weight-Control Programs

David Freestone, DO

15. Lipid Disorders

Elizabeth L. Wright, MS, RDN, CSP, LDN, FAND, CLC
Danielle H. Campbell, MS, RDN, LDN
James Gherardi, BS, DTR

10

Nutrition and Early Development

Ricardo Rueda, MD, PhD; Paula Soriano, MSc; Esther Castanys-Muñoz, PhD; José M. López-Pedrosa, PhD; and Yen-Ling Low, PhD

Learning Objectives

1. Describe the normal physiology and metabolism of the fetus and enumerate nutrient deficiencies associated with adverse pregnancy outcomes.
2. Explain common late adverse manifestations of early programming observed in epidemiologic and animal studies.
3. Establish potential mechanisms involved in late and transgenerational effects of early life programming.

Introduction

Dietary inadequacy, imbalance, or excess can all impact fetal development. Some of these changes persist throughout life or leave the individual vulnerable to later environmental and dietary conditions that can adversely impact health and longevity. This chapter provides an updated overview of the importance of nutrition during sensitive periods, such as pregnancy and lactation, and the crucial role it plays in fetal development and the long-term health of the offspring.

We will first address how maternal dietary deficiencies during pregnancy and nutrition during lactation affect the fetus and infant, respectively. In addition, we will evaluate the impact of nutrition and other stresses on fetal metabolism. We will then focus on how prenatal and postnatal programming effects are integrated, presenting a summary of the different animal models used in developmental programming studies. To conclude, we will discuss the persistence of adverse effects across several generations and the implications for future health and current practice.

Pregnancy

Physiology of Pregnancy

A healthy pregnancy is dependent on maternal nutrition status at conception and an adequate blood flow to deliver oxygen and nutrients to the placenta and fetus, as well as on the maintenance of the appropriate hormonal milieu (from maternal, fetal, and placental origins) to support placental and fetal development. Early in gestation, the placental-to-fetal weight ratio is high, and this ratio declines in later gestation. Initially, placental transport largely depends on increases in placental size, but later in pregnancy, both placental transport function and placental size must increase to meet the needs of the rapidly growing fetus.

The placenta acts as the main interface between mother and fetus and largely controls nutrient availability and, consequently, fetal growth. The primary barrier to placental nutrient transport is the syncytiotrophoblast, which features polarized microvillous maternal-facing membranes and fetal-facing basolateral membranes. This specialized multinucleated epithelial cell layer produces multiple hormones, expresses numerous nutrient transporters, and acts as the physical and immunological barrier between maternal and fetal circulation. Highly permeable molecules, like respiratory gases, are transported bidirectionally across the syncytiotrophoblast, and changes can largely influence their transport in blood flow. Less permeable nutrients and molecules are conveyed by both passive and active transport mechanisms intrinsic to the placenta. As such, alterations in placental transport can play a key role as a mediator–integrator of maternal nutrition effects on fetal overgrowth and

undergrowth and the later lifelong health outcomes associated with these conditions.[1]

The major energy source for the fetus is glucose, which is transported by facilitated diffusion and therefore largely driven by maternal−fetal concentration gradients.[2] It also uses lactate produced in the placenta and endogenously.[3] The fetal pancreas secretes insulin by midgestation and responds to variations in the glucose delivery rate. Normally the fetal liver is not active in gluconeogenesis. Fetal tissue glucose transporters and intracellular downstream metabolic regulators are modulated by glucose and insulin levels in the fetus. Insulin-responsive fetal tissues include the heart, liver, skeletal muscle, and adipose tissue. Fetal glucose oxidation is maintained even when fetal glucose supply is limited, which indicates that placental glucose uptake is not regulated by insulin.[4] According to Hay, "The fetus develops with mechanisms that tend to keep its energy metabolism relatively constant, while growth is, at times of deficient energy supply, expendable."[4]

Amino acids are the second most important macronutrient in the fetus, with at least 14 complex amino acid transporter systems on both syncytiotrophoblast membranes.[5] The transport of large neutral and branched-chain amino acids is the most directly proportional to their maternal concentration.[6] All amino acids, except tryptophan, are more highly concentrated in the placenta than in maternal blood. Leucine appears to have specific trophic effects on the placenta and the fetus, possibly because of its impact on the mammalian target of rapamycin (mTOR), which is a critical regulator of protein synthesis and is involved in placental nutrient sensing mechanisms.[7] Fetuses with intrauterine growth restriction (IUGR) have reduced fetal enrichment of leucine relative to the maternal circulation.[8] Other specific amino acids, such as arginine, also have nutrient effects along with similar regulatory and developmental effects as well.[5]

When less oxygen, glucose, and amino acids are available to the fetus because of reduced umbilical vein blood flow (associated with placental transport insufficiency), fetal weight gain slows. Compensatory increases occur in fetal amino acid catabolism to minimize changes in fetal blood amino acid concentrations. This situation is associated with altered substrate

distribution and changes in relative organ growth. When glucose (and other substrates) supply is limited and the fetus is relatively hypoglycemic, growth of the brain, kidney, and adrenals is protected to the detriment of other organs, such as the spleen, liver, pancreas, and lung.[9] A redistribution of blood flow leads to slower growth, altered fetal liver metabolism, and reduced pancreatic β-cell mass or function, depending on the stage of pregnancy. The most common cause of IUGR is placental transport insufficiency (eg, of oxygen, glucose, amino acids), which may be related to local uterine factors, maternal malnutrition, advanced maternal diabetes, hypertension, or other maternal or placental pathology.[10,11]

Central metabolic mediators for regulatory hormone and metabolic changes in the fetus are fetal insulin, cortisol, and insulin-like growth factors (IGFs), which are critical for placental development and function and protein synthesis in fetal tissues.[12,13] In particular, increased levels of cortisol are associated with reduced glucose uptake, increased gluconeogenesis, and slower fetal growth.

Common metabolic/hormonal imbalances that influence organ growth and metabolic development of the fetus include hypoglycemia, hyperglycemia, maternal or gestational diabetes, and activation of the fetal hypothalamic–pituitary–adrenal (HPA) axis by a variety of intrauterine insults.[14,15] The fetus and uteroplacental support system are highly adaptive to vascular supply, oxygenation state, and metabolic substrate availability. In this formative stage of life, a multitude of responses at the fetal, organ, tissue, membrane, cytosolic, and nuclear levels determine the survival, health, and function of the fetus. Some of these adaptations are transient and others, particularly with prolonged exposure, appear to be permanent.[16] Epigenetic modifications of cells in specific organs help determine the final metabolic phenotype, which is a product of both genetic inheritance and developmental, environmental influences on gene expression. Vulnerability to environmental and dietary influences appears to continue well past the time of birth. Fetal and early postnatal plasticity allows survival, but it may also set the stage for later maladaptive metabolic responses, particularly to metabolic environments different from those experienced early in development (eg, food surfeit vs scarcity).[1,14]

Impact of Maternal Dietary Deficiencies on the Fetus

Maternal nutrition during pregnancy can exert long-lasting effects on the health of offspring.[17] These effects may be due to undernutrition, a deficit of specific nutrients, or an excess of energy or nutrients. Epidemiological and animal studies suggest that fetal adaptive responses to the intrauterine environment, including maternal malnutrition, overnutrition, or diabetes, may increase the risk of many chronic diseases in adulthood, including type 2 diabetes and coronary heart disease (CHD).[18] Animal studies also show that both maternal undernutrition and overnutrition reduce placental-fetal blood flow and slow fetal growth. Impaired placental synthesis of nitric oxide (a major vasodilator and angiogenesis factor) and polyamines (key regulators of DNA and protein synthesis) may explain IUGR in response to the two extremes of nutrition problems with the same pregnancy outcome. Placental and fetal growth is the most vulnerable to maternal nutrition status during the peri-implantation period and the period of rapid placental development (the first trimester of gestation).

Extensive clinical research, using both observational and interventional study designs, has allowed some quantification of the effects of maternal anthropometric indices, dietary intake in pregnancy, and nutritional supplements to measures of fetal size, maturity at birth, and developmental outcomes. Overall, these studies find a strong positive association between maternal prepregnancy nutrition status and the ability of a mother to nourish her growing fetus. Accumulating evidence also suggests that both periconceptional undernutrition and pregnancy undernutrition are important determinants of the length of gestation and fetal growth and development.[19] Gestational weight gain and nutrition interventions during pregnancy can modify this association by altering the rate of fetal growth, although the extent of the modification is modest and depends on maternal baseline nutrition status.[20] Current estimates of nutrition needs are provided in Table 10-1.

TABLE 10-1. Recommended Daily Nutrient Intakes During Pregnancy

Nutrient	Recommended Daily Intake
Water	3 L
Energy	Varies by age, pregnancy stage, body mass index, activity
Carbohydrate	175 g
Total fiber	28 g
Linoleic acid	13 g
Linolenic acid	1.4 g
Protein	71 g
Vitamin A	750–770 mcg[a]
Vitamin C	80–85 mg/d[a]
Vitamin D	15 mcg
Vitamin E	15 mg
Vitamin K	75–90 mcg[a]
Thiamin	1.4 mg
Riboflavin	1.4 mg
Niacin	18 mg
Vitamin B_6	1.9 mg
Folate	600 mcg
Vitamin B_{12}	2.6 mcg
Pantothenic acid	6 mg
Biotin	30 mcg
Choline	450 mg
Calcium	1000–1300 mg[a]
Chromium	29–30 mcg[a]
Copper	1000 mcg
Fluoride	3 mg
Iodine	220 mcg
Iron	27 mg
Magnesium	350–400 mg[a]

Nutrient	Recommended Daily Intake
Manganese	2 mg
Molybdenum	50 mcg
Phosphorus	700–1250 mg[a]
Selenium	60 mcg
Zinc	11–12 mg[a]
Potassium	2,6–2,9 g[a]
Sodium	1.5 g
Chloride	2.3 g

Data from Summary Tables: Dietary Reference Intakes: Estimating Average Requirements and from Dietary Reference Intakes: Recommended Dietary Allowances and Adequate Intakes, Vitamins. Food and Nutrition Board, National Academies of Science Institute of Medicine. https://www.nal.usda.gov/sites/fnic.nal.usda.gov/files/uploads/SummaryTables.pdf

[a] Varies by age group.

Macronutrients

During pregnancy, extra energy (and therefore macronutrient intake) is required by the mother to support the growth of the fetus, placenta, and various maternal tissues, such as in the uterus and breast, and for the deposition of fat stores. In terms of maternal macronutrient status, deficiency of macronutrients, specifically protein and carbohydrates, during pregnancy and gestation results in lower infant birth weight, a surrogate marker of fetal growth, and may predispose the offspring to insulin resistance, glucose intolerance, hypertension, and adiposity in adulthood.[21] Some studies have also demonstrated that a low-protein diet in utero has a deleterious effect on bone development in offspring that persists into adulthood.[22] In these studies, the offspring displayed significant differences in bone structure and density at various sites. These differences are indicative of significantly altered bone turnover.[23]

Several nutritional interventions have been evaluated regarding maternal needs during pregnancy. The most promising macronutrient intervention to prevent adverse perinatal outcomes is balanced protein-energy supplementation, where protein provides less than 25% of the total energy

content.[24] A Cochrane Review published in 2015 found that balanced energy and protein supplementation in pregnant women is associated with clear increases in mean birth weight, with fewer stillbirths and fewer small-for-gestational-age (SGA) births. In contrast, high-protein supplementation or isocaloric protein supplementation (in which protein replaces an equal quantity of nonprotein energy) showed no benefit.[25] Hence, current evidence indicates that balanced protein-energy supplementation is an effective intervention to reduce the prevalence of low birth weight (LBW) and SGA births, especially in undernourished women.

Calcium

During pregnancy, the fetus exerts additional calcium demand on the mother as calcium is transferred across the placenta to support fetal skeletal mineralization. The additional demand can usually be achieved through calcium mobilization from the skeleton, increased intestinal calcium absorption efficiency, and enhanced renal calcium retention or greater dietary calcium intake of the mother.[26] Observational studies have generally found a positive relationship between maternal dietary calcium intake during pregnancy and bone outcomes of offspring, with positive bone outcomes in children at 9 years of age.[27] Calcium supplementation during pregnancy can be linked directly to increased bone density and bone length of neonates.

Apart from calcium's effect on bone health of the fetus, two Cochrane systematic reviews have investigated whether calcium supplementation daily during pregnancy safely improved maternal and infant outcomes. Calcium supplementation during pregnancy was found to significantly reduce the risk of preeclampsia and high blood pressure (with or without proteinuria).[28,29]

Iron

A recent World Health Organization review found that iron supplementation during pregnancy was associated with a reduced likelihood of having LBW babies compared with controls, and the mean birth weight was 30.81 g greater for infants whose mothers received iron during pregnancy (95% CI, 5.94–55.68 g, 14 studies).[30] In addition, reduced iron availability for brain

iron accretion is associated with persistent developmental and behavioral changes. Several conditions associated with fetal growth retardation or macrosomia, such as diabetes, placental insufficiency, and smoking, restrict iron availability during gestation and create a predisposition to later iron deficiency.[31,32]

Iodine

The importance of iodine for fetal growth and development is well established, and severe iodine deficiency during pregnancy results in cretinism. Strong evidence indicates that adequate iodine during pregnancy is important to support healthy neurodevelopment of the fetus.[33,34] Several intervention studies have shown that iodine supplementation during pregnancy in iodine-deficient mothers improved intelligence quotient (IQ) points in children several years later. Pregnancy seems to be a critical period because children whose mothers were given iodine during pregnancy performed better on a psychomotor test than children who were supplemented from 2 years of age.[35] Ensuring adequate iodine intake in early life is an important way to promote healthy brain development in children.

Folic Acid and Vitamin B_{12}

Folic acid is very important both preconceptionally and periconceptionally in protecting the fetus from neural tube defects. In well-nourished populations, folic acid needs are usually met by dietary intake. However, in some countries (eg, the United States), pregnant women are advised to consume 600 mcg of folic acid per day to reduce the risk of neural tube defects (see Table 10-1). Low maternal folate intake (< 240 mcg/d) has been associated with a greater than threefold increase in the risk of LBW and preterm delivery. A metabolic effect of folate deficiency is an elevation of homocysteine, and women with high homocysteine levels are more likely to have a reproductive history of preeclampsia, preterm delivery, LBW, or fetal growth restriction.[17] A study conducted in India highlighted the major role that dietary methyl donors, including vitamin B_{12} and folate, seem to play in fetal programming. Maternal low vitamin B_{12} status along with

normal to high folate status predicted later adiposity and insulin resistance in children. Thus, 1-C (methyl) metabolism seems to have a key role in fetal programming.[36]

Vitamin D

Vitamin D deficiency during pregnancy predisposes newborns to neonatal hypocalcemia and, later,rickets. Maternal vitamin D status during pregnancy may have long-term effects on bone mineral accretion in childhood. Vitamin D insufficiency during pregnancy appears to be increasingly common in developed countries,[37] and the consequences may extend beyond the recognized influence of neonatal calcium deficiency and rickets. Several studies have also proposed low vitamin D concentrations during prenatal or early life development as a cause of a greater risk of later development of multiple sclerosis, cancer, insulin-dependent diabetes mellitus, recurrent wheeze, and schizophrenia, though the evidence is still inconclusive.[38] A recent meta-analysis suggests vitamin D supplementation during pregnancy reduces fetal or neonatal mortality and is associated with improved fetal linear growth.[39]

Vitamin E

The plasma concentration of α-tocopherol, the most common isomer of vitamin E, is positively related to fetal growth (birth weight for gestation), reduced SGA births, and increased risk of large-for-gestational-age births. Concentrations of α-tocopherol were positively related to the use of prenatal multivitamins before and during pregnancy and to vitamin E in the maternal diet. Emerging evidence suggests that the effect of vitamin E on fetal growth may occur via increased blood flow and nutrient supply to the fetus.[17]

Multiple Micronutrients

Few published studies have examined whether supplements of multiple micronutrients might be more beneficial than single micronutrients. Evidence exists for interactions of several micronutrients at the metabolic level. Little is yet known about the significance of these interactions for pregnancy outcomes, especially in developing countries where nutrient

deficiencies rarely occur in isolation and multiple micronutrient deficiencies are common. A meta-analysis of global multi-nutrient supplementation studies found a small effect on birth weight between iron-folate supplementation and placebo.[40] A Cochrane Review in 2019 found that supplementation with multiple micronutrients significantly affects SGA and LBW outcomes compared to supplementation with two or fewer micronutrients, no supplementation, or a placebo. Comparing multiple micronutrient supplementation with iron and folate showed similar beneficial effects on SGA and LBW outcomes.[41]

Lactation

Physiology of Lactation

Lactation is the process of milk production and secretion, which involves the maturation of alveolar cells.[42] (See Chapter 11, "Human Milk" for information about the different phases of lactation.) During pregnancy, full alveolar development and maturation are induced by the hormones of pregnancy, including progesterone, prolactin, placental lactogen, glucocorticoid, and oxytocin. Each breast contains lobules with alveoli that are surrounded by myoepithelial cells and contain acinar cells, which produce milk. During early pregnancy, growth and development of the ductal trees occur along with further formation of lobules, which is followed by increased secretory activity, and the alveoli starting to become engorged with milk.[43] Colostrum secretion, which is a sticky substance, can be squeezed from the breast by approximately the 12th week of pregnancy, and by about the 16th week, it will be thick and yellowish.

Major hormonal changes occur after delivery that allow for the onset of stage 2 of lactogenesis. The most important change is the withdrawal of progesterone and estrogen, allowing prolactin to enable milk secretion. Progesterone levels decrease about tenfold in the first few days after delivery. Upon infant suckling, nerves in the areola communicate to the hypothalamus and subsequently to the anterior and posterior pituitary gland, which secretes prolactin and oxytocin, respectively. Prolactin stimulates the production of milk in the alveolar cells, and oxytocin stimulates the myoepithelial cells to squeeze the alveoli and eject milk into the larger

ducts for suckling by the infant.[44] Prolactin is the most important hormone to lactation; although oxytocin controls the "letdown" of the milk, milk cannot be made without prolactin.[39]

Components of human milk are secreted into the alveolar lumina in 5 distinct pathways, which operate in parallel to make the components of human milk from precursors in the interstitial fluid and blood. These pathways operate with the following processes:

1. Exocytosis is the pathway used for the aqueous fraction of human milk and is similar to that of other cells of the body.
2. Lipid synthesis and secretion are unique to the mammary gland. Through this pathway, triglycerides are synthesized from fatty acids and glycerol in the smooth endoplasmic reticulum of the alveolar cells. After the lipid droplet is enveloped in the apical plasma membrane, it is expelled as a milk-fat globule.
3. Transport across the apical membrane involves direct transport of monovalent ions, water, and glucose across the apical membrane. Currently, exact transport mechanisms are not well understood.
4. Transcytosis of interstitial molecules involves the transport of proteins from the interstitial space across the mammary epithelium. Immunoglobulin A is the most studied of these proteins. After being synthesized in the body, it binds to receptors on the basal surface of the alveolar cell, and the entire complex undergoes endocytosis and is transferred to the apical membrane. Many other proteins, hormones, and growth factors use a similar method but are not as well studied.
5. The paracellular pathway involves the movement of substances between, rather than through, the alveolar cells. During mature lactation, the tight junctions between cells do not allow substances to pass between them; however, it appears that immune cells can undergo diapedesis and be incorporated into human milk. The tight junctions can become leakier during pregnancy, with mastitis, and after involution.[38]

Impact of Maternal Nutrition During Lactation on the Infant

Lactation is one of the most nutritionally demanding times in a woman's life, with increased needs for almost all nutrients beyond those in

pregnancy. The caloric expenditure of 6 to 9 months of lactation can exceed that of pregnancy by 42% and 98%, respectively.[45] To preserve the survival of the species, mammary glands are still able to produce a sufficient volume of human milk for infant survival, even in times of poor maternal nutrition. However, the nutrition adequacy for optimal infant growth and development may still be at risk; therefore, the nutrition status of the lactating woman is important to the nutrition received by the infant via human milk.

Several nutrients are of greater importance than others in the maternal diet and body stores because their deficiency can greatly impact their levels in human milk. Such nutrients include B vitamins, choline, vitamins A and D, and iodine. However, many of the major minerals, including calcium, iron, and zinc, as well as calories and protein are not influenced by maternal intake and stores. Other human milk nutrients, such as polyunsaturated fatty acids and carotenoids that are important for infant development, may also be influenced by maternal intake. Most studies of the dietary intake of lactating women suggest that the nutrients in human milk that are the most sensitive to maternal intake are the most likely to be deficient in the maternal diet.[46–49]

Because B vitamins are water-soluble and not stored, they must come from the diet. Maternal deficiency of thiamin (B_1) and riboflavin (B_2) can rapidly impact human milk concentration[50] of these vitamins, which are readily transported across the mammary gland into the milk. Supplementation may improve human milk status for those who are undernourished.[51,52] A strong correlation exists between human milk concentration and infant status and maternal intake.[53] Supplementation in well-nourished women does not seem to increase concentrations,[54] suggesting the presence of a feedback mechanism that ensures an adequate human milk concentration with intake that is appropriate.

Similar to the other B vitamins, infant status of vitamin B_6 is strongly related to maternal intake,[55,56] and B_6 supplementation in reasonably nourished women does demonstrate a significant increase in human milk concentration.[57] Higher doses of 10 mg/d resulted in infants meeting the adequate intake for vitamin B_6.[56] Vitamin B_{12} may be of even greater

concern for many, especially women who are following a strict vegetarian or vegan diet or for whom animal food sources are scarce because almost all vitamin B_{12} in the food chain is from animals. Little research has been done on vitamin B_{12} supplementation in lactating women; however, data suggest that human milk concentration may respond to vitamin B_{12} supplementation in undernourished women.[50,58,59]

Finally, maternal choline intake is also correlated to human milk and plasma concentrations, and choline supplementation can increase concentrations, which seem to be impacted by individual genotypes.[60] Given the impact of maternal nutrition on human milk concentration of B vitamins, it is noteworthy that infants who are exclusively breastfed by mothers with a dietary deficiency are at significant risk of inadequate intake.[50]

The recommendation for vitamin A for lactating women is almost 70% greater than that during pregnancy, and it represents the largest increase for any single vitamin/mineral between pregnancy and lactation. On average, infants received approximately 400 mcg/d of vitamin A from human milk during the first 6 months of lactation,[61] and almost 60 times more vitamin A is transferred to the infant during this time than during gestation.[55] Vitamin A status of human milk is dependent on maternal stores. In parts of the world with low vitamin A intake and high rates of deficiency, the average vitamin A content of mature milk is about 1 μmol/L, compared to about 7 μmol/L for well-nourished women, suggesting that infants may have subclinical vitamin A deficiency by 6 months of age.[62] Vitamin A supplementation in women who are breastfeeding offers limited benefits for improving maternal and infant vitamin A deficiency.[63]

As described in Chapter 11, "Human Milk," vitamin D supplementation is recommended for all breastfed infants due to low human milk concentration, even in well-nourished women. Researchers continue to study whether larger doses of vitamin D given to lactating women can result in adequate infant plasma vitamin D in breastfed infants. A few studies with supplement doses of at least 2000 IU vitamin D per day in lactating women have demonstrated that the level of circulating 25(OH)-D_2 in exclusively breastfed infants was similar to that in infants receiving the recommended

400 IU/d supplement.[64,65] These studies demonstrated that these higher doses appear to be safe, even though they are greater than the 600 IU/d recommended by the Institute of Medicine. A recent meta-analysis of randomized controlled trials found a linear relationship between maternal vitamin D supplementation and the level of circulating vitamin 25(OH)D in their infants.[66] Further research is needed in this area to determine the longer-term impact on the breastfeeding dyad regarding higher vitamin D supplementation.

Iodine deficiency is still a problem that is often overlooked because it is expected that this condition was mostly eliminated with iodized tabled salt, which was introduced in the United States in 1924. Deficiency during pregnancy can have a significant negative impact on cognitive outcomes in the infant that may not be reversible;[33] it is also likely to be of concern if human milk is not adequate in iodine. Concern about the iodine intake of lactating women is ongoing because recent research has shown that they tend to consume only about 30% of the amount recommended by the Institute of Medicine.[48] Most salt intake is from packaged and processed foods, which do not use iodized salt. The other main dietary sources of iodine are seafood and dairy, and consumption is also generally well below recommendations.[48]

It is not surprising that iodine intake is low and the risk for deficiency is high. The mammary gland can concentrate iodine, which is likely why infant iodine status may be maintained even if the mother has overt iodine deficiency.[67] Supplementation during pregnancy has been shown to improve maternal iodine status,[68] and human milk concentration is related to maternal intake.[69] Therefore, given the important role that iodine has in infant development and the concern of low dietary intakes, iodine should be monitored during lactation and supplemented if needed.[70]

Other nutrients in human milk, such as polyunsaturated fatty acids, carotenoids (lutein in particular), and docosahexaenoic acid (DHA) are predominant components in the infant brain[71] and eye[72] and have important roles in the development of these organs.[73,74] The consumption of dietary sources of these nutrients is well below recommendations of fatty fish (4 oz portion) 3 times per week, and dark leafy greens (2-cup portion) once per

week.[75] Given the strong correlation of human milk DHA[76] and lutein[77] to maternal intake, these nutrients may be lacking for infants fed human milk if maternal intake is low. Research has shown human milk to be highly responsive to lutein[78] and DHA[79] supplementation, suggesting that women who are not consuming recommended amounts of fish and vegetables could benefit from supplementation.[80]

Impact of Nutrition and Other Stresses on Fetal Metabolism, Organ Growth, and Development

Deprivation of nutrients and/or oxygen in utero alters fetal metabolism in a manner that changes body growth and the development of individual fetal tissues.[40] The effects of varying nutrient availability on fetal metabolism depend on the specific nature of the nutrition variation and on the duration, severity, and gestational age at the onset of the insult. Deprivation of oxidative substrates such as glucose produces a different metabolic response in the fetus from that seen with oxygen deprivation alone or in the presence of combined oxygen and substrate deficiency. These different nutrition challenges also have different effects on the uteroplacental tissues and on the fetal hormonal environment, both of which influence the availability and metabolic fate of specific nutrients in the fetus.[81]

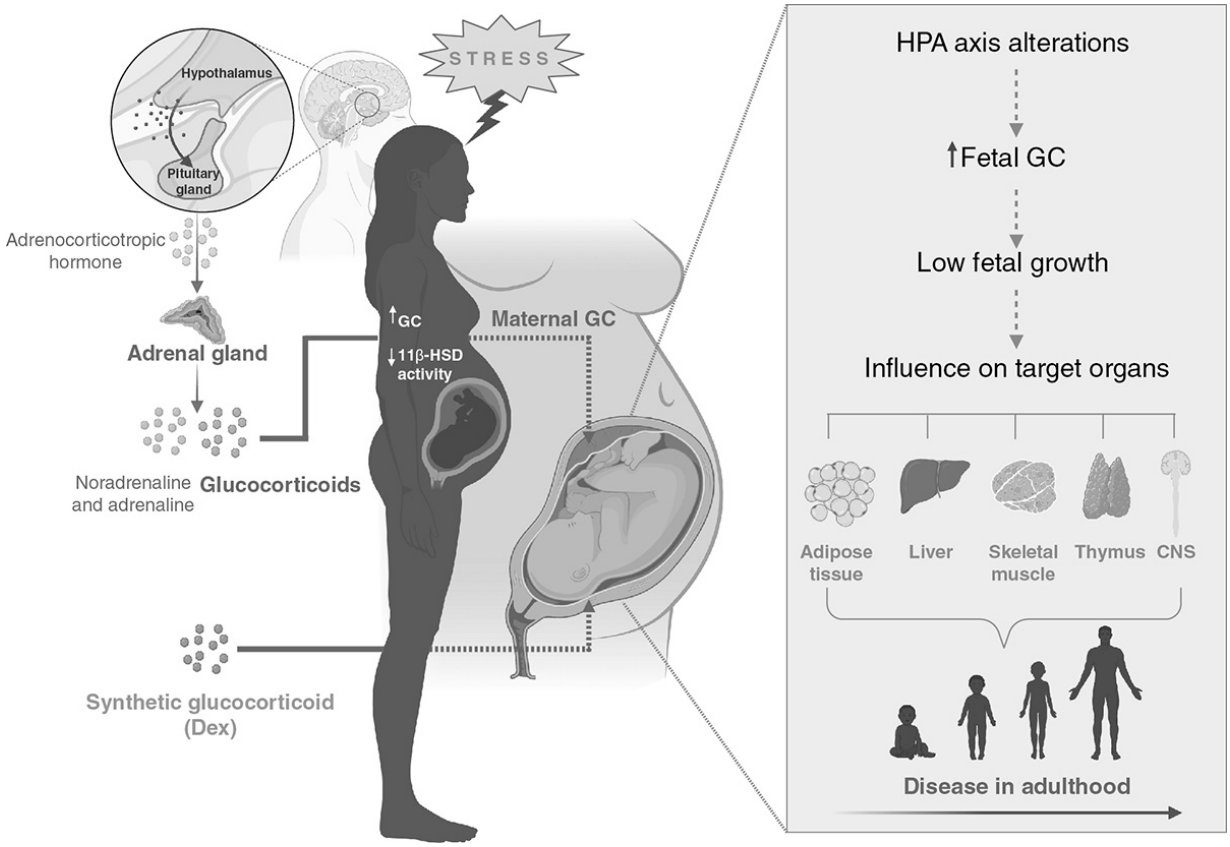
Many of the nutritionally induced alterations in fetal metabolism and growth are likely to be mediated by hormonal changes in either the mother or the fetus. Dietary restriction is known to alter maternal concentrations of growth hormone, IGFs, insulin, glucocorticoids, leptin, thyroid hormones, and placental lactogen.[40] These hormones alter maternal metabolite concentrations, which in turn influence fetal substrate availability, particularly for metabolites crossing the placenta against a concentration gradient. In general, reducing fetal delivery of oxygen and nutrients lowers anabolic hormones (eg, insulin, IGFs, thyroid hormones) and increases catabolic hormone concentrations (eg, cortisol, catecholamines, glucagon, growth hormone). The anabolic hormones tend to increase the uptake and utilization of glucose and reduce the oxidation of amino acids. They also

enhance protein accretion by stimulating protein synthesis, reducing proteolysis, or both. The catabolic hormones tend to increase fetal glucose production by activating hepatic gluconeogenesis. They also reduce protein accretion and fetal uptake of amino acids.

Animal studies convincingly demonstrate that prenatal stress can have a long-term effect on the function of the HPA axis in the offspring, also showing the variability and complexity of the possible effects. These effects vary depending on the nature of the stress, its timing in gestation, the genetic strain of the animal, the sex and age of the offspring, and whether basal or stimulated HPA axis responses are studied. Equivalent research with humans is only just starting, but experimental evidence suggests that there might be similar effects. These data are also variable, suggesting that prenatal stress or anxiety is associated with increased basal cortisol or increased cortisol reactivity in the offspring.[82]

Programming of the fetal HPA axis appears to play a central role in the link between fetal growth and long-term disease in adulthood (see Figure 10-1). Molecular mechanisms underlying the developmental programming effects of excess glucocorticoids and prenatal stress include epigenetic changes in target gene promoters. Crucially, changes in gene expression persist long after the initial challenge, predisposing the individual to disease in later life. Intriguingly, the effects of a challenged pregnancy are possibly transmitted to one or two subsequent generations, suggesting that these epigenetic effects persist.[83,84]

FIGURE 10-1. Scheme of the Role That Programming of the Fetal Hypothalamic–Pituitary–Adrenal Axis During Development Plays in the Link Between Fetal Growth and Long-Term Disease in Adulthood



Abbreviations: 11β-HSD, 11β-hydroxysteroid dehydrogenase; CNS, central nervous system; Dex, dexamethasone; GC, glucocorticoids; HPA, hypothalamic pituitary adrenal. The figure was created with BioRender software accessible at biorender.com.

A variety of prenatal stress insults can have long-term effects on the child's behavioral and cognitive outcomes.[82] Exposure of the fetus to elevated glucocorticoids appears to be the central link between prenatal stress and modification of HPA axis development and function. Evidence exists that antenatal stress/anxiety has a programming effect on the fetus that lasts at least until mid-childhood and results in higher rates of behavioral and emotional problems.[85,86] Cognitive and behavioral modifications have also been linked to alterations in HPA axis activity and prenatal glucocorticoid exposure. Prenatal stress has been associated with memory and behavior changes as well as depression, anxiety, chronic

fatigue syndrome, and schizophrenia.[87] These alterations in HPA axis function, behavior, and cognition resulting from prenatal stress relate to changes in brain corticosteroid receptor populations and alterations in hippocampal and hypothalamic neuronal development.[88]

Prenatal stress has also been linked to fetal programming of metabolic syndrome. In-utero stress causes a predisposition to disease that is manifested only if additional stress, such as obesity or a high-fat diet (HFD), occurs later in postnatal life. This is exemplified by the increasing incidence of diabetes in low-income and middle-income countries, where the combination of poor nutrition in utero and overnutrition in later life is common.[89] Effects of in-utero stress differ according to the timing of occurrence during pregnancy, and the differences can be explained by the cellular events that occur during those periods of pregnancy. However, glucose intolerance is independent of the timing of stress occurrence. Stress in early gestation leads to a greater risk of an abnormal atherogenic lipid profile, obesity in women, and coronary artery disease. Stress in the second trimester of pregnancy, during which the numbers of nephrons increase rapidly, is associated with increased risk for microalbuminuria. Finally, stress during the third trimester of pregnancy, when fat deposition occurs, has a relatively higher effect in reducing birth weight. Additional sensitivity periods include the preconception and early postnatal periods.[89,90]

The influence of maternal prenatal stress on the immune system development of offspring has also been described. The hypothesis is that the impact of maternal prenatal stress and anxiety on the fetal immune system alters the maternal HPA axis, ultimately altering the function of the child's HPA axis, with a higher set point or greater reactivity of the infant HPA axis predicting a suppressed immune response. Another hypothesis is that immunological changes in the mother associated with maternal prenatal stress and anxiety, such as proinflammatory cytokines, could cross the placenta and/or alter placental function, consequently exposing the fetus to an elevated immune response early in development.[91]

Numerous studies in animals and humans have demonstrated that synthetic glucocorticoid administration can also promote HPA hyperactivity.[92] Synthetic glucocorticoids are poorly catabolized by placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) and

readily pass to the fetus.[93] Fetal glucocorticoid exposure alters the expression of glucocorticoid receptors and impacts every level of the HPA axis. Synthetic glucocorticoids are often administered to women who are at risk for preterm delivery to enhance fetal lung maturation and reduce morbidity and mortality at a point in gestation when endogenous fetal cortisol levels would normally be quite low. Due to recent clinical observations and animal studies of this practice, international experts have voiced concerns. Despite these concerns, administering repeated doses of antenatal corticosteroids to pregnant patients continues to be common clinical practice.[83]

Because regulation of energy and food intake under stress is important for survival, it is not surprising that the HPA axis drives appropriate stress responses but is also tightly intertwined with the regulation of appetite.[94] The early life environment has a critical role in programming the circuitry that later integrates stress and feeding behavior. A hyperactive HPA axis, programmed because of a stressful early life environment, can lead to excess glucocorticoids and an exacerbation of their typical appetite-stimulatory effects. Glucocorticoid interactions with feeding-related hormones, such as leptin and insulin, are also affected.[95] In addition, the early life environment has specific influences on brain development, such as ensuring appropriate connectivity between the various parts of the hypothalamus necessary for regulating feeding. Stress and the early life nutrition environment can acutely affect this brain development, leading to abnormal feeding behavior long term.[96]

History and Epidemiology of Fetal Origins of Disease

Hypothesis

Early nutrition programming is the concept that nutrition experiences in early life can program an individual's metabolism and development and influence later health outcomes. In a landmark study in 1962, McCance observed that the size of a weanling rat could be altered to vary inversely with the number of littermates suckled by the dam.[97] Further experimental

study in both rats and pigs illustrated that the earlier in life the animal was exposed to undernutrition, the more permanent the effects on adult size, despite attempts to obtain catch-up growth.[98] Competition among fetuses for intrauterine food supply or littermates for milk may lead to periods of undernutrition during critical periods of development. The fetus or neonate adapts by slowing the rate of cell division in certain organs in such a way that it permanently changes or programs metabolism and growth potential. The influence of nutrition during pregnancy and early postnatal life has an impact on later health outcomes.

Barker and colleagues proposed the "developmental or fetal origins of adult disease" in humans in 1986.[99] The hypothesis was based on observations that the highest rates of CHD in a geographical region of England were associated with increased infant mortality in the same population decades earlier. Further epidemiological evidence was provided by 2 large studies of males from Hertfordshire and Sheffield, England, that demonstrated a strong correlation between the variables LBW, low weight for length at 1 year of age, and small head circumference and death from CHD.[100,101] Interestingly, the relationship between LBW and CHD was related to slow fetal/infant growth rather than prematurity.

Cohort studies in various countries have confirmed the association between reduced birth size and CHD risk factors, including obesity, hypertension, hyperlipidemia, and non-insulin-dependent diabetes (NIDDM).[102–108] A systematic review of 80 studies found that there was a 2-mm Hg decrease in systolic blood pressure per kilogram increase in birth weight.[106] A review of 48 papers examining the relationship between birth weight and later glucose and insulin metabolism demonstrated that LBW was correlated with adverse glucose and insulin metabolism, possibly related to insulin resistance.[107] Fetal overnutrition in infants of diabetic mothers may also cause an increased risk of glucose intolerance and NIDDM in later life.[109]

A study in Pima Indians demonstrated a U-shaped relationship between birth weight and prevalence of NIDDM with high birth weight explained by the presence of gestational diabetes.[110] A recent meta-analysis suggested that birth weight was associated with the risk of T2DM and CVD in a J-shaped manner, more pronounced among females.[111] The epidemiological

evidence is substantial that events occurring during intrauterine life may have profound implications for future health.[112,113]

Expansion to Postnatal Growth Period

Although nutrition effects during fetal development are important determinants of susceptibility to later health effects, postnatal events modify the influence of prenatal growth. In evaluations of the fetal origins of disease hypothesis, it has been recognized that adjusting for early weight gain and current body size is important. Numerous epidemiological studies indicate that the highest risk for cardiovascular disease and associated disorders occurs in adults who were small at birth and had overweight or obesity during childhood or adulthood.[102,114–117]

The "thrifty phenotype" hypothesis proposed by Hales and Barker postulates that the fetus selectively distributes nutrients to certain organs during periods of undernutrition, leading to permanent metabolic changes that bolster the chances of survival during periods of limited postnatal nutrition.[118] If adequate food becomes available postnatally, the prenatal metabolic adaptations to undernutrition could then be detrimental, and obesity and related metabolic disorders may develop.[119]

Lucas proposed the term *programming* to explain the mechanism whereby an early stimulus or insult occurring at a critical or sensitive period would result in a permanent or long-term change.[120] Recent evidence suggests that rapid weight gain during infancy may be associated with an increased incidence of childhood or adult obesity and cardiovascular risk factors.[121] Most of the studies show consistent associations between LBW and rapid weight gain in infancy with increased CHD risk. Conversely, an observational study from Helsinki demonstrated that slow weight gain during infancy followed by rapid weight gain after 1 year of age increased the risk of CHD, irrespective of birth size.[115] A systematic review of 15 studies examining the role of rapid growth in infancy and childhood on the prevalence of obesity later in life found 13 publications that validated this association.[122] Another review that evaluated both size at birth and rate of growth in infancy concluded that infants who are at the highest end of the distribution for weight or who grew rapidly during infancy are at increased

risk of subsequent obesity.[123] A recent systematic review of 17 studies concluded that rapid weight gain in infancy was a predictor of adiposity later in life.[124] Although controversy exists as to the specific periods of infancy and childhood that predict later adiposity, several observational studies have indicated that weight gain in the first half of infancy may be a critical period.[125–128] In formula-fed infants for whom repeated measures of infant weight gain were available, Stettler and colleagues showed that rapid weight gain in the first week of life was associated with overweight risk in adulthood.[129]

Several reviews have demonstrated that human milk feeding may reduce the risk of later obesity, but the literature is controversial.[130,131] They suggest that the benefits of human milk are due to slower growth in breastfed infants compared to formula-fed infants. The differences in growth rates between infants fed human milk and formula-fed infants are greatest in the first few weeks of life, a critical period for the programming of obesity.[129] In a recent meta-analysis, formula-fed infants were found to consume a substantially higher volume of milk of greater energy density and protein content in early life, which, as shown previously, could potentially program a greater risk of long-term obesity.[132]

Observational studies support the hypothesis that early postnatal nutrition plays an important role in the development of obesity and related cardiovascular risk factors, but limited experimental evidence exists on the effects of early nutrition programming in term infants. In a recent study, SGA term infants randomly assigned to a nutrient-enriched formula at birth had higher diastolic blood pressure at ages 6 to 8 years, and the diastolic blood pressure was greater in children who had more rapid weight gain from birth to 9 months.[133] Support for the growth acceleration hypothesis in term infants was demonstrated in a study that utilized multiple growth measurements from birth to 5 years related to blood pressure.[134] Rapid increases in weight in the first 6 months of life predicted elevated diastolic blood pressure in adults, independent of fetal growth.[134] LBW and rapid postnatal growth are associated with later elevated blood pressure, indicating the importance of both prenatal and postnatal factors in the programming of later health effects. Improved maternal nutrition and

prevention of rapid percentile-crossing weight gain in infants could have a substantial impact on the development of adult chronic diseases.[135]

Integration of Prenatal and Postnatal Programming Effects

Epidemiological and prospective data support the concept that events occurring in early life are associated with later risks of obesity, cardiovascular disease, diabetes, and metabolic syndrome. Gluckman and colleagues use the term *developmental plasticity* (defined as the ability of an organism to develop in various ways, depending on the environment or setting) to help provide a framework for the observations on the impact of early growth on later health. [1]

The first models to explain the developmental origins of health and disease (DOHaD) idea were the thrifty phenotype hypothesis and the "fetal salvage" hypothesis, which proposes that a fetus adapts to survive in a deprived intrauterine environment.[118,136] These hypotheses were later expanded to include the postnatal environment, termed a *predictive adaptive response*.[137] The risk of disease is increased when the postnatal environment does not match what is predicted prenatally. In these programming or integrated responses, environmental events at critical periods can produce different phenotypes from a given genotype (plasticity). These processes may be mediated in part by epigenetic modulation of regulatory or developmental genes.[1] Epigenetics is the chemical modification of gene expression without changes in the inherited DNA code sequence. Epigenetic changes include DNA methylation, histone modifications, and alternation to noncoding RNAs. The mechanisms underlying epigenetic programming and developmental plasticity are still unclear, but the link between nutrition imbalances, epigenetic modifications, and later health outcomes is well accepted.[18,138,139]

Early Programming in Preterm Infants

The greatest body of evidence of early programming in humans comes from longitudinal studies in preterm infants. Prospective interventional studies of

preterm infants performed by Singhal et al demonstrated the importance of early nutrition for long-term health outcomes. [140] Over 900 preterm infants were randomly assigned in 2 parallel trials to receive (a) banked human milk or preterm formula or (b) standard term formula or preterm formula. The preterm infants who were fed human milk for a 4-week period had improved lipid profiles,[141] lower blood pressure,[142] lower leptin concentrations, and decreased insulin resistance[143,144] at 13 to 16 years of age compared to the infants who were fed preterm (nutrient-enriched) formula. The lipoprotein profile, C-reactive protein (a marker for the low-grade inflammatory response associated with the atherosclerotic process), and blood pressure did not differ significantly between infants randomized to standard infant formula and those fed preterm formula.[141,142] The ratio of leptin to fat mass (a marker of obesity) was significantly higher in children fed the preterm formula compared with the children who received human milk or standard term formula.[143] Fasting 32–33 split proinsulin concentration (a marker of insulin resistance) was significantly higher in children who received preterm formula, and further analysis demonstrated that weight differences (gain or loss) in the first 2 weeks of life were the only factor related to later proinsulin concentrations, irrespective of birth size.[144] These landmark studies provide the first experimental clinical evidence indicating that faster postnatal growth and a nutrient-dense diet may be risk factors for later cardiovascular disease.

Although slower growth in preterm infants may have benefits for later health outcomes, the risks of adverse consequences on cognition and bone health must be considered. Numerous studies have demonstrated that growth restriction in preterm infants is associated with long-term short-stature and cognitive deficits. Preterm infants fed standard formula compared to nutrient-enriched formula demonstrated a significant reduction in IQ and neurocognitive impairment at 7 to 8 years of age.[145] Higher bone mineralization and improved linear growth in childhood have been reported in preterm infants who were fed preterm formula versus unfortified human milk or standard formula.[146,147] Clear benefits exist for the use of specialized formulas in preterm infants relative to term formulas to support brain development and bone growth, and these benefits outweigh the later risks of cardiovascular disorders.[148]

Short-term advantages of dietary supplementation of at-risk infants have also been demonstrated in developing countries where more rapid weight gain up to 2 years of age was associated with decreased hospital admission and reduced mortality.[149] Further research is needed to determine optimal growth to achieve cognitive and bone benefits (in preterm infants) and short-term health benefits in at-risk populations while minimizing the longer-term risk of chronic disease.[150,151] Additional research is needed to assess the impact of early nutrition in term infants, but it is ethically difficult to perform clinical intervention studies.

Animal Models

Apart from the obvious ethical constraints, many factors limit the clinical investigation in humans, including small sample size, methodological difficulties, and genetic heterogeneity, as well as differences in disease and (intensive care) treatment. Therefore, animal models are an invaluable tool for studying physiological, metabolic, and cellular events related to early nutrition in both neonatal and later life under highly controlled circumstances; moreover, they are essential to the search for mechanisms involved in developmental programming. The use of animal models enables a strong level of control over confounding factors, the measurement of invasive endpoints, and the characterization of downstream events of the mother and offspring across the whole life span. Rodents (eg, mouse, rat, guinea pig) are the most used models; however, a variety of large animals (eg, sheep, pig, nonhuman primates) have also been widely used.[152]

Sex-specific differences in offspring outcomes from developmental programming are demonstrated in both rodents and large animals.[153] Therefore, male and female development could be treated by researchers as separate models in which sexual dimorphism should be considered when applying the results of developmental programming studies to designing diagnostic, preventive, and therapeutic approaches.[154]

Animal Models of Dietary Manipulation

Most animal models for investigating early nutrition programming have focused on inducing poor fetal growth resulting from maternal caloric

restriction, prenatal low-protein intake, and maternal iron deficiency during pregnancy. In recent years, there has been an increasing need for models that mimic the impact of maternal overnutrition on fetal development and long-term health. Several obesogenic animal models, mainly rodents, have shown a relatively common phenotype of metabolic disorders in offspring, but the magnitude of effects differed with the timing of the nutrition challenge and diet composition.[155] Collectively, these studies demonstrate that dietary manipulation in rodent models during pregnancy can lead to permanent alterations in postnatal physiological function and disease risk.[156]

Maternal Protein Restriction Model

One of the most widely studied rodent models is the maternal protein restriction model. In this model, striking parallels exist with the development of type 2 diabetes and/or metabolic syndrome. Rats are fed a low-protein (5%–8%) diet during pregnancy that restricts the growth of the offspring.[157] If such offspring are cross-fostered to mothers who were fed a control diet (20% protein) during lactation, they gain weight rapidly and have similar body weights to controls by weaning (21 days of age). However, this catch-up growth has a detrimental effect on longevity. Maternal protein restriction, even during lactation, has been shown to have long-term effects on the structure and function of individual organs such as the endocrine pancreas.[158]

Moreover, nutrition restriction is one of the most common experimental methods of fetal insult used to investigate the mechanisms of programmed hypertension.[156] Offspring of nutrient-restricted sheep had lower blood pressure than those fed normally, but they developed relative hypertension as they aged. A reduction of nephron number was observed when the nutrition insult coincided with the nephrogenic period.[159]

Severe food restriction during pregnancy has also been shown to induce acute IUGR in rats. In addition to suffering hypertension in adulthood, these offspring have increased fasting plasma insulin compared to controls.[160] Studies in rodent models also indicate that fetal undernutrition determines adult adiposity.[156,161] It is unclear whether the increase in central adiposity

is related to increased food intake or reduced energy expenditure, although evidence suggests that both may be involved. Rats subjected to intrauterine protein restriction exhibited increased preference for high-fat foods. Feeding energy-dense foods to rats that were undernourished in utero promoted a greater degree of obesity than noted in animals with adequate nutrition in fetal life. Appetite programming may stem from remodeling hypothalamic structures that control feeding and programming of gene expression involved in responses to orexigenic hormones.

Maternal Obesogenic Model

Early studies of dietary manipulation to induce overnutrition involved feeding dams an HFD and/or high-sugar purified diet or a "cafeteria diet." These obesogenic models were designed to mimic the dietary habits in Western society. The phenotypic outcome of the offspring exposed to a maternal obesogenic diet during development varies based on the species, diet composition, timing, and consumption length.[162]

Several studies in rodents have demonstrated that an HFD alters maternal food intake, substrate utilization, body composition, glucose and lipid metabolism, leptin levels, and placental nutrient transport.[163,164] In addition, chronic HFD feeding leads to maternal obesity, a major risk factor for adverse effects on the offspring.[165]

Maternal HFD in utero has been shown to enhance the susceptibility of the offspring to develop obesity, insulin and leptin resistance, hypertension, fatty pancreas disease, hepatic steatosis, and nonalcoholic fatty liver disease.[164] It has also been reported that maternal adiposity, and not dietary fat per se, induces hyperleptinemia and insulin resistance in offspring, as well as increased body weight that persists into adulthood.[166] Even mild maternal overnutrition has been shown to induce increased adiposity, glucose intolerance, and altered brain appetite regulators in offspring.[167]

A recent meta-analysis evaluated the evidence from animal models of the effects of maternal obesity on the offspring, concluding that it leads to increased adiposity and systolic blood pressure and is detrimental to lipid, insulin, and glucose homeostasis.[168,169] The detrimental effects of maternal HFD during pregnancy could be counteracted by diets containing

carbohydrates with slow digestion rates. Diets with slow-digesting carbohydrates have been shown to promote beneficial effects in adipose tissue and liver metabolism in the offspring, as well as in muscle metabolism.[170,171,172]

High-fat exposure in utero results in remodeling of the bone structure of the offspring in a sexually dimorphic manner and an HFD has been shown to affect bone structure and length.[173] These data provide insight into the maternal HFD effect on the skeletal structure of the offspring and how these alterations may lead to the development of future diseases such as osteoporosis. Although little is known about the effect of maternal HFD exposure on offspring behavior, it may increase anxiety behaviors in the offspring via alterations in the GABAergic and neurotrophin systems in early life.[174,175]

Sheep and nonhuman primate models are less studied than rodent models, but some evidence strongly suggests that exposure to a maternal HFD predisposes offspring to altered growth and metabolic sequelae, which closely parallels data from rodent models.[176] Interestingly, in the nonhuman primate models, many of the negative effects induced by the maternal HFD were reversible when the diet was switched postnatally or before pregnancy. In contrast, switching the diets in rodents did not completely reverse the effects.[164]

Maternal Iron Deficiency

Iron deficiency and anemia are common during pregnancy, particularly in the developing world. Maternal anemia is associated with LBW and increased rates of perinatal mortality and morbidity. In rats, maternal iron restriction causes fetal growth retardation and has been shown to affect blood pressure, glucose tolerance, and serum triglyceride in adult offspring.[177] Many studies have shown that iron deficiency during pregnancy results in long-term adverse neurodevelopment consequences for the offspring.[178] These animal studies have demonstrated that early iron deficiency affects neuronal and glial energy metabolism, monoamine metabolism, and myelination.

Animal Models Induced by Endocrine or Paracrine Mechanisms

Studies in a variety of animal models (eg, sheep, rats, mice, guinea pigs, nonhuman primates) have shown that early life exposure to glucocorticoids may lead to adverse metabolic effects.[83] Prenatal glucocorticoid excess, either from endogenous overproduction due to maternal stress or through exogenous administration to the mother or fetus, reduces birth weight, causes hypertension and hyperglycemia, and alters behavior in the offspring.[179] These effects may also be transmitted across generations without further exposure to glucocorticoids, an observation that supports an epigenetic mechanism.[92,180]

Studies on rat offspring exposed to an excess of prenatal glucocorticoids have shown that they undergo catch-up growth postnatally and normalize body weight by the time they wean.[181] Accumulating data on rodents suggest that prenatal glucocorticoid overexposure programs an adverse adult cardiovascular, metabolic, skeletal muscle, neuroendocrine, and behavioral phenotype.[182] The phenotypic outcome is similar to that of the low-protein model.[183] Fetal glucocorticoid overexposure may be a common mechanism for mediating fetal growth retardation and metabolic programming. This suggestion is based on the observation that dietary protein restriction during rat pregnancy reduces the activity of 11β-HSD2, which serves as a placental barrier to maternal glucocorticoids.[181]

Circulating glucocorticoid concentrations are tightly controlled by activation of the HPA axis, the regulation of which can be programmed by nutrient restriction. In fetal rats, nutrient restriction results in blunted diurnal patterns of adrenocorticotropic hormone at 4 weeks postnatal age, alterations in basal plasma corticosterone in adulthood, and altered basal HPA axis activity.[184]

Animal Models Induced by Surgical Manipulation

Reduction in placental blood flow and consequent restriction of oxygen, nutrient transport, and fetal growth can be produced in the rat by uterine artery ligation in late gestation, uterine and umbilical artery embolism, or carunclectomy.[181,185] In this model of IUGR, at 2 weeks of age, offspring have reduced numbers of nephrons. This nephron deficit is associated with

impaired renal function at 2 weeks despite compensatory hypertrophy of the remaining nephrons. In female offspring, after uterine artery ligation, growth restriction is associated with increased fasting blood glucose levels, impaired glucose tolerance, and lower insulin secretion during a glucose tolerance test.[181] Thompson et al showed that epigenetic dysregulation occurred in fetuses with IUGR near genes regulating abnormal IUGR islet processes, such as vascularization, β-cell proliferation, insulin secretion, and cell death.[186]

Litter Size Model

Litter size in rodents influences early growth and long-term metabolic health, partly due to nutrient availability during lactation. This suggests that litter size is a strong independent determinant of both early growth rate and long-term metabolic health.

The litter-size reduction model is used to mimic early overfeeding as a tool to evaluate the impact of early postnatal overnutrition on the development of metabolic diseases. In this model, based on a reduction of litter size (2–4 per female), offspring/pups have increased volume and caloric intake during the lactation period, resulting in early obesity. Subsequent adaptive responses (involving the endocrine system and energy metabolism) lead to hyperphagia, insulin resistance, energy expenditure, and reproductive changes in offspring raised in small litters, contributing to obesity and metabolic disorders later in life.[187]

Recent studies suggest that litter size reduction causes hyperphagia in the offspring by inducing long-term alterations in the gut–brain-axis.[188] The litter sizes model generates an environment for the offspring that can affect metabolism later in life as well as behavioral responses. The environment generated by litter size influences behavior, anxiety, and response to stress.[189] Large litters induce the opposite effects, with rodents showing slower growth rates during lactation. Rodents raised in larger litters have lower body weight and are leaner.[190] In general, evidence supports litter size as a determinant for early growth rate and programming of adult metabolism.

Third-Generation and Future-Generation Effects

Adverse events during pregnancy can affect the offspring as well as subsequent generations, regardless of whether they are exposed (multigenerational exposure) or unexposed (intergenerational or transgenerational inheritance) to the adverse effects, thus perpetuating the problem.[191–193] In a UK study examining the relationship of adult blood pressure to maternal fetal growth and size at birth, the mother's reduced fetal growth was associated with increased blood pressure of the offspring in adulthood.[194] The researchers concluded that restricted growth of a female fetus causes physiology and metabolism changes to occur that lead to elevated blood pressure in the next generation. This suggests that malnourishment of females during their fetal development affects their progeny's health.

The Dutch famine, which occurred toward the end of World War II (1944–1945), provides a unique opportunity to study the effects of severe undernutrition during pregnancy on the health of future generations.[195] Studies indicated that adults born during the Dutch famine whose mothers had inadequate nutrition during the first 2 trimesters of pregnancy were more likely to have obesity and abnormal lipid profiles than adults whose mothers had poor nutrition during the third trimester.[196] Infants born to mothers who were malnourished during the third trimester were leaner but had impaired glucose tolerance. In addition, individuals who had normal birth weights, and whose mothers were severely malnourished, had smaller babies in the next generation.[196]

One explanation for the intergenerational effects on birth weight is that the hormonal environment of the uterus of the undernourished mother may affect the developing germ cells that will form in the next generation.[197] Another study has reported that grandchildren of the women who were pregnant during the famine had increased neonatal adiposity and poor health later in life.[198] These data indicate that maternal undernutrition during gestation may have effects on the offspring's later health that are transmitted to subsequent generations. A possibly similar transgenerational transmission of longevity propensity has been identified for males in

epidemiologic studies of food supply during early spermatogenesis.[199] A recent study indicated that fluctuations in food availability during grandparents' early life impacted their granddaughter's cardiovascular mortality, supporting the belief that transmission occurs through the paternal line.[200]

Although the mechanisms behind these relationships are not clear, epigenetic dysregulation of the IGF-2 gene has been proposed. IGF-2 is a key factor in human development and growth and is maternally imprinted. Individuals who were prenatally exposed to malnutrition during the Dutch famine had less DNA methylation of the IGF-2 gene compared with their unexposed same-sex siblings 6 decades later.[201] Interestingly, a recent epidemiological study observed a similar degree of IGF-2 hypomethylation in newborns of fathers with obesity, suggesting that, besides in-utero exposures to nutrition or environmental factors, paternal malnutrition has a heritable influence on IGF-2 and may therefore impact subsequent generations.[202] These data support the hypothesis that environmental conditions early in life cause epigenetic changes in humans that persist throughout life.[139]

Implications for Future Health

In recent years, the influence of dietary inadequacy or imbalance and other stressors on morphological and functional changes during pregnancy and early infancy, and the resulting consequences in adulthood, has become a rapidly growing research area. We are beginning to understand the molecular determinants of these changes and the dietary and environmental factors controlling them. Both overnutrition and undernutrition in utero and early life can increase risks for adverse metabolic outcomes, including type 2 diabetes, cardiovascular disease, and obesity. The seriousness of these events is amplified by evidence that certain potentially adverse epigenetic effects induced in the female fetus may persist through at least an additional generation.

Current agricultural production and food distribution and changes in diet and activity patterns are associated with a historically high prevalence of obesity, diabetes, and their associated complications. Given the current

obesity rates and genetic predisposition, almost one-third of today's children are destined to become diabetic. In developed countries, a number of these individuals represent second or third generations of families expressing this phenotype, and many come from environments with a history of food and micronutrient scarcity. In various parts of the world, these contrasting nutrition states coexist contemporaneously.

The current phenomenon of the "thin, fat Indian" has given India the distinction of having the world's highest rate of diabetes, despite a lower ranking for obesity. Based on the emerging DOHaD literature and the investigation of epigenetics, the consequences of dietary scarcity and surfeit (and their coexistence) will cause adverse effects in future generations unless fresh insights are discovered to break this cycle. An inability to meet potentially major population increases in health care costs linked to morbidity patterns associated with DOHaD-related conditions could itself become a driver of morbidity and mortality, as well as a possible source of economic and political instability. It is already estimated that children in the United States today will not live longer lives than their parents, which will be the first time in generations.

Recent evidence also suggests that severe maternal stress during pregnancy may impact the developing fetus, causing increased susceptibility to childhood and adult obesity along with alterations in metabolic function. Reduced glucocorticoid output in response to stress in pregnancy may have important consequences for conserving energy supply to the fetus or fetuses, modulating immune system adaptations, and protecting against adverse fetal programming by glucocorticoids.

Understanding the mechanisms underpinning this pregnancy adaptation may provide insights for manipulating HPA axis responsiveness in later life, particularly in the context of resetting HPA axis hyperactivity associated with prenatal stress exposure, which may underlie several major pathologies, including metabolic, cognitive, and mood disorders.[203] Therefore, to prevent common complex health disorders, women of reproductive age should focus on their well-being prior to conception and during gestation to more effectively address health-related and disease-risk–related issues in their offspring.[204]

Implications for Current Practice

What implications can be drawn from current knowledge in this area for nutrition advice in the practice of obstetrics, pediatrics, neonatology, and public health? Given that preconceptual nutrition status is at least as important as nutrition status during pregnancy, planned pregnancy and good nutrition status is a highly desirable starting point. This requires approaches to maximize the nutrition status of fertile women of childbearing age beyond an exclusive focus on pregnancy and lactation, especially if pregnancies are likely to be unplanned. During pregnancy, adequate energy, protein, and micronutrients (including methyl donors) have a salutary effect on developmental outcomes related to fetal nutrition status. Some evidence indicates that excesses of fat and protein during pregnancy are to be avoided, and long-chain n-3 fatty acids, especially docosahexaneoic acid, may have beneficial impacts on mental, visual, and behavioral development. Monitoring fetal growth, maternal weight gain, and maternal blood sugar can detect deviations from expected developmental patterns.

Lactation is also one of the most nutritionally demanding times in a woman's life because of the increased need for almost all nutrients, and nutrition status is important to the nutrition the infant receives via human milk. Consequently, maintaining and optimizing the nutrition status of lactating women may have a considerable impact on promoting optimal infant growth and development.

For term infants, it is desirable to maintain a relative growth trajectory (percentile) similar to that experienced in utero. Traditionally, "normalizing" the growth of infants with in-utero growth retardation has been accepted as the de facto goal of good nutrition. Based on more recent findings, these children may be metabolically more suited to a slower growth rate. Percentile-crossing during infancy and later can increase the risk of DOHaD-associated conditions.

In the first 2 weeks of life and after about 4 months of age, breastfeeding may lead to less weight gain than formula feeding and is particularly beneficial in this population. Brain development support for these infants is an important concern, but most of the data regarding the importance of early nutrition for brain development are from studies of preterm infants. It remains unknown whether nutritional supplementation and growth

acceleration are beneficial for brain development of term infants with delayed growth. For infants in underdeveloped countries who experience extrauterine growth retardation later in infancy and early childhood, short-term nutritional supplementation has been found to reduce acute morbidity and mortality (as well as malnutrition progression).

Preterm infants, especially those with extremely low birth weight (ELBW), are at high risk of extrauterine growth restriction. Given their immature development and body composition, their nutrition requirements exceed those of term infants. In infants with ELBW, developmental achievement and reduced neurological complications are associated with higher growth rates. Preterm infants are very responsive to nutrition supplementation while in the hospital and following discharge.

Data from Singhal and Lucas indicated that preterm infants had higher blood pressure, leptin, blood lipids, and split proinsulin values when they were fed preterm formula compared to term formula or human milk, therefore, rapid growth should not be encouraged in this population.[140] These markers of cardiovascular risk, however, were not elevated above those for typical term infants. The same investigators found developmental disadvantages in these infants (at least through childhood) from receiving standard term formula versus more nutrient-rich preterm formula. Interestingly, while preterm infants who were fed preterm formula grew faster than breastfed infants, their neurodevelopmental status was not better. Bone mineralization is improved in preterm infants given mineral-rich preterm and postdischarge formulas compared to standard term formulas. However, this may not persist into adulthood.[205]

Human milk with human milk fortifier is currently recommended for small preterm infants because it can preserve the beneficial nutrition and immunological effects of human milk while providing additional energy, protein, minerals, and other micronutrients. Preterm formula (vs term formula) is recommended for formula-fed preterm infants. However, there is no evidence indicating that postdischarge formulas improve developmental outcomes more than standard term formulas after hospital discharge. Nevertheless, in the smallest infants, postdischarge formulas have been observed to enhance head growth. Data from Ehrenkranz et al regarding the positive developmental outcome of encouraging early growth

in preterm infants advise against any go-slow approach for these infants to possibly reduce markers of future cardiovascular risk (to values below those observed in healthy term infants).[206]

Future Research Needs

Nutrition and early development present a rich area for potential investigation at all levels of biological research. At the molecular level, we need specific descriptions of the changes underlying the DOHaD phenomenon in various organs and the mechanisms (including nutritional influences) controlling these molecular changes. In physiology, opportunities remain to explore the developmental impact of organ-specific effects of general and nutrient-specific undernutrition and overnutrition at various stages of fetal and infant development.[207]

Epidemiologists, who initiated this field of research, can explain more about the similarities and differences of effects of various stressors (eg, gestational malnutrition vs diabetes) on the expression of DOHaD-related morbidity. More research is needed to elucidate the relationship between intrauterine and postnatal effects (and their interaction). Clinical investigators can prospectively study the developmental impact of growth acceleration in various populations and age groups of infants and young children, reviewing infection and immune outcomes, cardiovascular and metabolic risk factors, bone health, and neurodevelopment. There may be benefits in catch-up growth for certain populations and during specific timeframes. Exploring very early or later drug or hormonal interventions has great potential to reverse the underlying molecular basis of some DOHaD-associated conditions.

Using a multilevel approach, more research on the effects of intrauterine stress exposure on metabolic function and obesity risk of offspring is needed to develop specific diagnostic and primary or secondary intervention strategies.[204] Novel biomarkers of in-utero stress need to be identified, and advanced high-throughput technology is required to discern the cellular mechanisms that are altered by in-utero stress.[89] Future work should consider more potentially relevant variables including timing and the nature of prenatal exposure, delivery method, birth weight, sex, genetic

vulnerabilities of mother/offspring, testing age, and nature of the postnatal care. The underlying mechanisms, such as the epigenetic changes in relevant genes, should also be considered. Preliminary human evidence shows that methylation levels of genes involved in glucocorticoid action are altered by the early life environment. Further detailed longitudinal studies are needed to confirm whether such changes are identifiable at birth and hence may be useful biomarkers of risk.[179]

The preimplantation period is particularly sensitive to stress, and artificial reproductive technology constitutes a potential new form of preimplantation stress. Additional follow-up studies on children conceived by artificial reproductive technology are needed.[208] Finally, strategies, such as the use of specific nutrients or hormones, to counteract the effect of in-utero stress are needed. Such research could be particularly important for populations in developing countries.[89]

Test Your Knowledge Questions

1. Which of the following is the dominant fuel source for a healthy fetus?
   A. Fatty acids because they are the richest source of energy
   B. Amino acids because they promote rapid growth
   C. Galactose because the fetus cannot use glucose
   D. Glucose transported from the maternal circulation
2. Which of the following describes the nutrition programming process?
   A. It is specific to the fetus
   B. It occurs only in animals
   C. It occurs early in life and may extend beyond a single generation
   D. It is a transient response to nutrient availability
3. Which of the following is attributed to upward growth-percentile crossing in infancy and early childhood?
   A. Reduces short-term infectious mortality and leads to lower adult blood pressure
   B. Has been associated with an increased risk for the development of features of the metabolic syndrome
   C. Helps prevent subsequent rebound obesity
   D. Improves glucose control later in life

References

1. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med*. 2008;359(1):61–73. https://doi.org/10.1056/nejmra0708473
2. Hay WW, Jr. Placental-fetal glucose exchange and fetal glucose metabolism. *Trans Am Clin Climatol Assoc*. 2006;117:321–339.
3. Sparks JW, Hay WW, Jr., Bonds D, Meschia G, Battaglia FC. Simultaneous measurements of lactate turnover rate and umbilical lactate uptake in the fetal lamb. *J Clin Invest*. 1982;70(1):179–192. https://doi.org/10.1172/jci110591
4. Hay WW, Jr. Recent observations on the regulation of fetal metabolism by glucose. *J Physiol*. 2006;572(Pt 1):17–24. https://doi.org/10.1113/jphysiol.2006.105072
5. Grillo MA, Lanza A, Colombatto S. Transport of amino acids through the placenta and their role. *Amino Acids*. 2008;34(4):517–523. https://doi.org/10.1007/s00726-007-0006-5
6. Battaglia FC. In vivo characteristics of placental amino acid transport and metabolism in ovine pregnancy—a review. *Placenta*. 2002;23(suppl A):S3–S8. https://doi.org/10.1053/plac.2002.0812
7. Jansson N, Rosario FJ, Gaccioli F, et al. Activation of placental mTOR signaling and amino acid transporters in obese women giving birth to large babies. *J Clin Endocrinol Metab*. 2013;98(1):105–113. https://doi.org/10.1210/jc.2012-2667
8. Battaglia FC. Clinical studies linking fetal velocimetry, blood flow and placental transport in pregnancies complicated by intrauterine growth retardation (IUGR). *Trans Am Clin Climatol Assoc*. 2003;114:305–313. https://pubmed.ncbitrails.nlm.nih.gov/12813927/
9. Myers RE, Hill DE, Holt AB, Scott RE, Mellits ED, Cheek DB. Fetal growth retardation produced by experimental placental insufficiency in the rhesus monkey. I. Body weight, organ size. *Biol Neonate*. 1971;18(5):379–394. https://doi.org/10.1159/000240380
10. Bloomfield FH, Spiroski AM, Harding JE. Fetal growth factors and fetal nutrition. *Semin Fetal Neonatal Med*. 2013;18(3):118–123. https://doi.org/10.1016/j.siny.2013.03.003

11. Wu G, Imhoff-Kunsch B, Girard AW. Biological mechanisms for nutritional regulation of maternal health and fetal development. *Paediatr Perinat Epidemiol*. 2012;26(suppl):14–26. https://doi.org/10.1111/j.1365-3016.2012.01291.x
12. de Onis M, Villar J, Gulmezoglu M. Nutritional interventions to prevent intrauterine growth retardation: evidence from randomized controlled trials. *Eur J Clin Nutr*. 1998;52(suppl 1):S83–93.
13. Shiell AW, Campbell DM, Hall MH, Barker DJ. Diet in late pregnancy and glucose-insulin metabolism of the offspring 40 years later. *BJOG*. 2000;107(7):890–895. https://doi.org/10.1111/j.1471-0528.2000.tb11088.x
14. Burdge GC, Lillycrop KA. Nutrition, epigenetics, and developmental plasticity: Implications for understanding human disease. *Annu Rev Nutr*. 2010;30(1):315–339. https://doi.org/10.1146/annurev.nutr.012809.104751
15. McMillen IC, MacLaughlin SM, Muhlhausler BS, Gentili S, Duffield JL, Morrison JL. Developmental origins of adult health and disease: the role of periconceptional and fetal nutrition. *Basic Clin Pharmacol Toxicol*. 2008;102(2):82–89. https://doi.org/10.1111/j.1742-7843.2007.00188.x
16. Georgieff MK. The role of iron in neurodevelopment: fetal iron deficiency and the developing hippocampus. *Biochem Soc Trans*. 2008;36(Pt 6):1267–1271. https://doi.org/10.1042/BST0361267
17. Scholl TO. Maternal nutrition before and during pregnancy. *Nestle Nutr Workshop Ser Pediatr Program*. 2008;6179-89. https://doi.org/10.1159/000113172
18. Martin-Gronert MS, Ozanne SE. Maternal nutrition during pregnancy and health of the offspring. *Biochem Soc Trans*. 2006;34(Pt 5):779–782. https://doi.org/10.1042/bst0340779
19. Young MF, Ramakrishnan U. Maternal undernutrition before and during pregnancy and offspring health and development. *Ann of Nutr and Metab*. 2020;76(suppl 3):41–53. https://doi.org/10.1159/000510595
20. Morton SMB. Maternal nutrition and fetal growth and development. In: Gluckman PD, Hanson MA, ed. *Developmental Origins of Health and Disease*. Cambridge University Press; 2006: 98–129.

21. Lakshmy R. Metabolic syndrome: role of maternal undernutrition and fetal programming. *Rev Endocr Metab Disord*. 2013;14(3):229–240. https://doi.org/10.1007/s11154-013-9266-4
22. Lanham SA, Roberts C, Cooper C, Oreffo RO. Intrauterine programming of bone. Part 1: alteration of the osteogenic environment. *Osteoporos Int*. 2008;19(2):147–156. https://doi.org/10.1007/s00198-007-0443-8
23. Lanham SA, Roberts C, Perry MJ, Cooper C, Oreffo RO. Intrauterine programming of bone. Part 2: alteration of skeletal structure. *Osteoporos Int*. 2008;19(2):157–167. https://doi.org/10.1007/s00198-007-0448-3
24. Imdad A, Bhutta ZA. Maternal nutrition and birth outcomes: effect of balanced protein-energy supplementation. *Paediatr Perinat Epidemiol*. 2012;26(suppl 1):178–190. https://doi.org/10.1111/j.1365-3016.2012.01308.x
25. Ota E, Hori H, Mori R, Tobe-Gai R, Farrar D. Antenatal dietary education and supplementation to increase energy and protein intake. *Cochrane Database Syst Rev*. 2015(6):Cd000032. https://doi.org/10.1002/14651858.cd000032.pub3
26. Olausson H, Goldberg GR, Laskey MA, Schoenmakers I, Jarjou LM, Prentice A. Calcium economy in human pregnancy and lactation. *Nutr Res Rev*. 2012;25(1):40–67. https://doi.org/10.1017/s0954422411000187
27. Hacker AN, Fung EB, King JC. Role of calcium during pregnancy: maternal and fetal needs. *Nutr Rev*. 2012;70(7):397–409. https://doi.org/10.1111/j.1753-4887.2012.00491.x
28. Buppasiri P, Lumbiganon P, Thinkhamrop J, Ngamjarus C, Laopaiboon M. Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes. *Cochrane Database Syst Rev*. 2011(10):CD007079. https://doi.org/10.1002/14651858.cd007079.pub2
29. Hofmeyr JG, Lawrie TA, Atallah ÁN, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database Syst Rev*. 2018(10):CD001059. https://doi.org/10.1002/14651858.cd001059.pub5

30. World Health Organization. Guideline: daily iron and folic acid supplementation in pregnant women. World Health Organization; 2012.
31. Rao R, Georgieff MK. Iron in fetal and neonatal nutrition. *Semin Fetal Neonatal Med*. 2007;12(1):54–63. https://doi.org/10.1016/j.siny.2006.10.007
32. Georgieff MK. Iron deficiency in pregnancy. *Am J of Obstet & Gynecol*. 2020;223(4):516–524. https://doi.org/10.1016/j.ajog.2020.03.006
33. Bath SC, Steer CD, Golding J, Emmett P, Rayman MP. Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). *Lancet*. 2013;382(9889):331–337. https://doi.org/10.1016/s0140-6736(13)60436-5
34. Bath SC. The effect of iodine deficiency during pregnancy on child development. *Proc Nutr Soc*. 2019;78(2):150–160. https://doi.org/10.1017/s0029665118002835
35. O'Donnell KJ, Rakeman MA, Zhi-Hong D, et al. Effects of iodine supplementation during pregnancy on child growth and development at school age. *Dev Med Child Neurol*. 2002;44(2):76–81. https://doi.org/10.1017/s0012162201001712
36. Yajnik CS, Deshmukh US. Maternal nutrition, intrauterine programming and consequential risks in the offspring. *Rev Endocr Metab Disord*. 2008;9(3):203–211. https://doi.org/10.1007/s11154-008-9087-z
37. Vandevijvere S, Amsalkhir S, Van Oyen H, Moreno-Reyes R. High prevalence of vitamin D deficiency in pregnant women: a national cross-sectional survey. *PLoS One*. 2012;7(8):e43868. https://doi.org/10.1371/journal.pone.0043868
38. Berti C, Biesalski HK, Gartner R *et al.* Micronutrients in pregnancy: current knowledge and unresolved questions. *Clin Nutr*. 2011;30(6):689–701. https://doi.org/10.1016/j.clnu.2011.08.004
39. Liu Y, Ding C, Xu R *et al.* Effects of vitamin D supplementation during pregnancy on offspring health at birth: A meta-analysis of randomized controlled trails. *Clinical Nutrition*. 2022;41(7):1532–1540. https://doi.org/10.1016/j.clnu.2022.05.011

40. Fowden AL, Ward JW, Forhead A. Control of fetal metabolism: relevance to developmental origins of health and disease. In: Gluckman PD, Hanson MA, ed. *Developmental Origins of Health and Disease*. Cambridge University Press; 2006: 143–158.
41. Keats EC, Haider BA, Tam E, Bhutta ZA. Multiple-micronutrient supplementation for women during pregnancy. *Cochrane Database Syst Rev*. 2019(3). https://doi.org/10.1002/14651858.cd004905.pub6
42. Neville MC. Anatomy and physiology of lactation. *Pediatr Clin North Am*. 2001;48(1):13–34. https://doi.org/10.1016/s0031-3955(05)70283-2
43. Riordan J, Wambach K. *Breastfeeding and Human Lactation*. 4th ed. Jones and Bartlett Publishers; 2010.
44. Hannan FM, Elajnaf T, Vandenberg LN, Kennedy SH, Thakker RV. Hormonal regulation of mammary gland development and lactation. *Nat Rev Endocrinol*. 2023;19:46–61 https://doi.org/10.1038/s41574-022-00742-y
45. Picciano MF. Nutrient composition of human milk. *Pediatr Clin North Am*. 2001;48(1):53–67. https://doi.org/10.1016/s0031-3955(05)70285-6
46. Durham HA, Lovelady CA, Brouwer RJ, Krause KM, Ostbye T. Comparison of dietary intake of overweight postpartum mothers practicing breastfeeding or formula feeding. *J Am Diet Assoc*. 2011;111(1):67–74. https://doi.org/10.1016/j.jada.2010.10.001
47. Lovelady CA, Stephenson KG, Kuppler KM, Williams JP. The effects of dieting on food and nutrient intake of lactating women. *J Am Diet Assoc*. 2006;106(6):908–912. https://doi.org/10.1016/j.jada.2006.03.007
48. Pratt NS, Sherry CL. Lactating women consume less than the recommendations for many nutrients (810.1). *FASEB J*. 2014;28:810.1. https://doi.org/10.1096/fasebj.28.1_supplement.810.1
49. Wang D, Thielecke F, Fleith M, et al. Analysis of dietary patterns and nutritional adequacy in lactating women: a multicentre European cohort (ATLAS study). *J Nutr Sci*. 2021;10:e17. https://doi.org/10.1017/jns.2021.7
50. Allen LH. B vitamins in breast milk: relative importance of maternal status and intake, and effects on infant status and function. *Adv Nutr*.

2012;3(3):362–369. https://doi.org/10.3945/an.111.001172
51. Deodhar AD, Rajalakshmi R, Ramakrishnan CV. Studies on human lactation. IV. Lactic and malic dehydrogenases and xanthine oxidase in breast milk and their variation with the progress of lactation and dietary vitamin supplementation. *Acta Paediatr*. 1964;53:101–104. https://doi.org/10.1111/j.1651-2227.1963.tb03806.x
52. Prentice AM, Roberts SB, Prentice A, et al. Dietary supplementation of lactating Gambian women. I. Effect on breast-milk volume and quality. *Hum Nutr Clin Nutr*. 1983;37(1):53–64.
53. Kodentsova VM, Vrzhesinskaya OA. Evaluation of the vitamin status in nursing women by vitamin content in breast milk. *Bull Exp Biol Med*. 2006;141(3):323–327. https://doi.org/10.1007/s10517-006-0161-9
54. Thomas MR, Sneed SM, Wei C, Nail PA, Wilson M, Sprinkle EE, 3rd. The effects of vitamin C, vitamin B6, vitamin B12, folic acid, riboflavin, and thiamin on the breast milk and maternal status of well-nourished women at 6 months postpartum. *Am J Clin Nutr*. 1980;33(10):2151–2156. https://doi.org/10.1093/ajcn/33.10.2151
55. Kang-Yoon SA, Kirksey A, Giacoia G, West K. Vitamin B-6 status of breast-fed neonates: influence of pyridoxine supplementation on mothers and neonates. *Am J Clin Nutr*. 1992;56(3):548–558. https://doi.org/10.1093/ajcn/56.3.548
56. Chang SJ, Kirksey A. Pyridoxine supplementation of lactating mothers: relation to maternal nutrition status and vitamin B-6 concentrations in milk. *Am J Clin Nutr*. 1990;51(5):826–831. https://doi.org/10.1093/ajcn/51.5.826
57. Hamaker BR, Kirksey A, Borschel MW. Distribution of B-6 vitamers in human milk during a 24-h period after oral supplementation with different amounts of pyridoxine. *Am J Clin Nutr*. 1990;51(6):1062–1066. https://doi.org/10.1093/ajcn/51.6.1062
58. Duggan C, Srinivasan K, Thomas T, et al. Vitamin B-12 supplementation during pregnancy and early lactation increases maternal, breast milk, and infant measures of vitamin B-12 status. *J Nutr*. 2014;144(5):758–764. https://doi.org/10.3945/jn.113.187278
59. Dror DK, Allen LH. Vitamin B-12 in human milk: a systematic review. *Adv Nutr*. 2018;9(suppl 1):358s-366s.

https://doi.org/10.1093/advances/nmx019
60. Fischer LM, da Costa KA, Galanko J, et al. Choline intake and genetic polymorphisms influence choline metabolite concentrations in human breast milk and plasma. *Am J Clin Nutr*. 2010;92(2):336–346. https://doi.org/10.3945/ajcn.2010.29459
61. Institute of Medicine. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. National Academies Press; 2001. https://doi.org/10.17226/10026
62. Stoltzfus RJ, Underwood BA. Breast-milk vitamin A as an indicator of the vitamin A status of women and infants. *Bull World Health Organ*. 1995;73(5):703–711.
63. Oliveira JM, Allert R, East CE. Vitamin A supplementation for postpartum women. *Cochrane Database Syst Rev*. 2016;3(3):CD005944. https://doi.org/10.1002/14651858.CD005944.pub3
64. Hollis BW, Wagner CL. Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. *Am J Clin Nutr*. 2004;80(6 Suppl):1752S-1758S. https://doi.org/10.1093/ajcn/80.6.1752s
65. Wagner CL, Hulsey TC, Fanning D, Ebeling M, Hollis BW. High-dose vitamin D3 supplementation in a cohort of breastfeeding mothers and their infants: a 6-month follow-up pilot study. *Breastfeed Med*. 2006;1(2):59–70. https://doi.org/10.1089/bfm.2006.1.59
66. Kazemain E, Ansari S, Davoodi SH, et al. The effect of maternal vitamin D supplementation on vitamin D status of exclusively breastfeeding mothers and their nursing infants: a systematic review and meta-analysis of randomized clinical trials. *Adv Nutr*. 2021;13(2):568–585. https://doi.org/10.1093/advances/nmab126
67. Zimmermann MB. The impact of iodised salt or iodine supplements on iodine status during pregnancy, lactation and infancy. *Public Health Nutr*. 2007;10(12A):1584–1595. https://doi.org/10.1017/s1368980007360965
68. Charlton KE, Yeatman H, Brock E, et al. Improvement in iodine status of pregnant Australian women 3 years after introduction of a

mandatory iodine fortification programme. *Prev Med*. 2013;57(1):26–30. https://doi.org/10.1016/j.ypmed.2013.03.007
69. Kurtoglu S, Akcakus M, Kocaoglu C, et al. Iodine status remains critical in mother and infant in Central Anatolia (Kayseri) of Turkey. *Eur J Nutr*. 2004;43(5):297–303. https://doi.org/10.1007/s00394-004-0474-2
70. Dror DK, Allen LH. Iodine in human milk: a systematic review. *Adv Nutr*. 2018;9(suppl 1):347s-357s. https://doi.org/10.1093/advances/nmy020
71. Innis SM. Dietary (n-3) fatty acids and brain development. *J Nutr*. 2007;137(4):855–859. https://doi.org/10.1093/jn/137.4.855
72. Vishwanathan R, Kuchan MJ, Sen S, Johnson EJ. Lutein is the predominant carotenoid in infant brain: preterm infants have decreased concentrations of brain carotenoids. *J Pediatr Gastroenterol Nutr*. 2014;59(5):659–665. https://doi.org/10.1097/mpg.0000000000000389
73. Zimmer JP, Hammond BR, Jr. Possible influences of lutein and zeaxanthin on the developing retina. *Clin Ophthalmol*. 2007;1(1):25–35.
74. Innis SM. Impact of maternal diet on human milk composition and neurological development of infants. *Am J Clin Nutr*. 2014;99(3):734S-741S. https://doi.org/10.3945/ajcn.113.072595
75. *Dietary Guidelines for Americans, 2020–2025*. U.S. Department of Agriculture, Department of Health and Human Services; 2020.
76. Fidler N, Sauerwald T, Pohl A, Demmelmair H, Koletzko B. Docosahexaenoic acid transfer into human milk after dietary supplementation: a randomized clinical trial. *J Lipid Res*. 2000;41(9):1376–1383. https://doi.org/10.1016/S0022-2275(20)33449-0
77. Cena H, Castellazzi AM, Pietri A, Roggi C, Turconi G. Lutein concentration in human milk during early lactation and its relationship with dietary lutein intake. *Public Health Nutr*. 2009;12(10):1878–1884. https://doi.org/10.1017/s1368980009004807
78. Sherry CL, Oliver JS, Renzi LM, Marriage BJ. Lutein supplementation increases breast milk and plasma lutein concentrations in lactating women and infant plasma concentrations

but does not affect other carotenoids. *J Nutr*. 2014;144(8):1256–1263. https://doi.org/10.3945/jn.114.192914
79. Meldrum SJ, D'Vaz N, Casadio Y, et al. Determinants of DHA levels in early infancy: differential effects of breast milk and direct fish oil supplementation. *Prostaglandins Leukot Essent Fatty Acids*. 2012;86(6):233–239. https://doi.org/10.1016/j.plefa.2012.03.006
80. Schaefer E, Demmelmair H, Horak J, et al. Multiple micronutrients, lutein, and docosahexaenoic acid supplementation during lactation: a randomized controlled trial. *Nutrients*. 2020;12(12):3849. https://doi.org/10.3390/nu12123849
81. Fowden AL, Forhead A. The role of hormones in intrauterine development. In: Barker DJ, ed. *Fetal Origins of Cardiovascular and Lung Disease*. Marcel Dekker Inc; 2000:199–228.
82. Glover V, O'Connor TG, O'Donnell K. Prenatal stress and the programming of the HPA axis. *Neurosci Biobehav Rev*. 2010;35(1):17–22. https://doi.org/10.1016/j.neubiorev.2009.11.008
83. Braun T, Challis JR, Newnham JP, Sloboda DM. Early-life glucocorticoid exposure: the hypothalamic-pituitary-adrenal axis, placental function, and long-term disease risk. *Endocr Rev*. 2013;34(6):885–916. https://doi.org/10.1210/er.2013-1012
84. Matthews SG, McGowan PO. Developmental programming of the HPA axis and related behaviours: epigenetic mechanisms. *Journal of Endocrinology*. 2019;242(1):T69–T79. https://doi.org/10.1530/joe-19-0057
85. O'Connor TG, Heron J, Golding J, Glover V. Maternal antenatal anxiety and behavioural/emotional problems in children: a test of a programming hypothesis. *J Child Psychol Psychiatry*. 2003;44(7):1025–1036. https://doi.org/10.1111/1469-7610.00187
86. Van den Bergh BRH, van den Heuvel MI, Lahti M, et al. Prenatal developmental origins of behavior and mental health: The influence of maternal stress in pregnancy. *Neuroscience & Biobehavioral Reviews*. 2020;117:26–64. https://doi.org/10.1016/j.neubiorev.2017.07.003
87. Sloboda D, Newnham J, Moss T, Challis J. The fetal hypothalamic-pituitary-adrenal axis: relevance to developmental origins of health and disease. In: Gluckman PD, Hanson MA, eds. Developmental

Origins of Health and Disease. Cambridge University Press; 2006:191–205.
88. Welberg LA, Seckl JR. Prenatal stress, glucocorticoids and the programming of the brain. *J Neuroendocrinol*. 2001;13(2):113–128. https://doi.org/10.1046/j.1365-2826.2001.00601.x
89. Rinaudo P, Wang E. Fetal programming and metabolic syndrome. *Ann Rev Physiol*. 2012;74(1):107–130. https://doi.org/10.1146/annurev-physiol-020911-153245
90. Zhu Z, Cao F, Li X. Epigenetic programming and fetal metabolic programming. *Front Endocrinol*. 2019;10. https://doi.org/10.3389/fendo.2019.00764
91. Marques AH, O'Connor TG, Roth C, Susser E, Bjorke-Monsen AL. The influence of maternal prenatal and early childhood nutrition and maternal prenatal stress on offspring immune system development and neurodevelopmental disorders. *Front Neurosci*. 2013;7:120. https://doi.org/10.3389/fnins.2013.00120
92. McGowan PO, Matthews SG. Prenatal stress, glucocorticoids, and developmental programming of the stress response. *Endocrinology*. 2017;159(1):69–82. https://doi.org/10.1210/en.2017-00896
93. Seckl JR, Holmes MC. Mechanisms of disease: glucocorticoids, their placental metabolism and fetal 'programming' of adult pathophysiology. *Nat Clin Pract Endocrinol Metab*. 2007;3(6):479–488. https://doi.org/10.1038/ncpendmet0515
94. Adam TC, Epel ES. Stress, eating and the reward system. *Physiol Behav*. 2007;91(4):449–458. https://doi.org/10.1016/j.physbeh.2007.04.011
95. Zeltser LM. Feeding circuit development and early-life influences on future feeding behaviour. *Nat rRev Neurosci*. 2018;19(5):302–316. https://doi.org/10.1038/nrn.2018.23
96. Spencer SJ. Perinatal programming of neuroendocrine mechanisms connecting feeding behavior and stress. *Front Neurosci*. 2013;7:109. https://doi.org/10.3389/fnins.2013.00109
97. McCance RA. Food, growth, and time. *Lancet*. 1962;2(7258):671–676. https://doi.org/10.1016/s0140-6736(62)90499-3
98. Widdowson EM, McCance RA. A review: new thoughts on growth. *Pediatr Res*. 1975;9(3):154–156. https://doi.org/10.1203/00006450-

197503000-00010
99. Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet*. 1986;1(8489):1077–1081. https://doi.org/10.1016/s0140-6736(86)91340-1
100. Barker DJ, Osmond C, Simmonds SJ, Wield GA. The relation of small head circumference and thinness at birth to death from cardiovascular disease in adult life. *BMJ*. 1993;306(6875):422–426. https://doi.org/10.1136/bmj.306.6875.422
101. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. *Lancet*. 1989;2(8663):577–580. https://doi.org/10.1016/s0140-6736(89)90710-1
102. Frankel S, Elwood P, Sweetnam P, Yarnell J, Smith GD. Birthweight, body-mass index in middle age, and incident coronary heart disease. *Lancet*. 1996;348(9040):1478–1480. https://doi.org/10.1016/s0140-6736(96)03482-4
103. Stein CE, Fall CH, Kumaran K, Osmond C, Cox V, Barker DJ. Fetal growth and coronary heart disease in south India. *Lancet*. 1996;348(9037):1269–1273. https://doi.org/10.1016/s0140-6736(96)04547-3
104. Leon DA, Lithell HO, Vagero D, et al. Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15000 Swedish men and women born 1915–29. *BMJ*. 1998;317(7153):241–245. https://doi.org/10.1136/bmj.317.7153.241
105. Forsen T, Osmond C, Eriksson JG, Barker DJ. Growth of girls who later develop coronary heart disease. *Heart*. 2004;90(1):20–24. https://doi.org/10.1136/heart.90.1.20
106. Huxley RR, Shiell AW, Law CM. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. *J Hypertens*. 2000;18(7):815–831. https://doi.org/10.1097/00004872-200018070-00002
107. Newsome CA, Shiell AW, Fall CH, Phillips DI, Shier R, Law CM. Is birth weight related to later glucose and insulin metabolism? A systematic review. *Diabet Med*. 2003;20(5):339–348. https://doi.org/10.1046/j.1464-5491.2003.00871.x

108. Jornayvaz FR, Vollenweider P, Bochud M, Mooser V, Waeber G, Marques-Vidal P. Low birth weight leads to obesity, diabetes and increased leptin levels in adults: the CoLaus study. *Cardiovasc Diabetol*. 2016;15(1):73. https://doi.org/10.1186/s12933-016-0389-2
109. Dabelea D, Pettitt DJ. Intrauterine diabetic environment confers risks for type 2 diabetes mellitus and obesity in the offspring, in addition to genetic susceptibility. *J Pediatr Endocrinol Metab*. 2001;14(8):1085–1091. https://doi.org/10.1515/jpem-2001-0803
110. McCance DR, Pettitt DJ, Hanson RL, Jacobsson LT, Knowler WC, Bennett PH. Birth weight and non-insulin dependent diabetes: thrifty genotype, thrifty phenotype, or surviving small baby genotype? *BMJ*. 1994;308(6934):942–945. https://doi.org/10.1136/bmj.308.6934.942
111. Knop MR, Geng TT, Gorny AW et al. Birth weight and risk of type 2 diabetes mellitus, cardiovascular disease, and hypertension in adults: a meta-analysis of 7646267 participants from 135 studies. *Am Heart J*. 2018;7(23):e008870. https://doi.org/10.1161/jaha.118.008870
112. Eriksson JG. Developmental pathways and programming of diabetes: epidemiological aspects. *J Endocrinol*. 2019;242(1):T95–T104. https://doi.org/10.1530/joe-18-0680
113. Chatmethakul T, Roghair RD. Risk of hypertension following perinatal adversity: IUGR and prematurity. *J Endocrinol*. 2019;242(1):T21–T32. https://doi.org/10.1530/JOE-18-0687
114. Fall CH, Osmond C, Barker DJ, et al. Fetal and infant growth and cardiovascular risk factors in women. *BMJ*. 1995;310(6977):428–432. https://doi.org/10.1136/bmj.310.6977.428
115. Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJ. Early growth and coronary heart disease in later life: longitudinal study. *BMJ*. 2001;322(7292):949–953. https://doi.org/10.1136/bmj.322.7292.949
116. Eriksson JG, Forsen T, Tuomilehto J, Winter PD, Osmond C, Barker DJ. Catch-up growth in childhood and death from coronary heart disease: longitudinal study. *BMJ*. 1999;318(7181):427–431. https://doi.org/10.1136/bmj.318.7181.427
117. Rich-Edwards JW, Kleinman K, Michels KB, et al. Longitudinal study of birth weight and adult body mass index in predicting risk of

coronary heart disease and stroke in women. *BMJ*. 2005;330(7500):1115. https://doi.org/10.1136/bmj.38434.629630.e0
118. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia*. 1992;35(7):595–601. https://doi.org/10.1007/bf00400248
119. Ozanne SE, Hales CN. Early programming of glucose-insulin metabolism. *Trends Endocrinol Metab*. 2002;13(9):368–373. https://doi.org/10.1016/s1043-2760(02)00666-5
120. Lucas A. Programming by early nutrition in man. *Ciba Found Symp*. 1991;15638-50.
121. Singhal A. Long-term adverse effects of early growth acceleration or catch-up growth. *Ann of Nutr and Metab*. 2017;70(3):236–240. https://doi.org/10.1159/000464302
122. Monteiro PO, Victora CG. Rapid growth in infancy and childhood and obesity in later life—a systematic review. *Obes Rev*. 2005;6(2):143–154. https://doi.org/10.1111/j.1467-789x.2005.00183.x
123. Baird J, Fisher D, Lucas P, Kleijnen J, Roberts H, Law C. Being big or growing fast: systematic review of size and growth in infancy and later obesity. *BMJ*. 2005;331(7522):929. https://doi.org/10.1136/bmj.38586.411273.e0
124. Zheng M, Lamb KE, Grimes C, et al. Rapid weight gain during infancy and subsequent adiposity: a systematic review and meta-analysis of evidence. *Obes Rev*. 2018;19(3):321–332. https://doi.org/10.1111/obr.12632
125. Stettler N, Zemel BS, Kumanyika S, Stallings VA. Infant weight gain and childhood overweight status in a multicenter, cohort study. *Pediatrics*. 2002;109(2):194–199. https://doi.org/10.1542/peds.109.2.194
126. Stettler N, Kumanyika SK, Katz SH, Zemel BS, Stallings VA. Rapid weight gain during infancy and obesity in young adulthood in a cohort of African Americans. *Am J Clin Nutr*. 2003;77(6):1374–1378. https://doi.org/10.1093/ajcn/77.6.1374
127. Dennison BA, Edmunds LS, Stratton HH, Pruzek RM. Rapid infant weight gain predicts childhood overweight. *Obesity (Silver Spring)*. 2006;14(3):491–499. https://doi.org/10.1038/oby.2006.64

128. Wang G, Johnson S, Gong Y, et al. Weight gain in infancy and overweight or obesity in childhood across the gestational spectrum: a prospective birth cohort study. *Sci Rep*. 2016;6(1):29867. https://doi.org/10.1038/srep29867
129. Stettler N, Stallings VA, Troxel AB, et al. Weight gain in the first week of life and overweight in adulthood: a cohort study of European American subjects fed infant formula. *Circulation*. 2005;111(15):1897–1903. https://doi.org/10.1161/01.cir.0000161797.67671.a7
130. Horta BL, Loret de Mola C, Victora CG. Long-term consequences of breastfeeding on cholesterol, obesity, systolic blood pressure and type 2 diabetes: a systematic review and meta-analysis. *Acta Paediatr*. 2015;104(S467):30–37. https://doi.org/10.1111/apa.13133
131. Yan J, Liu L, Zhu Y, Huang G, Wang PP. The association between breastfeeding and childhood obesity: a meta-analysis. *BMC public health*. 2014;14:1267.
132. Hester SN, Hustead DS, Mackey AD, Singhal A, Marriage BJ. Is the macronutrient intake of formula-fed infants greater than breast-fed infants in early infancy? *J Nutr Metab*. 2012;2012:891201. https://doi.org/10.1155/2012/891201
133. Singhal A, Cole TJ, Fewtrell M, et al. Promotion of faster weight gain in infants born small for gestational age: is there an adverse effect on later blood pressure? *Circulation*. 2007;115(2):213–220. https://doi.org/10.1161/circulationaha.106.617811
134. Ben-Shlomo Y, McCarthy A, Hughes R, Tilling K, Davies D, Smith GD. Immediate postnatal growth is associated with blood pressure in young adulthood: the Barry Caerphilly growth study. *Hypertension*. 2008;52(4):638–644. https://doi.org/10.1161/hypertensionaha.108.114256
135. Koletzko B, Godfrey KM, Poston L, et al. Nutrition during pregnancy, lactation and early childhood and its implications for maternal and long-term childealth: the early nutrition project recommendations. *Ann Nutr Metab*. 2019;74(2):93–106. https://doi.org/10.1159/000496471
136. Cianfarani S, Germani D, Branca F. Low birthweight and adult insulin resistance: the “catch-up growth” hypothesis. *Arch Dis Child Fetal*

Neonatal Ed. 1999;81(1):F71–73. https://doi.org/10.1136/fn.81.1.f71
137. Gluckman PD, Hanson MA. The consequences of being born small—an adaptive perspective. *Horm Res*. 2006;65(suppl 3):5–14. https://doi.org/10.1159/000091500
138. Jimenez-Chillaron JC, Diaz R, Martinez D, et al. The role of nutrition on epigenetic modifications and their implications on health. *Biochimie*. 2012;94(11):2242–2263. https://doi.org/10.1016/j.biochi.2012.06.012
139. Breton CV, Landon R, Kahn LG, et al. Exploring the evidence for epigenetic regulation of environmental influences on child health across generations. *Comm Biol*. 2021;4(1):769. https://doi.org/10.1038/s42003-021-02316-6
140. Singhal A, Lucas A. Early origins of cardiovascular disease: is there a unifying hypothesis? *Lancet*. 2004;363(9421):1642–1645. https://doi.org/10.1016/s0140-6736(04)16210-7
141. Singhal A, Cole TJ, Fewtrell M, Lucas A. Breastmilk feeding and lipoprotein profile in adolescents born preterm: follow-up of a prospective randomised study. *Lancet*. 2004;363(9421):1571–1578. https://doi.org/10.1016/s0140-6736(04)16198-9
142. Singhal A, Cole TJ, Lucas A. Early nutrition in preterm infants and later blood pressure: two cohorts after randomised trials. *Lancet*. 2001;357(9254):413–419. https://doi.org/10.1016/s0140-6736(00)04004-6
143. Singhal A, Farooqi IS, O'Rahilly S, Cole TJ, Fewtrell M, Lucas A. Early nutrition and leptin concentrations in later life. *Am J Clin Nutr*. 2002;75(6):993–999. https://doi.org/10.1093/ajcn/75.6.993
144. Singhal A, Fewtrell M, Cole TJ, Lucas A. Low nutrient intake and early growth for later insulin resistance in adolescents born preterm. *Lancet*. 2003;361(9363):1089–1097. https://doi.org/10.1016/s0140-6736(03)12895-4
145. Lucas A, Fewtrell MS, Morley R, et al. Randomized trial of nutrient-enriched formula versus standard formula for postdischarge preterm infants. *Pediatrics*. 2001;108(3):703–711. https://doi.org/10.1542/peds.108.3.703
146. Chan GM. Growth and bone mineral status of discharged very low birth weight infants fed different formulas or human milk. *J Pediatr*.

1993;123(3):439–443. https://doi.org/10.1016/s0022-3476(05)81754-8
147. Fewtrell MS, Prentice A, Jones SC, et al. Bone mineralization and turnover in preterm infants at 8–12 years of age: the effect of early diet. *J Bone Miner Res*. 1999;14(5):810–820. https://doi.org/10.1359/jbmr.1999.14.5.810
148. Ruys CA, van de Lagemaat M, Rotteveel J, Finken MJJ, Lafeber HN. Improving long-term health outcomes of preterm infants: how to implement the findings of nutritional intervention studies into daily clinical practice. *Eur J Pediatr*. 2021;180(6):1665–1673. https://doi.org/10.1007/s00431-021-03950-2
149. Victora CG, Barros FC, Horta BL, Martorell R. Short-term benefits of catch-up growth for small-for-gestational-age infants. *Int J Epidemiol*. 2001;30(6):1325–1330. https://doi.org/10.1093/ije/30.6.1325
150. Ong KK, Kennedy K, Castañeda-Gutiérrez E, et al. Postnatal growth in preterm infants and later health outcomes: a systematic review. *Acta Paediatr*. 2015;104(10):974–986. https://doi.org/10.1111/apa.13128
151. Castanys-Muñoz E, Kennedy K, Castañeda-Gutiérrez E, et al. Systematic review indicates postnatal growth in term infants born small-for-gestational-age being associated with later neurocognitive and metabolic outcomes. *Acta Paediatr*. 2017;106(8):1230–1238. https://doi.org/10.1111/apa.13868
152. Chavatte-Palmer P, Tarrade A, Rousseau-Ralliard D. Diet before and during pregnancy and offspring health: the importance of animal models and what can be learned from them. *Inter J of Envir Res Pub Health*. 2016;13(6). https://doi.org/10.3390/ijerph13060586
153. Maloney CA, Hay SM, Young LE, Sinclair KD, Rees WD. A methyl-deficient diet fed to rat dams during the peri-conception period programs glucose homeostasis in adult male but not female offspring. *J Nutr*. 2011;141(1):95–100. https://doi.org/10.3945/jn.109.119453
154. Aiken CE, Ozanne SE. Sex differences in developmental programming models. *Reproduction*. 2013;145(1):R1–13. https://doi.org/10.1530/rep-11-0489
155. Li M, Sloboda DM, Vickers MH. Maternal obesity and developmental programming of metabolic disorders in offspring: evidence from

animal models. *Exp Diabetes Res*. 2011;2011:592408. https://doi.org/10.1155/2011/592408
156. Grzęda E, Matuszewska J, Ziarniak K, et al. Animal foetal models of obesity and diabetes—from laboratory to clinical settings. *Front Endocrinol (Lausanne)*. 2022;13:785674. https://doi.org/10.3389/fendo.2022.785674
157. Martin-Gronert MS, Ozanne SE. Experimental IUGR and later diabetes. *J Intern Med*. 2007;261(5):437–452. https://doi.org/10.1111/j.1365-2796.2007.01800.x
158. Dahri S, Snoeck A, Reusens-Billen B, Remacle C, Hoet JJ. Islet function in offspring of mothers on low-protein diet during gestation. *Diabetes*. 1991;40(suppl 2):115–120. https://doi.org/10.2337/diab.40.2.s115
159. Gopalakrishnan GS, Gardner DS, Dandrea J, et al. Influence of maternal pre-pregnancy body composition and diet during early-mid pregnancy on cardiovascular function and nephron number in juvenile sheep. *Br J Nutr*. 2005;94(6):938–947. https://doi.org/10.1079/bjn20051559
160. Vickers MH, Breier BH, Cutfield WS, Hofman PL, Gluckman PD. Fetal origins of hyperphagia, obesity, and hypertension and postnatal amplification by hypercaloric nutrition. *Am J Physiol Endocrinol Metab*. 2000;279(1):E83–87. https://doi.org/10.1152/ajpendo.2000.279.1.e83
161. Sarr O, Yang K, Regnault TR. In utero programming of later adiposity: the role of fetal growth restriction. *J Pregnancy*. 2012;2012:134758. https://doi.org/10.1155/2012/134758
162. Armitage JA, Lakasing L, Taylor PD, et al. Developmental programming of aortic and renal structure in offspring of rats fed fat-rich diets in pregnancy. *J Physiol*. 2005;565(Pt 1):171–184. https://doi.org/10.1113/jphysiol.2005.084947
163. Ainge H, Thompson C, Ozanne SE, Rooney KB. A systematic review on animal models of maternal high fat feeding and offspring glycaemic control. *Int J Obes (Lond)*. 2010;35(3):325–335. https://doi.org/10.1038/ijo.2010.149
164. Williams L, Seki Y, Vuguin PM, Charron MJ. Animal models of in utero exposure to a high fat diet: a review. *Biochim Biophys Acta*.

2014;1842(3):507–519. https://doi.org/10.1016/j.bbadis.2013.07.006
165. Nicholas LM, Ozanne SE. Early life programming in mice by maternal overnutrition: mechanistic insights and interventional approaches. *Philos Trans R Soc B: Biol Sci*. 2019;374(1770):20180116. https://doi.org/10.1098/rstb.2018.0116
166. White CL, Purpera MN, Morrison CD. Maternal obesity is necessary for programming effect of high-fat diet on offspring. *Am J Physiol Regul Integr Comp Physiol*. 2009;296(5):R1464–1472. https://doi.org/10.1152/ajpregu.91015.2008
167. Hartil K, Vuguin PM, Kruse M, et al. Maternal substrate utilization programs the development of the metabolic syndrome in male mice exposed to high fat in utero. *Pediatr Res*. 2009;66(4):368–373. https://doi.org/10.1203/pdr.0b013e3181b33375
168. Ribaroff GA, Wastnedge E, Drake AJ, Sharpe RM, Chambers TJG. Animal models of maternal high fat diet exposure and effects on metabolism in offspring: a meta-regression analysis. *Obes Rev*. 2017;18(6):673–686. https://doi.org/10.1111/obr.12524
169. Menting MD, Mintjens S, van de Beek C, et al. Maternal obesity in pregnancy impacts offspring cardiometabolic health: systematic review and meta-analysis of animal studies. *Obes Rev*. 2019;20(5):675–685. https://doi.org/10.1111/obr.12817
170. Salto R, Girón MD, Manzano M, et al. Programming skeletal muscle metabolic flexibility in offspring of male rats in response to maternal consumption of slow digesting carbohydrates during pregnancy. *Nutrients*. 2020;12(2). https://doi.org/10.3390/nu12020528
171. Martin MJ, Manzano M, Bueno-Vargas P, et al. Feeding a slowly digestible carbohydrate diet during pregnancy of insulin-resistant rats prevents the excess of adipogenesis in their offspring. *J Nutr Biochem*. 2018;61183–196. https://doi.org/10.1016/j.jnutbio.2018.05.018
172. Salto R, Manzano M, Girón MD, et al. A slow-digesting carbohydrate diet during rat pregnancy protects offspring from non-alcoholic fatty liver disease risk through the modulation of the carbohydrate-response rlement and sterol regulatory element binding proteins. *Nutrients*. 2019;11(4). https://doi.org/10.3390/nu11040844
173. Lanham SA, Roberts C, Hollingworth T, et al. Maternal high-fat diet: effects on offspring bone structure. *Osteoporos Int*.

2010;21(10):1703–1714. https://doi.org/10.1007/s00198-009-1118-4
174. Peleg-Raibstein D, Luca E, Wolfrum C. Maternal high-fat diet in mice programs emotional behavior in adulthood. *Behav Brain Res*. 2012;233(2):398–404. https://doi.org/10.1016/j.bbr.2012.05.027
175. Hasebe K, Kendig MD, Morris MJ. Mechanisms underlying the cognitive and behavioural effects of maternal obesity. *Nutrients*. 2021;13(1). https://doi.org/10.3390/nu13010240
176. Reynolds CM, Segovia SA, Vickers MH. Experimental models of maternal obesity and neuroendocrine programming of metabolic disorders in offspring. *Front Endocrinol (Lausanne)*. 2017;8:245. https://doi.org/10.3389/fendo.2017.00245
177. Lewis RM, Petry CJ, Ozanne SE, Hales CN. Effects of maternal iron restriction in the rat on blood pressure, glucose tolerance, and serum lipids in the 3-month-old offspring. *Metabolism*. 2001;50(5):562–567. https://doi.org/10.1053/meta.2001.22516
178. Harvey L, Boksa P. Do prenatal immune activation and maternal iron deficiency interact to affect neurodevelopment and early behavior in rat offspring? *Brain Behav Immun*. 2014;35:144–154. https://doi.org/10.1016/j.bbi.2013.09.009
179. Reynolds RM. Glucocorticoid excess and the developmental origins of disease: two decades of testing the hypothesis—2012 Curt Richter award winner. *Psychoneuroendocrinology*. 2013;38(1):1–11. https://doi.org/10.1016/j.psyneuen.2012.08.012
180. Matthews SG, Phillips DI. Transgenerational inheritance of stress pathology. *Exp Neurol*. 2012;233(1):95–101. https://doi.org/10.1016/j.expneurol.2011.01.009
181. Ozanne SE. Metabolic programming in animals. *Br Med Bull*. 2001;60143–152. https://doi.org/10.1093/bmb/60.1.143
182. Maniam J, Antoniadis C, Morris MJ. Early-life stress, HPA axis adaptation, and mechanisms contributing to later health outcomes. *Front Endocrinol (Lausanne)*. 2014;5:73. https://doi.org/10.3389/fendo.2014.00073
183. Zambrano E, Nathanielsz PW. Mechanisms by which maternal obesity programs offspring for obesity: evidence from animal studies. *Nutr Rev*. 2013;71(suppl 1):S42–S54. https://doi.org/10.1111/nure.12068

184. Langley-Evans SC. Fetal programming of CVD and renal disease: animal models and mechanistic considerations. *Proc Nutr Soc*. 2013;72(3):317–325. https://doi.org/10.1017/s0029665112003035
185. Armitage JA, Khan IY, Taylor PD, Nathanielsz PW, Poston L. Developmental programming of the metabolic syndrome by maternal nutritional imbalance: how strong is the evidence from experimental models in mammals? *J Physiol*. 2004;561(Pt 2):355–377. https://doi.org/10.1113/jphysiol.2004.072009
186. Thompson RF, Fazzari MJ, Niu H, Barzilai N, Simmons RA, Greally JM. Experimental intrauterine growth restriction induces alterations in DNA methylation and gene expression in pancreatic islets of rats. *J Biol Chem*. 2010;285(20):15111–15118. https://doi.org/10.1074/jbc.m109.095133
187. Souza LL, Moura EG, Lisboa PC. Litter size reduction as a model of overfeeding during lactation and its consequences for the development of metabolic diseases in the offspring. *Nutrients*. 2022;14(10):2045. https://doi.org/10.3390/nu14102045
188. Rodrigues VST, Moura EG, Peixoto TC, et al. The model of litter size reduction induces long-term disruption of the gut-brain axis: an explanation for the hyperphagia of Wistar rats of both sexes. *Physiol Rep*. 2022;10(3):e15191. https://doi.org/10.14814/phy2.15191
189. Enes-Marques S, Rojas VCT, Batista TH, et al. Neonatal overnutrition programming impairs cholecystokinin effects in adultmale rats. *J Nutr Biochem*. 2020;86108494. https://doi.org/10.1016/j.jnutbio.2020.108494
190. Parra-Vargas M, Ramon-Krauel M, Lerin C, Jimenez-Chillaron JC. Size does matter: litter size strongly determines adult metabolism in rodents. *Cell Metab*. 2020;32(3):334–340. https://doi.org/10.1016/j.cmet.2020.07.014
191. Drake AJ, Liu L. Intergenerational transmission of programmed effects: public health consequences. *Trends Endocrinol Metab*. 2010;21(4):206–213. https://doi.org/10.1016/j.tem.2009.11.006
192. Bowers ME, Yehuda R. Intergenerational transmission of stress in humans. *Neuropsychopharmacology*. 2016;41(1):232–244. https://doi.org/10.1038/npp.2015.247

193. Yehuda R, Lehrner A. Intergenerational transmission of trauma effects: putative role of epigenetic mechanisms. *World Psych*. 2018;17(3):243–257. https://doi.org/10.1002/wps.20568
194. Barker DJ, Shiell AW, Barker ME, Law CM. Growth in utero and blood pressure levels in the next generation. *J Hypertens*. 2000;18(7):843–846. https://doi.org/10.1097/00004872-200018070-00004
195. Roseboom TJ. Epidemiological evidence for the developmental origins of health and disease: effects of prenatal undernutrition in humans. *J Endocrinol*. 2019;242(1):T135–T144. https://doi.org/10.1530/joe-18-0683
196. Stein AD, Lumey LH. The relationship between maternal and offspring birth weights after maternal prenatal famine exposure: the Dutch Famine Birth Cohort Study. *Hum Biol*. 2000;72(4):641–654.
197. Benyshek DC. The "early life" origins of obesity-related health disorders: new discoveries regarding the intergenerational transmission of developmentally programmed traits in the global cardiometabolic health crisis. *Am J Phys Anthropol*. 2013;152(suppl 57):79–93. https://doi.org/10.1002/ajpa.22393
198. Painter RC, Osmond C, Gluckman P, Hanson M, Phillips DI, Roseboom TJ. Transgenerational effects of prenatal exposure to the Dutch famine on neonatal adiposity and health in later life. *BJOG*. 2008;115(10):1243–1249. https://doi.org/10.1111/j.1471-0528.2008.01822.x
199. Pembrey ME, Bygren LO, Kaati G, et al. Sex-specific, male-line transgenerational responses in humans. *Eur J Hum Genet*. 2006;14(2):159–166. https://doi.org/10.1038/sj.ejhg.5201538
200. Bygren LO, Tinghog P, Carstensen J, et al. Change in paternal grandmothers' early food supply influenced cardiovascular mortality of the female grandchildren. *BMC Genet*. 2014;15:12. https://doi.org/10.1186/1471-2156-15-12
201. Heijmans BT, Tobi EW, Stein AD, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc Natl Acad Sci USA*. 2008;105(44):17046–17049. https://doi.org/10.1073/pnas.0806560105

202. Soubry A, Schildkraut JM, Murtha A, et al. Paternal obesity is associated with IGF2 hypomethylation in newborns: results from a Newborn Epigenetics Study (NEST) cohort. *BMC Med*. 2013;11:29. https://doi.org/10.1186/1741-7015-11-29
203. Brunton PJ. Resetting the dynamic range of hypothalamic-pituitary-adrenal axis stress responses through pregnancy. *J Neuroendocrinol*. 2010;22(11):1198–1213. https://doi.org/10.1111/j.1365-2826.2010.02067.x
204. Entringer S. Impact of stress and stress physiology during pregnancy on child metabolic function and obesity risk. *Curr Opin Clin Nutr Metab Care*. 2013;16(3):320–327. https://doi.org/10.1097/MCO.0b013e32835e8d80
205. Fewtrell MS, Williams JE, Singhal A, Murgatroyd PR, Fuller N, Lucas A. Early diet and peak bone mass: 20 year follow-up of a randomized trial of early diet in infants born preterm. *Bone*. 2009;45(1):142–149. https://doi.org/10.1016/j.bone.2009.03.657
206. Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. *Pediatrics*. 2006;117(4):1253–1261. https://doi.org/10.1542/peds.2005-1368
207. Beardsall K, Diderholm BM, Dunger DB. Insulin and carbohydrate metabolism. *Best Pract Res Clin Endocrinol Metab*. 2008;22(1):41–55. https://doi.org/10.1016/j.beem.2007.10.001
208. Velazquez MA, Fleming TP, Watkins AJ. Periconceptional environment and the developmental origins of disease. *J Endocrinol*. 2019;242(1):T33–T49. https://doi.org/10.1530/joe-18-0676

Test Your Knowledge Question Answers

1. The correct answer is **D**. Glucose is the major energy source for the fetus. Amino acids are the second most important macronutrient.
2. The correct answer is **C**. Early nutrition programming indicates that nutrition experiences in early life can program an individual's

metabolism and development, and influence later health outcomes. The changes may be long term and transmitted to future generations.

3. The correct answer is **B**. Rapid weight gain during infancy may be associated with an increased incidence of childhood or adult obesity and cardiovascular risk factors.

Richard W. Gelling, PhD; Barbara Marriage, PhD, RD; Russell J. Merritt, MD, PhD, FAAP; and Christina Sherry, PhD, RD contributed to previous editions of this text.

11

Human Milk Feeding and Clinical Considerations

Christina J. Valentine, MD, MS, RD, FAAP, FASPEN, and Amy Gates, PhD, RDN, LD

Learning Objectives

1. List 2 etiologies for the failure of adequate milk volume in lactogenesis II.
2. Outline 3 components in human milk that provide immune health benefits.
3. List 3 nutrient differences between mother's own milk and donor human milk.

Introduction

Human milk is not simply nourishment; it's a powerful biological fluid containing numerous different bioactive compounds that have various functions. Human milk plays a pivotal role in the first years of a child's life. The initial reliance on human milk, followed by the transition to complementary feeding, constitutes a major step in infant health and development. For most mothers and newborns, the breastfeeding journey begins in the hospital. Nutrition professionals play a critical role in breastfeeding education, goals, and support of the mother–infant dyad. As such, practitioners should have a strong foundation in the science of human

milk, including the components and nutrient variability, to provide accurate nutrition recommendations and the best possible support. Clinicians must further understand the impact of maternal diet and breastfeeding on both mother and child. This chapter highlights these features and offers practical considerations.

Exclusive breastfeeding for the first 6 months of an infant's life is recommended by all major professional societies, including the World Health Organization (WHO) and the American Academy of Pediatrics, because of its many health benefits for mother and baby.[1–2] The U.S. Department of Health and Human Services reports that 35% of infants nationwide are exclusively breastfed through 6 months of age, demonstrating no appreciable change from previous years.[3] The goal of Healthy People 2030 is to increase the percentage of infants who are breastfed through age 12 months from 35% to 54.1%.[4] Of concern is that despite 83.2% of American mothers initiating breastfeeding at birth, only 35.6% of infants are still receiving any breastmilk by their first birthday.[3]

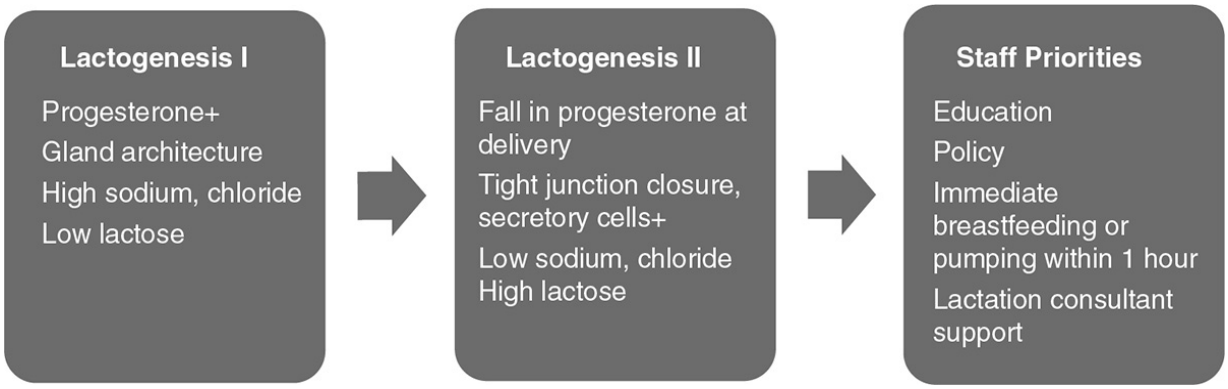
Human milk offers unique health benefits and protections for infants, such as improved feeding tolerance, fewer ear infections, improved immunity, ideal growth, and improved cognitive ability.[5–10] Once complementary foods begin around 6 months of life, breastfeeding can continue to be a healthful complement to the infant's solid food diet for up to 2 years of life or as long as it is mutually beneficial to both mother and child.[2] It is crucial to avoid nutrient deficiencies in the first thousand days of a child's life (beginning at conception to 2 years), which can result in stunted growth and immune dysregulation as well as cognitive and behavioral sequela, impacting lifelong health.[11–12]

Breast Physiology and Milk Expression

It is important to understand breast physiology and risk factors for insufficient milk production so that timely, relevant, and appropriate education and support can be provided.[13–14] Breast development begins at puberty with formation of the milk ducts and lobules. During pregnancy, because of hormonal influences by progesterone and prolactin changes, the

cells for secretory differentiation occur, called lactogenesis I.[15] This is when the breast tissue undergoes further changes to prepare for milk production. With the hormonal changes of delivery, the breast undergoes a stage defined as lactogenesis II that occurs from the surge in prolactin and decrease in progesterone, resulting in the onset of milk production and corresponding reduction in sodium and chloride concentrations in the milk, reflecting tight junction closure.[13–15] For a diagram of lactogenesis stages, see Figure 11-1.

FIGURE 11-1. Lactogenesis Stages and Staff Priorities



As prolactin continues to be expressed, milk synthesis and secretion continues. Full milk volume reaches 750–900 ml/d by weeks 1 to 2.[15] This is a helpful benchmark to use when counseling parents regarding inadequate nutrition/low volume, which is considered <500 ml/d. Of particular importance, low volume at week 2 predicts week 6 amounts, so it is vital to ensure early success.[16] Delays in lactogenesis II can be the result of hormonal, architecture surgical augmentation, stress, hormonal contraception, or lack of breast emptying.[13,15,17,18]

Hospital staff training, policies, and supportive practices have demonstrated improvements in the percentage of women providing human milk at discharge and follow-up.[19] Early infant attachment or pumping within an hour predicts the most success.[20] Maternal perception of volume should also be addressed early on, and test weighing used when possible as many mothers cannot accurately assess let-down volume. Another technique for increasing milk volume is skin-to-skin contact, which can be

done safely even with critically ill infants.[21–23] Finally, diet strategies may support mammary cell health.

A pilot trial of women who delivered infants at <28 weeks demonstrated secretory gene up-regulation with improved maternal docosahexaenoic acid (DHA) intake at 1000 mg/d as compared with 200 mg, creating a new opportunity for nutrition support clinicians to recommend both mechanical and nutritional interventions.[24] For more information on developing policies to support breastfeeding, refer to the Academy of Breastfeeding Medicine's "ABM Clinical Protocol #7: Modeling Maternity Policy Supportive of Breastfeeding."[25]

Human Milk Composition

Human milk is a complex, variable biological fluid that is comprised of macronutrients, vitamins, and minerals, along with important compounds for immune and developmental health.[11,26–29] Complicating the ability to assess the intake of an infant fed human milk, however, is that mothers can have variable milk composition based on diet; genetics; and environmental, ethnic, and genetic diversity.[18,29–31] In addition, many studies evaluated milk composition in small samples but the analytic techniques differ.[28,32] Systematic reviews evaluating milk volume and average composition have provided a baseline understanding. In general, term infants ingesting > 750 ml of milk per day and growing along the WHO growth charts are considered the gold standard.[36]

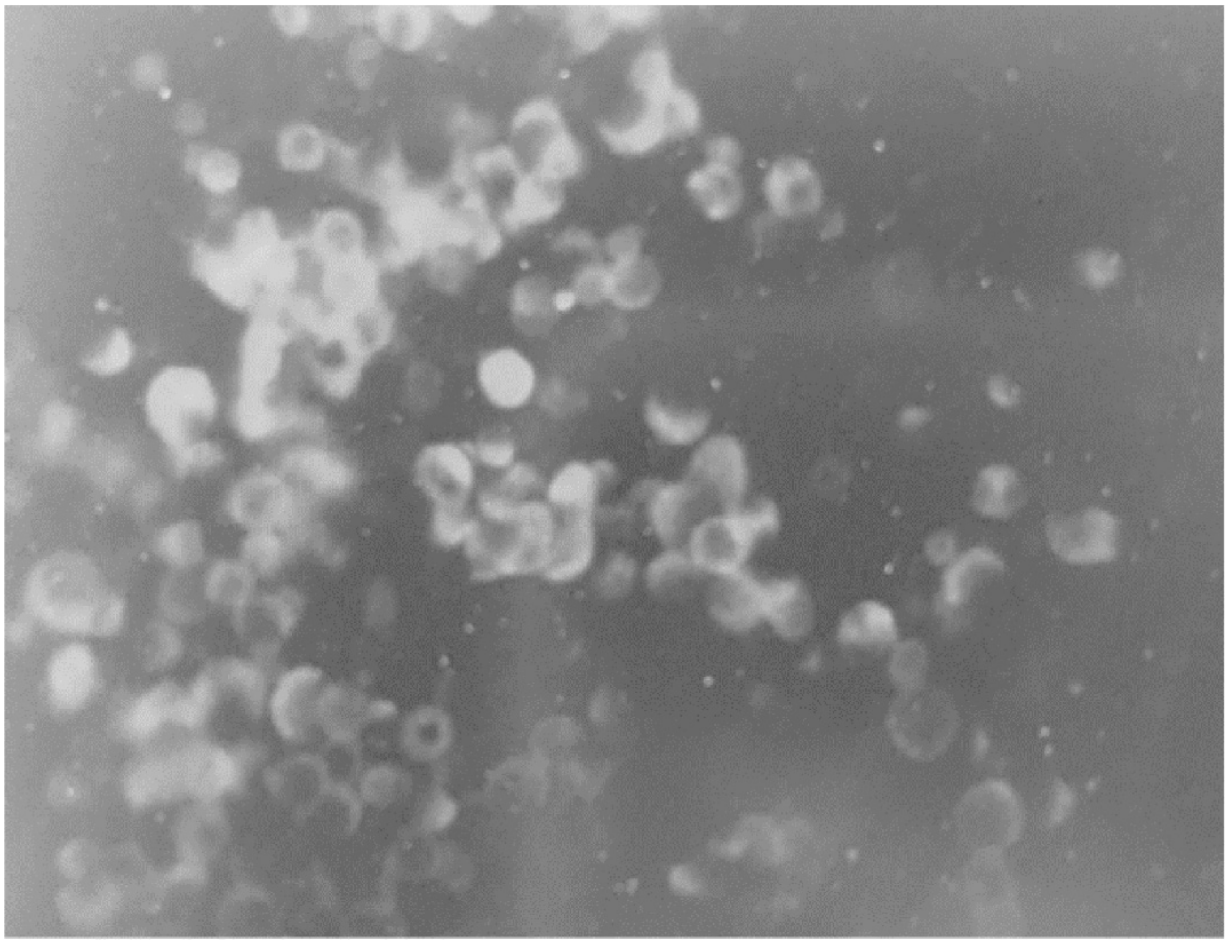
Numerous bioactives in human milk offer protection against infection, otitis media, and diarrheal illness.[5–6] Much of the structure-function results have been in animal, cell, and epidemiological studies. The most compelling components translating to human studies have included specifically lactoferrin, secretory immunoglobulin A (sIgA), lysozyme, and human milk oligosaccharides.

Human Milk Bioactivity

Lactoferrin is an antimicrobial glycoprotein that is abundant in human milk.[15,37] Lactoferrin is an important component of colostrum (600 mg/dL) as it has a bacteriostatic effect on several microorganisms.[38] The concentration of lactoferrin in colostrum acts as an antibacterial agent on gram-negative bacteria in the infant's gut, preventing the colonization of harmful pathogens.[39] Provision of fresh colostrum to all hospitalized infants is an important step toward infection prevention and the establishment of the immune system. Concentrations of lactoferrin decrease over time and settle at 180 mg/dL by 5 months of lactation.[38] Lactoferrin is necessary for iron absorption from human milk and is affected by maternal protein-energy malnutrition.[40] Mothers who are protein-energy malnourished but not iron-deficient are lactoferrin-deficient.[15]

Immunoglobins, or antibodies, are an important component of human milk because of their biologic activity. sIgA is the most abundant immunoglobulin in human milk and is protective against many pathogens including *E coli.*15 Unlike lactoferrin, levels of sIgA are consistent throughout lactation for up to 2 years,[43–44] and sIgA withstands heat/storage and still demonstrates immunofluorescence in fresh and pasteurized milk (see Figure 11-2). Lysozyme is an acid-stable enzyme that has 300 times the concentration in human milk compared with cow's milk. Lysozyme is protective against gram-positive bacteria and Enterobacteriaceae.[45] In addition to lactoferrin, sIgA, and lysozymes, many other bioactives in human milk act as anti-inflammatory agents and impart immunological benefits. These immune health benefits are especially important for immunocompromised, hospitalized infants.

FIGURE 11-2. Secretory IgA in Human Milk



sIgA immunofluorescence of fresh pumped human milk of pooled (n = 5 mothers) 24-hour collected 5-ml samples.

Human Milk Oligosaccharides

Human milk oligosaccharides (HMOs) are the third most abundant substance in human milk after lipids and lactose, contributing 5 to 20 g/L.[15] HMOs promote the growth of beneficial bacteria (Bifidobacterium, Bacteroides), block pathogens from binding to cell-surface receptors, and inhibit the colonization of proteobacteria. HMOs have been shown to protect against diarrhea, gastroenteritis, and respiratory tract infections.[46–47] HMOs are poorly absorbed and digested and remain in the gut where they act as anti-inflammatory, antipathogenic, and prebiotic agents necessary for probiotic growth and maintenance. The variability of HMO concentration in

human milk is influenced by lactational stage, maternal differences, and processing of donor human milk (DHM). DHM has less abundant HMOs compared to mother's own milk (MOM).[48]

Long-Chain Polyunsaturated Fatty Acids and the Milk Fat Globule Membrane

Long-chain polyunsaturated fatty acids (LCPUFA) are biologically pertinent fatty acids from the essential fatty acid omega-3 precursor linolenic acid-docosahexaenoic acid (DHA) and the essential fatty acid omega 6 fatty acid linoleic acid-arachidonic acid (ARA) respectively providing impacts on cognitive development.[49] Maternal concentrations are very dependent on diet, and genetic guidance affects the amount of transfer to the baby through human milk.[50] Recent imaging of infants with increased LCPUFA illustrated enhanced myelin in critical areas of the brain during development.[51] For these reasons, it is important for the nutrition support team to also counsel mothers on the impact of dietary intake.[52]

The delivery of lipids, many proteins, and cholesterol begins in the golgi apparatus of the mammary epithelial cell, and once extruded from the secretory cell carries the membrane compounds with it in a unique trilayer membrane, the milk fat globule membrane (MFGM), which is present in all mammalian milk.[56] The most studied MFGM components include sphingomyelin and phosphatidyl choline.[53–59] Magnetic resonance imaging (MRI) of the brains of infants who were fed milk showed that varying these concentrations had a significant impact on myelin accumulation and a correlation to cognitive testing.[60] For a list of selected components in human milk and their related functions, see Table 11-1.

TABLE 11-1. Selected Components From Human Milk

Breast Milk Component	Function
Glycoproteins	Resists digestion and impacts microbiome
HMOs	Resists digestion and impacts immune health

Breast Milk Component	Function
Lactoferrin	Acts as anti-infective protein
Lysozyme	Cleaves cell walls of pathogens
sIgA	Provides immune protection in the gut

Human Milk and the Hospitalized Infant

Preterm or term infants with congenital defects, cardiac anomalies, hypoxic-ischemic encephalopathy, or intestinal injury often have volume and nutrient needs that differ significantly from healthy, term infants. Provision of MOM to newborns who are admitted to the neonatal intensive care unit (NICU) directly after birth is complicated, and many barriers to breastfeeding must be overcome. Depending on the diagnosis, hospitalized newborns may have enteral feedings delayed, be unable to latch or bottle feed, or have acute medical needs requiring life-saving interventions that take precedence over feeding. Many of these infants are nourished with a combination of parenteral and enteral nutrition (via feeding tube) for the first days or weeks of life.

Direct breastfeeding may not be possible for newborns in the NICU because of mother-infant separation, surgical interventions for the infant, immature oral feeding coordination, or diagnoses that prevent oral feedings. MOM is not homogenized and thus clinicians should be cautious about the hang time and continuous feeding of human milk, which can result in lipid and mineral losses.[57] If the infant is on a feeding tube, human milk and fortified human milk should be bolus-fed with the syringe pump facing upward to help with losses in the tubing (results deliver >90% of the fat using this technique).[58] For most NICU patients, the provision of MOM is dependent on mothers expressing breastmilk that is then processed, stored, prepared, and delivered via a feeding tube.

When designing feeding plans for hospitalized infants, healthcare providers must consider their nutrient needs as well as the safe provision of expressed human milk. Nutrient needs for hospitalized infants depend on the infant's diagnosis and factors that contribute to energy expenditure, nutrient absorption, and fluid needs. Regardless of diagnosis, hospitalized term infants have different nutrient needs than preterm infants. In the next

section, we discuss the nutrient needs of each population and the role of human milk in meeting these needs.

Preterm Infants

Preterm infants are at risk for several feeding-related and nutrient-related complications. Preterm infants have immature digestive and immune systems, which place them at risk for necrotizing enterocolitis (NEC), gut dysbiosis, feeding intolerance, and infection.[33,61] In addition, the growth rate necessary to match in-utero rates requires nutrient-dense feedings.[33,61–64] The placenta transfers stores of nutrients (zinc, iron, calcium, phosphorus) in the third trimester of pregnancy. Infants born before 34 weeks of gestation are at risk for deficiency of these nutrients because they have limited stores from which to draw, leaving them at risk for iron-deficiency anemia, zinc deficiency, and osteogenic rickets.[61]

Human milk offers solutions to many of the feeding-related problems that preterm infants experience. Preterm infants who are fed MOM have a reduced risk of infection and NEC, have fewer days of parenteral nutrition (PN), and have fewer days in the NICU.[63] NEC is a devastating bowel disease associated with preterm birth and is the second leading cause of death for preterm infants.[64] Although NEC is a multifactorial disease, human milk has been shown to decrease the risk of developing severe NEC when compared to alternative feedings.[64] Gut dysbiosis is often associated with NEC risk; it results when disease-causing bacteria take over the immature digestive system because of inadequate colonization of beneficial bacteria (prebiotics and probiotics) and lactoferrin.[65–66]

Colostrum, the first milk produced after delivery, offers a concentrated source of protein, vitamins, minerals, and bioactives that colonize the neonatal gut and offer protection from proteobacteria.[67–68.] The provision of colostrum as oral care can be provided for the newborn preemie, even before enteral feedings begin.[69] Swabbing colostrum in the infant's mouth can improve bacterial biodiversity and impart immunity-enhancing benefits.[69–72] It is important to remember, however, that colostrum alone cannot meet the fluid and nutrient needs of the newborn preemie, and PN

will be required in the first days of life for very low birth weight (VLBW) infants.[61]

Preterm MOM is more nutrient-dense than MOM from a mother delivering at term.[28–29,32,61] Protein concentration in early preterm MOM (days 0–14) is an estimated 1 g/dL higher than it will be by the 28th day of lactation.[28–29,32] This downward trend in protein concentration continues throughout lactation. Micronutrients such as sodium and zinc are more concentrated in early preterm milk and decrease significantly over time. Nutrient concentrations naturally change during lactation to suit the maturing infant's needs. As infant feeding volume increases, the concentration of nutrients decreases. As the infant matures past 6 months of life, the time at which solid foods are introduced, the concentration of many nutrients begins to decrease as nutrient demands are met elsewhere through complementary feeds.

Because preterm infants' suck–swallow–breathe coordination does not mature until 32 to 34 weeks of gestational age, they are dependent on tube feedings for up to 12 weeks.[73] During this time of tube-feeding dependence, mothers must express their milk every 3 to 4 hours daily to provide adequate volume to feed their infant.[61] Maintaining lactation during the often lengthy NICU stay is challenging for many mothers. Mother–infant separation, maternal illness that necessitated preterm delivery, family dynamics, lack of access to appropriate lactation counseling and support, socioeconomic status, transportation, and other factors may contribute to a mother's success or failure to maintain lactation.[74] Many pump-dependent mothers experience a reduction in milk supply when they are not able to latch their infant.[75]

Preterm MOM is preferred over other milk sources because of its unique nutrient density and bioactivity. It is imperative that mothers receive timely, appropriate, and continued lactation support and education throughout the NICU stay. Mothers who begin milk expression soon after delivery, preferably within 4 hours, will experience earlier lactogenesis and will sustain lactation longer.[21] Immediate separation of mother and infant may compromise lactogenesis, but separation is often a medical necessity for preterm infants and mothers. In the preterm MOM–baby dyad, immediate lactation support to advance lactogenesis holds particular importance and

requires collaboration from the labor and delivery staff and the NICU staff.[31] Mothers require education on milk expression, access to hospital-grade electric breast pumps/supplies, and guidance on the safe handling and storage of expressed milk. Additional information on the promotion and protection of mother's milk feeding can be found in the American Academy of Breastfeeding Model Maternity Policy Supportive of Breastfeeding.[25]

When MOM is unavailable or low in volume, the current guidance is to provide DHM to complement MOM volume or as a substitute.[2,71] Despite being primarily late-lactational-stage milk, DHM maintains some bioactivity and anti-infective properties that are not found in currently marketed preterm formulas.[72] Some data suggest that DHM reduces the risk of NEC for VLBW (<1500 g) infants during the first month of life.[79–80] However, growth and long-term developmental outcomes may be compromised.[80] Nutrient density (protein, fat, micronutrients) trends down over time and is influenced by milk volume, maternal diet, maternal body mass index (BMI), and environmental factors.[28–29]

Milk donors tend to be in a later lactation stage, and as a result, DHM is less nutrient-dense than MOM.[32,76,81] Protein concentration in DHM is 0.8–1 g/dL, compared with 2.1–2.2 g/dL in early preterm MOM, and 1.5–1.6 g/dL in mature preterm MOM.[28–31] This protein deficit can result in inadequate intake for preterm infants, whose protein demands are 3.5 to 4.5 g/kg/d, which must be consumed in an average of 150 to 160 mL/kg/d. Lipid concentrations are relatively stable in both MOM and DHM, but the capture of lipids in expressed milk depends on the timing of milk expression and lipid loss can be affected by storage containers and feeding tubes.[84] In addition, the heat treatment of DHM reduces bile salt-stimulated lipase, which compromises the absorption of lipids.[85–87]

Sodium concentrations in DHM are one-third of that of preterm MOM (8 mg/dL vs 35 mg/dL).[29] The sodium demands of preterm infants are high compared with the needs of healthy, term infants, and infants with sodium depletion will struggle to maintain adequate growth. In addition, diuretic or ostomy output losses contribute to the need for close monitoring of electrolyte and fluid balance in preterm infants who are fed human milk. Other nutrients of concern for preterm infants fed DHM are iron, zinc,

vitamins C and D, and the fatty acids DHA and ARA (see Table 11-2 for selected nutrient composition).

TABLE 11-2. Nutrient Comparison of Preterm MOM and DHM

Nutrients	Preterm MOM[28–29] Lactation Day 7	Preterm MOM[28–29] Lactation Day 28	DHM[30–32]
Energy, g/dL	66.3 ± 10.7	65.5 ± 9.6	59.38 ± 7.81
Protein, g/dL	2.2 ± 0.08	1.6 ± 0.10	0.8–1.0
Fat, g/dL	3.1 ± 1	3.2 ± 1	2.75 ± 0.84
Sodium, mg/dL	36.1 ± 25	34.5 ± 37.6	8.3
Potassium, mg/dL	64.2 ± 11.4	50.4 ± 11.7	39
Zinc, mg/dL	0.5 ± 0.2	0.4 ± 0.1	0.12–0.17
Calcium, mg/dL	24.2 ± 8.9	21.2 ± 5.5	22–23.7
Phosphorus, mg/dL	15.0 ± 4.8	13.0 ± 3.8	13.2–39

Abbreviations: DHM, donor human milk; MOM, mother's own milk.

Later lactational stage, heat treatment, milk pooling, and maternal dietary variations contribute to the differences in the concentration of these nutrients in DHM as compared to MOM. Preterm infants fed DHM must be closely monitored for growth (weight, length, and head circumference) and nutrient deficiency. Therefore, the clinical emphasis should prioritize MOM during the first month of life to improve nutrient delivery and reduce the risk of feeding-related complications.[64] The early neonatal period is considered a nutritional emergency for preterm infants because the brain should undergo rapid myelination and growth.[62] Nutrient deficits during this period can result in poor neurocognitive outcomes later in life.[8,10,12,88] As infants mature, it is important to prioritize adequate nutrient intake to support brain development. Clinicians should consider transitioning from

DHM to nutrient-dense preterm formula when the risk of inadequate growth outweighs the risk of feeding-related complications.

Human Milk Fortification and Nutrient Supplementation

Multi-nutrient fortification of human milk is commonplace for preterm infants and is usually needed because of the low total volume of milk. Although human milk offers benefits for preterm infants, it alone doesn't meet the high nutrient demands of this population.[33,62] Human milk fortifiers (HMFs) add energy, fat, varying levels of protein, and micronutrients to support growth. HMFs vary in nutrient composition, protein source, and osmolality and are available as partially or extensively hydrolyzed bovine milk or human–milk derived. Bovine milk–derived HMFs are safe and effective for meeting nutrient intake goals when used according to the manufacturer's instructions.[89–92] Human milk–derived HMFs offer an alternative to bovine but are less nutrient-dense and displace more human milk.[93] In blinded randomized clinical trials (RCTs) and meta-analysis, fortification with either bovine or human-derived fortifiers has demonstrated no difference in NEC or death in infants, thus clinicians can utilize either safely. A recent blinded RCT of bovine HMF showed lower NEC rates than those reported in studies using human milk–derived HMFs.[94–95] It is important to remember that the protective effects of fortified human milk come directly from the milk, not from the fortifier. A recent study found that adding either bovine or human milk–derived HMF imparted no benefits to infant microbiome, but rather the source of milk (mother or donor) was the most important factor for gut colonization and protection.[96]

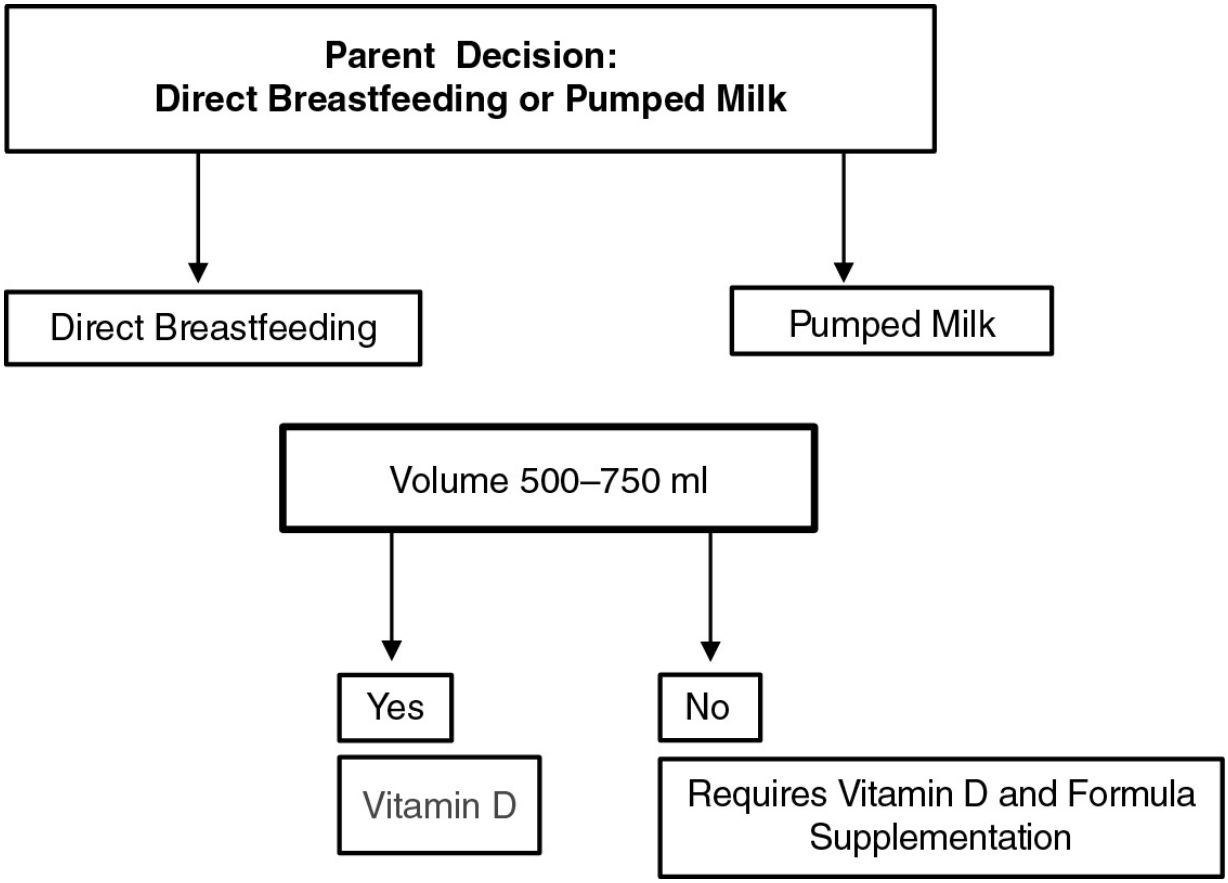
The benefits of human milk are directly proportional to the amount of human milk consumed—the higher the percentage of feeding that comes from human milk, the more benefits imparted.[97–98] The goal of fortification should be to prioritize the provision of MOM or offer DHM when appropriate. When human milk needs to be augmented, clinicians must be careful to limit milk displacement with additives. Concentrated, multi-

nutrient HMFs are preferred as they provide more nutrients in less volume. Sterile, liquid HMFs have been developed that offer protein ranges (2.8–3.3 g/dL) that allow for customization of protein intake based on the individual infant's needs. HMFs with higher protein density will be necessary for preterm infants on low protein DHM or those VLBW infants with protein needs at the upper range (4–4.5 g/kg/d). As the preterm infant ages, the protein requirements decrease, and an HMF with lower protein density can provide the additional protein within the targeted ranges (3–3.5 g/kg/d) while still providing supplemental micronutrients.

The standard dilution recommended by HMF manufacturers is an estimated 24-kcal/oz mixture (5 mL of bovine HMF added to 25 mL of human milk or 20 mL of human-milk-derived HMF added to 80 mL of human milk).[84–88] Increasing energy density beyond 24 kcal/oz will displace more human milk and could increase the osmotic load above 400 mOsm/kg of water.[89–93] Preterm infants may be vulnerable to hyperosmotic feedings, thus, experts advise using caution when feeding solutions with >450 mOsm/dL.[99] It is common practice to use single-nutrient modulars and infant formulas (powders, liquids, liquid concentrates) to fortify human milk. However, these components are not designed to balance the nutrients in human milk and can lead to excessive human milk displacement and hyperosmolality. Ideally, sterile, liquid, multi-nutrient HMFs should be used with preterm infants during NICU hospitalization.

Fortification of human milk may be necessary post discharge for up to 6 weeks of corrected gestational age.[37] The earlier the gestational age at birth, the longer fortification will be needed. Careful monitoring of growth and micronutrient status should guide the decision to transition to unfortified human milk. There are multiple post-discharge strategies for human milk fortification depending on the parents' feeding goals; for example, if direct breastfeeding, providing 3 to 4 feedings per day of nutrient-dense preterm-discharge formula has demonstrated good growth, bone mineralization, and neurodevelopment.[99] Expressed milk feedings can be supplemented by mixing each feed with an HMF or preterm formula. Clinicians should include the family when planning prescriptions. For a parent-centered algorithm to use at discharge, see Figure 11-3.

FIGURE 11-3. Hospitalized Infant: Parent-Centered Feeding Algorithm at Discharge



Term Infants

Hospitalized term infants often have a diagnosis that impacts nutrient requirements, absorption, and delivery. As with preterm infants, hospitalized term infants are separated from their mothers and may undergo surgery and/or intubation, which may temporarily prevent direct breastfeeding. The provision of expressed MOM is important to protect these infants from common infections in immunocompromised infants. Human milk fortification is necessary for term infants who have

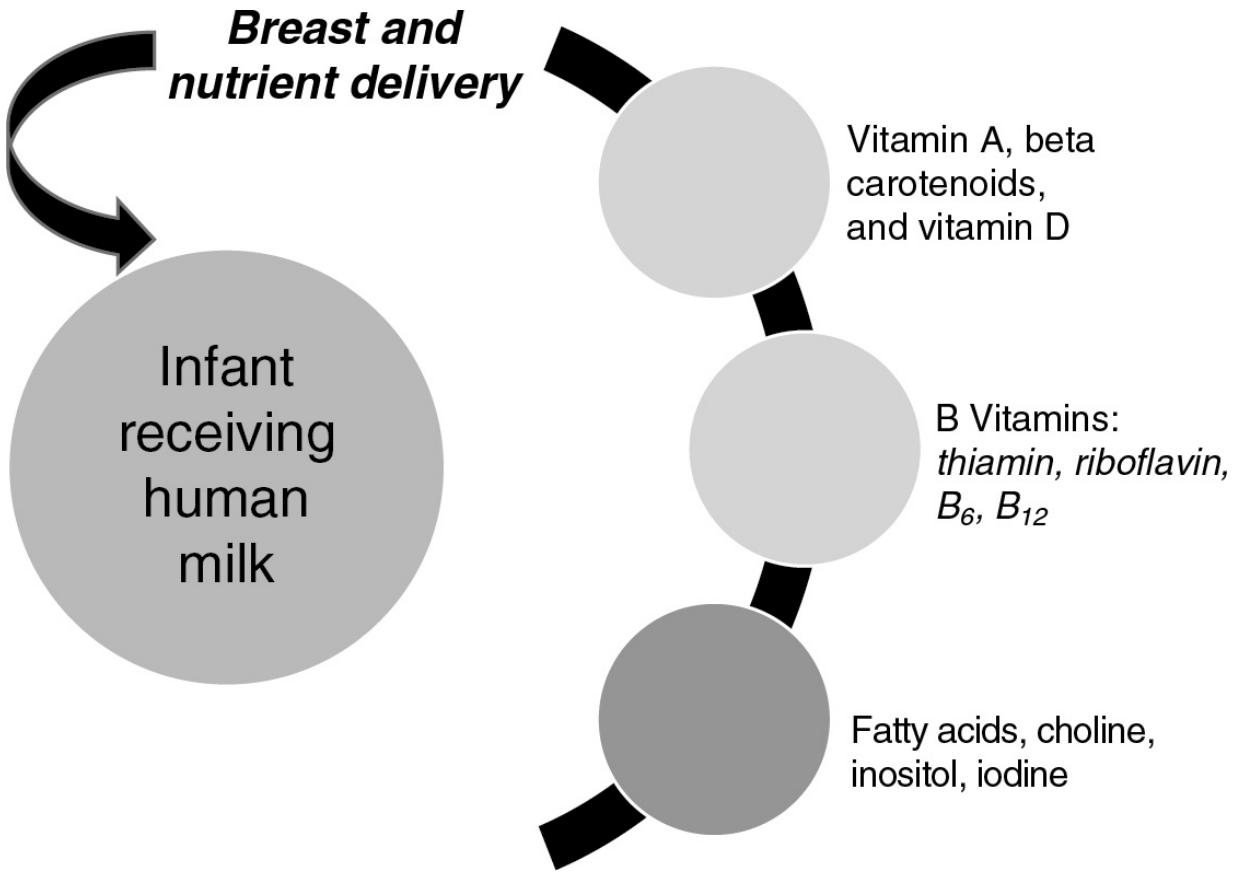
- fluid restrictions (<140 mL/kg/d);
- increased energy needs (with cardiac or pulmonary disorders); and
- excess nutrient losses or poor absorption from diuretic use, ostomies (colostomy, jejunostomy, thoracostomy), dialysis, cystic fibrosis, hepatic, or renal failure.

The supplemental nutrients will depend on the diagnosis. Increased energy needs can be supplemented with pumping practices using hindmilk and single-nutrient modifiers such as fat, protein, or carbohydrate modulars.[100] Nutrient-dense term formulas (24 or 30 kcal/oz) can be used as single feedings to supplement total nutrient intake or can be mixed directly with expressed human milk. There are no HMFs designed specifically for term infants, however, multi-nutrient HMFs can be used (with caution) while monitoring for excessive intake of protein and some micronutrients. Multi-nutrient HMFs or formulas designed for preterm infants should be used with caution when feeding volumes that exceed 500 mL/d.[89–93]

Maternal Diet and Other Factors That Influence Nutrient Composition

The first step in human milk fortification is ensuring adequate maternal intake of some essential nutrients that are diet-dependent. Not all nutrients in human milk can be increased through maternal intake, but the concentration of some nutrients is dependent upon adequate dietary intake. The mammary gland is dependent on dietary sources of vitamins A, B_1, B_2, B_{12}, choline, zinc, and iodine to deliver adequate amounts in the milk for the baby (see Figure 11-4).[32,101,102]

FIGURE 11-4. Maternal Diet Nutrients That Impact Human Milk Composition



Fatty-acid secretion—docosahexaenoic acid (DHA) in particular—is directly correlated to maternal intake of DHA-rich food sources such as cold water fatty fish.[103] Mothers whose diets are high in processed foods, sodium, and energy but low in DHA and other essential nutrients are at higher risk of preterm birth and other pregnancy complications.[104] Pregnant and lactating mothers need nutrient-dense foods, such as salmon, mackerel, tuna, nuts, seeds, and dark green and orange vegetables in their diet. Mothers are often unaware of (or may not be educated on) the need to continue prenatal vitamins postdelivery for these nutrients to impact their milk. Continuing prenatal vitamins during lactation may offset the lack of nutrients in the maternal diet.

The nutrition support team can review key foods or supplements to meet recommended dietary intakes.[105] Lactating mothers should be encouraged to consult with a registered dietitian for healthy diet recommendations

while lactating. Women who meet the economic criteria for inclusion should be referred to the Special Supplemental Nutrition Program for Women, Infants, and Children. This government-funded program offers nutritious foods at no cost to pregnant and lactating mothers. Eligibility information can be found online (https://www.fns.usda.gov/wic).[105]

Protein and fat concentrations in human milk can be affected by maternal BMI, age, and race.[106–110] Mothers with overweight or obesity produce higher concentrations of lipids in their milk.[106–110] In addition, human milk from mothers with obesity has a proinflammatory fatty-acid profile and decreased concentrations of DHA and carotenoids that are known to be critical for neurodevelopmental outcomes and visual development.[111] These findings support the need for nutrition counseling prenatally, as well as during pregnancy and lactation.

In addition to diet and BMI, race and possibly the sex of the infant can influence human milk nutrient composition. In one study, mothers of preterm infants in African American populations had higher protein (2.1 vs 1.5 g/dL) at day 28 of lactation compared with mothers in White populations who delivered prematurely.[29] Some evidence suggests that MOM nutrient concentrations may differ based on the gender of the infant, with higher fat and energy components for mothers who deliver male infants.[109] These findings validate the need for the provision of MOM to vulnerable infants, rather than DHM because MOM is ideally suited for biological infants.

Safe Preparation and Storage

Hospitalized infants who are breastfed depend on expressed human milk. Expression of human milk impacts nutrients such as fat, which can be variable based on milk expression timing; vitamin C, which is vulnerable to light exposure; and bioactive ingredients, which may be diminished during freezing.[112,113] Healthcare facilities should prepare, store, and deliver human milk safely to protect and preserve the milk. Accurate track-and-trace systems must also be in place to prevent incorrect administration of human milk.[113,114]

Expressed human milk is a medium for bacterial growth and is at risk for cross-contamination during milk collection, storage, transport, and delivery.

Parents of hospitalized infants should be provided with instructions on safe milk collection, storage, refrigeration, freezing, and transportation to the hospital. Rigorous hospital policies and procedures should be in place for breast pump sanitation, milk preparation, and fortification. Temperature control is important to prevent bacterial overgrowth, thus, expressed human milk must be stored in refrigerators and freezers that can maintain appropriate temperatures (refrigerator, 35°F–39°F; freezer, –20°F).[113]

Holding times for expressed human milk for hospital use must also be carefully managed to prevent harmful bacteria growth. These holding times depend on several factors, including how and where the milk is stored, whether it is DHM or MOM, and whether it has been fortified. When stored in a hospital refrigerator, 48 hours is recommended, and if frozen, a temperature of –20 degrees Fahrenheit for up to 6–12 months is recommended, recognizing nutrient values may deteriorate.[113] Access to hospital-grade, electric breast pumps and appropriate milk-collection supplies can improve human milk provision for hospitalized infants. More detailed information on the safe preparation of human milk in a hospital setting can be found in *Infant and Pediatric Feedings: Guidelines for Preparation of Human Milk and Formula in Health Care Facilities.*[114]

Maternal Medications and Substance Considerations

Most medications consumed by lactating mothers are compatible with breastfeeding; however, mothers should consult with their healthcare provider to determine whether prescription or over-the-counter medications they are taking are safe.[115] The most current and comprehensive resource on medication safety while breastfeeding is the Drugs and Lactation Database (LactMed), published by the National Institute of Child Health and Human Development. [116]

Moderate alcohol consumption (up to 1 alcoholic beverage per day) is not known to be harmful to breastfeeding infants,[2,117] however, alcohol concentrations in human milk mirror blood alcohol concentrations, peaking 30 to 60 minutes post consumption of alcohol.[117] Therefore, waiting 2 hours after a single drink before breastfeeding or expressing milk may reduce the risk of potential effects of the alcohol on the infant. Consuming

more than 2 standard alcoholic drinks daily while breastfeeding is discouraged.[2,117]

Marijuana use has become more common since its legalization in many states.[115–121] Current data are insufficient to accurately assess the impact of maternal marijuana use during breastfeeding.[2] The transfer of tetrahydrocannabinol (THC) into human milk depends on the type, strength, and duration of THC ingested by the mother, but recent data suggest 60 to 105 ng/ml of THC is transferred into human milk when marijuana is smoked 1 to 7 times per day.[119,120] The American Academy of Pediatrics discourages the use of marijuana while breastfeeding and recommends informing mothers of the potential risk of exposure to THC during lactation.[2] Mothers should be encouraged to abstain from using any marijuana products and avoid secondhand marijuana smoke exposure while lactating.[2,119–121] Breastfeeding mothers should also be encouraged to stop smoking tobacco products and to minimize secondhand exposure.[2,119–121]

Contraindications for Human Milk Feeding

There are few contraindications for breastfeeding or human milk feeding. The Centers for Disease Control and Prevention advises against breastfeeding or feeding expressed human milk under the following circumstances[122]:

- Infant is diagnosed with classic galactosemia.[2]
- Mother has HIV, is not on antiretroviral therapy (ART), and/or does not have a suppressed viral load during pregnancy (at a minimum throughout the third trimester), delivery, and postpartum.
- Mother is infected with human T-cell lymphotropic virus type I or type II (HTLV-1/HTLV-2).[2]
- Mother is using illicit drugs, such as opioids, PCP (phencyclidine), or cocaine (For mothers who discontinue illicit opioids or other substances and are on stable methadone or buprenorphine maintenance therapy, breastfeeding should be encouraged.)[2]
- Mother has suspected or confirmed Ebola virus disease.

In addition, breastfeeding or feeding expressed human milk should be temporarily discontinued under the following conditions[124]:

- Mother is infected with untreated brucellosis.[2]
- Mother is taking certain medications (see "Maternal Medications and Substance Considerations" section).[2]
- Mother is undergoing diagnostic imaging with radiopharmaceuticals.
- Mother has an active herpes simplex virus infection with lesions present on the breast. (Mothers can breastfeed directly from the unaffected breast if lesions on the affected breast are covered completely to avoid transmission.)
- Mother has a monkeypox virus infection. (Breastfeeding should not be resumed until all lesions have resolved, scabs have fallen off, and a fresh layer of intact skin has formed.)[123]
- Mothers with an untreated, active tuberculosis or active varicella (chickenpox) infection. (Feeding expressed milk is ok[2,122] but contact and airborne precautions should be followed per physician recommendations.)

Mothers may resume breastfeeding after consulting with a physician to determine when their milk is safe for their infant. Lactation support should be provided to ensure that milk production is maintained during breastfeeding cessation. In addition, guidance should be given for the use of infant feeding supplements, such as infant formula or previously (as appropriate) expressed human milk, until breastfeeding can resume.

Growth

Infants who are fed human milk should achieve growth according to the expert guidelines for preterm infants and have set reference goals using the WHO growth charts according to the corrected term.[61,124,125] Average weight gain should be 20 g/d, with 1 cm head circumference growth and 1 cm/wk of length gain (measured on a length board). Length boards should be used until 2 years of age and can slide easily in the incubator or crib using a 2-person technique for accuracy.

Conclusion

Human milk is uniquely designed to fulfill the nutritional needs of infants. The numerous bioactive and immunological benefits of human milk help to establish a healthy gut microbiome and immune system. Human milk changes in nutritional composition over time, gradually declining in nutrient concentrations to match the volume and needs of the infant. Maternal diet, lifestyle, and health impact the nutrients in human milk, thus, healthcare providers must recognize that mothers play a critical role in the provision of the most nutritionally robust milk possible. Dietary guidance should emphasize healthful meals that are rich in omega-3-rich fish, eggs, nuts, and seeds, as well as dark green and orange vegetables. Early and ongoing lactation support will help to establish breastfeeding and maintain lactation as long as desired by the mother and baby. Healthcare facilities should develop protocols that provide supportive care so that mothers and families can make the best choices for their infants.

Hospitalized infants who are sick or were born preterm depend on expressed human milk, either MOM or DHM, rather than direct breastfeeding. Because of the increased dietary needs of these infants, the nutrient profile of milk used must be carefully considered to match the individual infant's needs. Multi-nutrient or single-nutrient supplementation or fortification may also be required to meet the nutritional needs of this vulnerable population. The nutrition support team or clinician can provide guidance and solutions regarding human milk feeding for at-risk infants.

Test Your Knowledge Questions

1. What are the possible causes of delayed lactogenesis II?
   A. Prior surgical augmentation of the breast
   B. Restarting hormonal contraception
   C. Stress
   D. All of the above
2. Which of the following components of human milk provide immune health benefits?
   A. Milk proteins
   B. Long-chain polyunsaturated fatty acids

C. Lactoferrin
D. Cholesterol

3. Which of the following statements is correct about DHM compared with MOM?
   A. DHM is usually more nutrient-dense than MOM
   B. DHM has less abundant oligosaccharides than MOM
   C. DHM contains no bioactives, similar to infant formulas.
   D. DHM has a higher protein concentration compared with early preterm MOM

References

1. U.S. Department of Health and Human Services. Healthy People 2030: Increase the proportion of infants who are breastfed at 1 year—MICH 16. Accessed February 26, 2023. https://health.gov/healthypeople/objectives-and-data/browse-objectives/infants/increase-proportion-infants-who-are-breastfed-1-year-mich-16
2. Meek JY, Noble L. Section on Breastfeeding. American Academy of Pediatrics policy statement: breastfeeding and the use of human milk. *Pediatrics*. 2022;150(1):e2022057988. https://doi.org/10.1542/peds.2022-057988
3. Centers for Disease Control and Prevention. *Breastfeeding Report Card, United States 2022*. Accessed February 26, 2023. https://www.cdc.gov/breastfeeding/data/reportcard.htm
4. U.S. Department of Health and Human Services. Healthy People 2030: Increase the proportion of infants who are breastfed exclusively through age 6 months—MICH 15. Accessed February 26, 2023. https://health.gov/healthypeople/objectives-and-data/browse-objectives/infants/increase-proportion-infants-who-are-breastfed-exclusively-through-age-6-months-mich-15
5. WHO Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries:

a pooled analysis. *Lancet*. 2000;355:451–455. https://doi.org/10.1016/S0140-6736(00)82011-5
6. Li R, Ware J, Chen A, et al. Breastfeeding and post-perinatal deaths in the United States, a national perspective cohort analysis. *Lancet Reg Health Am*. 2022;5:100094. https://doi.org/10.1016/j.lana.2021.100094
7. Gillman MW, Rifas-Shiman SL,Camargo CA, et al. Risk of overweight among adolescents who were breastfed as infants. *JAMA*. 2001;285(9): 2461–2467. https://doi.org/10.1001/jama.285.19.2461
8. Deoni S, Dean D, Johnson S, et al. Early nutrition influences developmental myelination and cognition in infants and young children. *Neuroimage*. 2018;178:649–659. https://doi.org/10.1016/j.neuroimage.2017.12.056
9. Vohr BR, Poindexter BB, Dusick AM, et al.; NICHD Neonatal Research Network. Beneficial effects of breast milk in the neonatal intensive care unit on the developmental outcome of extremely low birth weight infants at 18 months of age. *Pediatrics*. 2006; 118(1):e115–e123. https://doi.org/10.1542/peds.2005-2382
10. Belfort MB, Knight E, Chandarana S, et al. Associations of maternal milk feeding with neurodevelopmental outcomes at 7 years of age in former preterm infants. *JAMA Netw Open*. 2022;5(7):e2221608. https://doi.org/10.1001/jamanetworkopen.2022.21608
11. Schwarzenberg SJ, Georgieff MK; AAP Committee on Nutrition. Advocacy for improving nutrition in the first 1000 days to support childhood development and adult health. *Pediatrics*. 2018;141(2):e20173716. https://doi.org/10.1542/peds.2017-3716
12. Georgieff MK. Early life nutrition and brain development: breakthroughs, challenges, and new horizons. *Proc Nutr Soc*. 2022:1–9. https://doi.org/10.1017/S0029665122002774
13. Neville MC, Morton J. Physiology and endocrine changes underlying human lactogenesis II. *J Nutr*. 2001;131:3005S-3008S. https://doi.org/10.1093/jn/131.11.3005S
14. Neville MC, Keller R, Seacat J, et al. Studies in human lactation: milk volumes in lactating women during the onset of lactation and full lactation. *Am J Clin Nutr*. 1988;48:1375–1386. https://doi.org/10.1093/ajcn/48.6.1375

15. Lawrence RA. Physiology of lactation. In: Lawrence RA, Lawrence RM. *Breastfeeding: A Guide for the Medical Professional*. 9th ed. Elsevier; 2022:58–92.
16. Hoban R, Bigger H, Schoeny M, Engstrom J, Meier P, Patel AL. Milk volume at 2 weeks predicts mother's own milk feeding at neonatal intensive care unit discharge for very low birthweight infants. *Breastfeed Med*. 2018;13(2):135–141. https://doi.org/10.1089/bfm.2017.0159
17. Chapman DJ, Young S, Ferris AM, et al. Impact of breast pumping on lactogenesis stage II after caesarean delivery: a randomized clinical trial. *Pediatrics*. 2001;107:e94. https://doi.org/10.1542/peds.107.6.e94
18. Lau C, Hurst NM, Smith EO, Schanler RJ. Ethnic/racial diversity, maternal stress, lactation, and very low birthweight infants. *J Perinatol*. 2007;27(7):399–408. https://doi.org/10.1038/sj.jp.7211770
19. Lawrence RA, Lawrence RM. Breastfeeding in a new era. In: Lawrence RA, Lawrence RM. *Breastfeeding: A Guide for the Medical Professional*. 9th ed. Elsevier; 2022:1–37.
20. Geraghty S, Davidson B, Tabangin M, Morrow A. Predictors of breastmilk expression by 1 month postpartum and influence on breastmilk feeding duration. *Breastfeed Med*. 2012;7(2):112–117. https://doi.org/10.1089/bfm.2011.0029
21. Lawrence RA, Lawrence RM. Premature infants and breastfeeding. In: Lawrence RA, Lawrence RM. *Breastfeeding: A Guide for the Medical Professional*. 9th ed. Elsevier; 2022: 502–545. https://doi.org/10.1016/b978-0-323-68013-4.00014-6
22. Li L, Wang L, Niu C, et al. Early skin contact combined with mother's breastfeeding to shorten the process of premature infants ≤ 30 weeks of gestation to achieve full oral feeding: the study protocol of a randomized controlled trial. *Trials*. 2021;22(1):637. https://doi.org/10.1186/s13063-021-05605-x
23. Maastrup R, Rom AL, Walloee S, Sandfeld HB, Kronborg H. Improved exclusive breastfeeding rates in preterm infants after a neonatal nurse training program focusing on six breastfeeding-supportive clinical practices. *PLoS One*. 2021;16(2):e0245273. https://doi.org/10.1371/journal.pone.0245273

24. Adams JM, Valentine CJ, Karns RA, et al. DHA supplementation attenuates inflammation-associated gene expression in the mammary gland of lactating mothers who deliver preterm. *J Nutr*. 2022;152(6):1404–1414. https://doi.org/10.1093/jn/nxac043
25. Hernandez-Aguilar MT, Bartick M, Schreck P, Harrel C; Academy of Breastfeeding Medicine. Appendix I - ABM clinical protocol #7: Model maternity policy supportive of breastfeeding. In: Lawrence RA, Lawrence RM, eds. *Breastfeeding: A Guide for the Medical Professional*. 9th ed. Elsevier; 2022:830–846.
26. Goldman AS, Goldblum RM, Garza C. Immunologic components in human milk during the second year of lactation. *Acta Paediatr Scand*. 1983;72(3):461. https://doi.org/10.1111/j.1651-2227.1983.tb09748.x
27. Casavale KO, Ahuja JKC, Wu X, et al. NIH workshop on human milk composition. *Am J Clin Nutr*. 2019;110:769–779. https://doi.org/10.1093/ajcn/nqz123
28. Gates A, Marin T, Leo G, Stansfield BK. Review of preterm human-milk nutrient composition. *Nutr Clin Pract*. 2021;36(6):1163–1172. https://doi.org/10.1002/ncp.10570
29. Gates A, Marin T, De Leo G, Waller JL, Stansfield BK. Nutrient composition of preterm mother's milk and factors that influence nutrient content. *Am J Clin Nutr*. 2021;114(5):1719–1728. https://doi.org/10.1093/ajcn/nqab226
30. Piemontese P, Mallardi D, Liotto N, et al. Macronutrient content of pooled donor human milk before and after Holder pasteurization. *BMC Pediatr*. 2019;19(1):58. https://doi.org/10.1186/s12887-019-1427-5
31. Perrin MT, Belfort MB, Hagadorn JI, et al. The nutritional composition and energy content of donor human milk: a systematic review. *Adv Nutr*. 2020;11(4):960–970. https://doi.org/10.1093/advances/nmaa014
32. Gates A, Hair AB, Salas AA, Thompson AB, Stansfield BK. Nutrient composition of donor human milk and comparisons to preterm human milk. *J Nutr*. 2023;153(9):2622–2630. https://doi.org/10.1016/j.tjnut.2023.07.012
33. Butts CA, Hedderley DJ, Herath TD, et al. Human milk composition and dietary intakes of breastfeeding women of different ethnicity from

Manawatu-Wanganui region of New Zealand. *Nutrients*. 2018:1–16. https://doi.org/10.3390/nu10091231
34. Valentine CJ, Wagner CL. Nutritional management of the breastfeeding dyad. *Pediatr Clin North Am*. 2013;60(1):261–274. https://doi.org/10.1016/j.pcl.2012.10.008
35. Gidrewicz DA, Fenton TR. A systematic review and meta-analysis of the nutrient content of preterm and term breastmilk. *BMC Pediatr.* 2014;14:216. https://doi.org/10.1186/1471-2431-14-216
36. American Academy of Pediatrics Committee on Nutrition. Nutritional needs of the preterm infant. In: Kleinman RE, Greer FR, eds. *Pediatric Nutrition*. 8th ed. American Academy of Pediatrics; 2019:113–162.
37. Villavicencio A, Rueda MS, Turin CG, Ochoa TJ. Factors affecting lactoferrin concentration in human milk: how much do we know? *Biochem Cell Biol*. 2017;95(1):12–21. https://doi.org/10.1139/bcb-2016-0060
38. Lönnerdal B. Lactoferrin in milk. *Ann Nestlé*. 1996;54(3):79.
39. Gonzãlez Chãvez SA, Arévalo-Gallegos S, Rascón-Cruz Q. Lactoferrin structure, function and applications. *Int J Antimicrob Agents*. 2009;33(301):e1–e8. https://doi.org/10.1016/j.ijantimicag.2008.07.020
40. Lönnerdal B. Nutritional roles of lactoferrin. *Curr Opin Med Nutr Metab Care*. 2009;12:293–297. https://doi.org/10.1097/mco.0b013e328328d13e
41. Dingess KA, van Dam P, Zhu J, et al. Optimization of human milk-directed quantitative sIgA ELISA method substantiated by mass spectrometry. *Anal Bioanal Chem.* 2021;413:5037–5049. https://doi.org/10.1007/s00216-021-03468-4
42. Doare KL, Bellis K, Faal A, et al. SIgA, TGF-B1, IL-10, and TNF in colostrum are associated with infant Group B Streptococcus colonization. *Front Immunol*. 2017;8:1269. https://doi.org/10.3389/fimmu.2017.01269
43. Goldman AS, Goldblum RM. Transfer of maternal leukocytes to the infant by human milk. *Curr Top Microbiol Immunol*. 1997;222:205–213. https://doi.org/10.1007/978-3-642-60614-4_10

44. Goldman AS, Garza C, Nichols BL, et al. Immunologic factors in human milk during the first year of lactation. *J Pediatr*. 1982;100(4):563. https://doi.org/10.1016/s0022-3476(82)80753-1
45. Pickering LK, Kohl S. Human milk humoral immunity and infant defense mechanisms. In: Howell RR, Morriss RH, Pickering LK, eds. *Human Milk in Infant Nutrition and Health*. Charles C Thomas; 1986.
46. Donovan SM, Comstock SS. Human milk oligosaccharides influence neonatal mucosal and systemic immunity. *Ann Nutr Metab*. 2016;69(suppl 2):42–51 https://doi:10.1159/000452818.
47. Doherty AM, Lodge CJ, Dharmage SC, et al. Human milk oligosaccharides and associations with immune-mediated disease and infection in childhood: a systematic review. *Front Pediatr*. 2018;6:91–99. https://doi.org/10.3389/fped.2018.00091.
48. Coppa GV, Gabrielli O, Pierani P, et al. Changes in carbohydrate composition in human milk over 4 months of lactation. *Pediatrics*. 1993;91(3):637–641. https://doi.org/10.1542/peds.91.3.637
49. Innis SM. Omega-3 Fatty acids and neural development to 2 years of age: do we know enough for dietary recommendations? *J Pediatr Gastroenterol Nutr*. 2009;48 (suppl 1):S16–S24. https://doi.org/10.1097/mpg.0b013e31819773cf
50. Innis SM. Dietary omega 3 fatty acids and the developing brain. *Brain Res*. 2008;1237:35–43. https://doi.org/10.1016/j.brainres.2008.08.078
51. Deoni S, Dean D 3rd, Joelson S, O'Regan J, Schneider N. Early nutrition influences developmental myelination and cognition in infants and young children. *Neuroimage*. 2018;178:649–659. https://doi.org/10.1016/j.neuroimage.2017.12.056
52. Copp K, DeFranco EA, Kleiman J, Rogers LK, Morrow AL, Valentine CJ. Nutrition support team guide to maternal diet for the human-milk-fed infant. *Nutr Clin Pract*. 2018;33(5):687–693. https://doi.org/10.1002/ncp.10071
53. Wei W, Yang J, Yang D, et al. Phospholipid composition and fat globule structure I: comparison of human milk fat from different gestational ages, lactation stages, and infant formulas. *J Agric Food Chem*. 2019;67(50):13922–13928. https://doi.org/doi:10.1021/acs.jafc.9b04247

54. Albi E, Arcuri C, Kobayashi T, et al. Sphingomyelin in human breast milk might be essential for the hippocampus maturation. *Front Biosci (Landmark Ed)*. 2022;27(8):247. https://doi.org/10.31083/j.fbl2708247
55. Bosco A, Toto M, Pintus R, Fanos V, Dessì A. Human milk sphingomyelins and metabolomics: an enigma to be discovered. *J Matern Fetal Neonatal Med*. 2022;35(25):7649–7661. https://doi.org/10.1080/14767058.2021.1958314
56. Liu Q, Zhao J, Liu 刘妍 Y, et al. Study on the characteristics of glycerides and phospholipids in human milk from Tibet. *Food Res Int*. 2022;157:111025. https://doi.org/10.1016/j.foodres.2022.111025
57. Rogers SP, Hicks PD, Hamzo M, Veit LE, Abrams SA. Continuous feedings of fortified human milk lead to nutrient losses of fat, calcium and phosphorous. *Nutrients*. 2010;2(3):230–240. https://doi.org/10.3390/nu2030240
58. Jarjour J, Juarez AM, Kocak DK, et al. A Novel approach to improving fat delivery in neonatal enteral feeding. *Nutrients*. 2015;7(6):5051–5064. https://doi.org/10.3390/nu7065051
59. Zeisel SH, Char D, Sheard NF. Choline, phosphatidylcholine and sphingomyelin in human and bovine milk and infant formulas. *J Nutr*. 1986;116(1):50–58. https://doi.org/10.1093/jn/116.1.50
60. Schneider N, Hauser J, Oliveira M, et al. Sphingomyelin in brain and cognitive development: preliminary data. *eNeuro*. 2019;6(4):ENEURO.0421-18.2019. https://doi.org/10.1523/ENEURO.0421-18.2019
61. Koletzko B, Cheah F-C, Domellöf M, Poindexter BB, Vain N, van Goudoever JB, eds. Nutritional care of preterm infants: scientific basis and practical guidelines. *World Rev Nutr Diet*. 2021; 122:140–148. https://doi.org/10.1159/000514738
62. Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. *Pediatrics*. 2006;117(4):1253–1261. https://doi.org/10.1542/peds.2005-1368
63. Miller J, Tonkin E, Damarell RA, et al. A systematic review and meta-analysis of human milk feeding and morbidity in very low birth

weight infants. *Nutrients*. 2018;10(6):707. https://doi.org/10.3390/nu10060707
64. Juul SE, Wood TR, Comstock BA, et al. Deaths in a modern cohort of extremely pre term infants from the preterm erythropoietin neuroprotection trial. *JAMA Netw Open*. 2022;5(2):e2146404. https://doi.org/10.1001/jamanetworkopen.2021.46404
65. Cuna A, Morowitz MJ, Ahmed I, Umar S, Sampath V. Dynamics of the preterm gut microbiome in health and disease. *Am J Physiol Gastrointest Liver Physiol*. 2021;320(4):G411–G419. https://doi.org/10.1152/ajpgi.00399.2020
66. Pammi M, Cope J, Tarr PI, et al. Intestinal dysbiosis in preterm infants preceding necrotizing enterocolitis: a systematic review and meta-analysis. *Microbiome*. 2017;5(1):31. https://doi.org/10.1186/s40168-017-0248-8
67. Ballard O, Morrow AL. Human milk composition: nutrients and bioactive factors. *Pediatr Clin North Am*. 2013;60(1):49–74. https://doi.org/10.1016/j.pcl.2012.10.002
68. Palmeira P, Carneiro-Sampaio M. Immunology of breast milk. *Rev Assoc Med Bras*. 2016;62(6):584–593. https://doi.org/10.1590/1806-9282.62.06.584
69. Rodriguez NA, Meier PP, Groer MW, Zeller JM. Oropharyngeal administration of colostrum to extremely low birth weight infants: theoretical perspectives. *J Perinatol*. 2009;29(1):1–7. https://doi.org/10.1038/jp.2008.130
70. Gephart SM, Weller M. Colostrum as oral immune therapy to promote neonatal health. *Adv Neonatal Care*. 2014;14(1):44–51. https://doi.org/10.1097/ANC.0000000000000052
71. OuYang X, Yang CY, Xiu WL, Hu YH, Mei SS, Lin Q. Oropharyngeal administration of colostrum for preventing necrotizing enterocolitis and late-onset sepsis in preterm infants with gestational age ≤32 weeks: a pilot single-center randomized controlled trial. *Int Breastfeed J*. 2021;16(1):59. https://doi.org/10.1186/s13006-021-00408-x
72. Maraboli Aguilera M, Lavanderos Bustamante G, León Martínez C, Zúñiga Ulloa M, Mena Nannig P. Evaluación de un protocolo de calostro para prematuros de muy bajo peso de nacimiento [Colostrum

protocol evaluation for very low birth weight preterm infants]. *Andes Pediatr*. 2022;93(3):343–350. https://doi.org/doi:10.32641/andespediatr.v93l3.3870
73. Ghomi H, Yadegari F, Soleimani F, Knoll BL, Noroozi M, Mazouri A. The effects of premature infant oral motor intervention (PIOMI) on oral feeding of preterm infants: a randomized clinical trial. *Int J Pediatr Otorhinolaryngol*. 2019;120:202–209. https://doi.org/10.1016/j.ijporl.2019.02.005
74. Parker MG, Stellwagen LM, Noble L, et al. Promoting human milk and breastfeeding for the very low birth weight infant. *Pediatrics*. 2021;148(5):e2021054272. https://doi.org/10.1542/peds.2021-054272
75. Bendixen MM, Weaver MT, Parker LA. Milk volume outcomes in pump-dependent mothers of critically ill infants. *Adv Neonatal Care*. 2022;22(3):253–260. https://doi.org/10.1097/ANC.0000000000008881
76. American Academy of Pediatrics Committee on Nutrition. Nutritional needs of the preterm infant. In: Kleinman RE, Greer FR, eds. *Pediatric Nutrition*, 8th ed. American Academy of Pediatrics; 2019:113–162.
77. Valentine CJ, Morrow G, Reisinger A, Dingess KA, Morrow AL, Rogers LK. Lactational stage of pasteurized human donor milk contributes to nutrient limitations for infants. *Nutrients*. 2017;9(3):302. https://doi.org/10.3390/nu9030302
78. Corpeleijn WE, de Waard M, Christmann V, et al. Effect of donor milk on severe infections and mortality in very low-birth-weight infants: the early nutrition study randomized clinical trial. *JAMA Pediatr*. 2016;170(7):654–661. https://doi.org/10.1001/jamapediatrics.2016.0183
79. Quigley M, Embleton ND, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. *Cochrane Database Syst Rev*. 2018;6(6):CD002971. https://doi.org/doi:10.1002/14651858.CD002971.pub4
80. Madore LS, Bora S, Erdei C, Jumani T, Dengos AR, Sen S. Effects of donor breastmilk feeding on growth and early neurodevelopmental outcomes in preterm infants: an observational study. *Clin Ther*.

2017;39(6):1210–1220. https://doi.org/10.1016/j.clinthera.2017.05.341
81. Cooper AR, Barnett D, Gentles E, Cairns L, Simpson JH. Macronutrient content of donor human breast milk. *Arch Dis Child Fetal Neonatal Ed*. 2013;98(6):F539–F541. https://doi.org/10.1136/archdischild-2013-304422
82. Koh J, Victor AF, Howell ML, et al. Bile salt-stimulated lipase activity in donor breast milk influenced by pasteurization techniques. *Front Nutr*. 2020;7:552362. https://doi.org/10.3389/fnut.2020.552362
83. Brooks C, Vickers AM, Aryal S. Comparison of lipid and calorie loss from donor human milk among 3 methods of simulated gavage feeding: one-hour, 2-hour, and intermittent gravity feedings. *Adv Neonatal Care*. 2013;13(2):131–138. https://doi.org/10.1097/ANC.0b013e31827e225b
84. Koh J, Victor AF, Howell ML, et al. Bile salt-stimulated lipase activity in donor breast milk influenced by pasteurization techniques. *Front Nutr*. 2020;7:552362. https://doi.org/10.3389/fnut.2020.552362
85. Hernell O, Bläckburg L. Human milk bile salt-stimulated lipase: functional and molecular aspects. *J Pediatr*. 1994;125:S56–S61. https://doi.org/10.1016/s0022-3476(06)80737-7
86. Casper C, Carnielli VP, Hascoet J-M. BSSL improves growth and LCPUFA absorption in preterm infants fed formula or pasteurized breast milk. *J Pediatr Gastroenterol Nutr*. 2014;59:61–69. https://doi.org/10.1097/mpg.0000000000000365
87. Hopperton KE, O'Connor DL, Bando N, et al. Nutrient enrichment of human milk with human and bovine milk-based fortifiers for infants born <1250 g: 18-month neurodevelopment follow-up of a randomized clinical trial. *Curr Dev Nutr*. 2019;3(12):nzz129. https://doi.org/10.1093/cdn/nzz129
88. Enfamil Human Milk Fortifiers. Mead Johnson Nutrition. Healthcare Professionals Resource Center. Accessed July 5, 2022. https://www.hcp.meadjohnson.com/s/product/a4R4J000000Q3RxUAK/enfamil-human-milk-fortifiers
89. Similac Human Milk Fortifier Hydrolyzed Protein Concentrated Liquid. Abbott For Healthcare Professionals. Accessed July 5, 2022.

https://abbottnutrition.com/similac-human-milk-fortifier-hydrolyzed-protein-concentrated-liquid
90. Moya F, Sisk PM, Walsh KR, Berseth CL. A new liquid human milk fortifier and linear growth in preterm infants. *Pediatrics*. 2012;130(4):e928–e935. https://doi.org/10.1542/peds.2011-3120d
91. Kim JH, Chan G, Schanler R, et al. Growth and tolerance of preterm infants fed a new extensively hydrolyzed liquid human milk fortifier. *J Pediatr Gastroenterol Nutr*. 2015;61(6):665–671. https://doi.org/10.1097/MPG.0000000000001010
92. Prolacta Human Milk Fortifiers. Prolacta Bioscience. Accessed February 22, 2024. https://www.prolacta.com/en/resource-library/understanding-human-milk-fortifiers/
93. O'Connor DL, Kiss A, Tomlinson C, et al. Nutrient enrichment of human milk with human and bovine milk-based fortifiers for infants born weighing <1250 g: a randomized clinical trial. *Am J Clin Nutr*. 2018;108(1):108–116. https://doi.org/10.1093/ajcn/nqy067
94. Schanler RJ, Groh-Wargo SL, Barrett-Reis B, et al. Improved outcomes in preterm infants fed a nonacidified liquid human milk fortifier: a prospective randomized clinical trial. *J Pediatr*. 2018;202:31–37.e2. https://doi.org/doi:10.1016/j.jpeds.2018.07.005
95. Kumbhare SV, Jones WD, Fast S, et al. Source of human milk (mother or donor) is more important than fortifier type (human or bovine) in shaping the preterm infant microbiome. *Cell Rep Med*. 2022;3(9):100712. https://doi.org/10.1016/j.xcrm.2022.100712
96. Meinzen-Derr J, Poindexter B, Wrage L, Morrow AL, Stoll B, Donovan EF. Role of human milk in extremely low birth weight infants' risk of necrotizing enterocolitis or death. *J Perinatol*. 2009;29(1):57–62. https://doi.org/10.1038/jp.2008.117
97. Corpeleijn WE, Kouwenhoven SM, Paap MC, et al. Intake of own mother's milk during the first days of life is associated with decreased morbidity and mortality in very low birth weight infants during the first 60 days of life. *Neonatology*. 2012;102(4):276–281. https://doi.org/10.1159/000341335
98. Embleton ND, Moltu SJ, Lapillonne A, et al. Enteral nutrition in preterm infants: a position paper from the ESPGHAN Committee on Nutrition and Invited Experts. *J Pediatr Gastroenterol Nutr*.

2023;76(2):248–268. https://doi.org/10.1097/MPG.0000000000003642
99. Valentine CJ, Hurst NM, Schanler RJ. Hindmilk improves weight gain in low-birth-weight infants fed human milk. *J Pediatr Gastroenterol Nutr*. 1994;18(4):474–477. https://doi.org/10.1097/00005176-199405000-00013
100. Allen LH. Multiple micronutrients in pregnancy and lactation: an overview. *Am J Clin Nutr*. 2005;81(5):1206S-1212S. https://doi.org/10.1093/ajcn/81.5.1206
101. Bzikowska-Jura, A, Sobieraj P, Michaleska-Kacymirow M, Wesolowska A. Investigation iron and zinc concentrations in human milk in correlation to maternal factors: an observational pilot study in Poland. *Nutrients.* 2021; 303. https://doi.org/10.3390/nu13020303
102. Omega-3 fatty acids. U.S Department of Health and Human Services, Office of Dietary Supplements. Accessed March 14, 2023. https://ods.od.nih.gov/factsheets/Omega3FattyAcids-Consumer/
103. Valentine CJ, Khan AQ, Brown AR, et al. Higher-dose DHA supplementation modulates immune responses in pregnancy and is associated with decreased preterm birth. *Nutrients*. 2021;13(12):4248. https://doi.org/10.3390/nu13124248
104. Khelouf N, Haoud K, Meziani S, et al. Effect of infant's gender and lactation period on biochemical and energy breast milk composition of lactating mothers from Algeria, *J Food Composit and Anal*. 2023;115:104889. https://doi.org/10.1016/j.jfca.2022.104889
105. Special Supplemental Nutrition Program for Women, Infants, and Children: Am I Eligible for WIC? U. S. Department of Agriculture, Food and Nutrition Service. Accessed March 13, 2023. https://www.fns.usda.gov/wic
106. Daniel A, Shama S, Ismail S, et al. Maternal BMI is positively associated with human milk fat: a systematic review and meta-regression analysis. *Am J of ClNutr*. 2021;113(4):1009–1022. https://doi.org/10.1093/ajcn/nqaa410
107. Leghi GE, Netting MJ, Middleton PF, Wlodek ME, Geddes DT, Muhlhausler BS. The impact of maternal obesity on human milk macronutrient composition: a systematic review and meta-analysis. *Nutrients*. 2020; 12(4):934. https://doi.org/10.3390/nu12040934

108. Galante L, Milan AM, Reynolds CM, Cameron-Smith D, Vickers MH, Pundir S. Sex-specific human milk composition: the role of infant sex in determining early life nutrition. *Nutrients*. 2018;10(9):1194. https://doi.org/10.3390/nu10091194
109. Burianova I, Bronsky J, Pavilkova M, Janota J, Maly J. Maternal body mass index, parity and smoking are associated with human milk macronutrient content after preterm delivery. *Early Hum Dev*. 2019;137:104832. https://doi.org/10.1016/j.earlhumdev.2019.104832
110. Panagos PG, Vishwanathan R, Penfield-Cyr A, et al. Breastmilk from obese mothers has pro-inflammatory properties and decreased neuroprotective factors. *J Perinatol*. 2016;36(4):284–290. https://doi.org/10.1038/jp.2015.199
111. García-Lara NR, Escuder-Vieco D, García-Algar O, De la Cruz J, Lora D, Pallás-Alonso C. Effect of freezing time on macronutrients and energy content of breastmilk. *Breastfeed Med*. 2012;7(4):295–301. https://doi.org/10.1089/bfm.2011.0079
112. Italianer MF, Naninck EFG, Roelants JA, et al. Circadian variation in human milk composition, a systematic review. *Nutrients*. 2020;12(8):2328. https://doi.org/10.3390/nu12082328
113. Steele C, Bixby C. Centralized breastmilk handling and bar code scanning improve safety and reduce breastmilk administration errors. *Breastfeed Med*. 2014;9(9):426–429. https://doi.org/10.1089/bfm.2014.0077
114. Steele C, Collins E. *Infant and Pediatric Feedings: Guidelines for Preparation of Human Milk and Formula in Health Care Facilities*. 3rd ed. The American Academy of Nutrition and Dietetics; 2019.
115. Hale TW, Krutsch K. *Hale's Medications & Mothers' Milk*. 12th ed. Springer Publishing; 2023.
116. Drugs and Lactation Database (LactMed®). National Institute of Child Health and Human Development, National Institutes of Health. Accessed November 14, 2023. https://www.ncbi.nlm.nih.gov/books/NBK501922/?report=classic
117. Haastrup MB, Pottegård A, Damkier P. Alcohol and breastfeeding. *Basic Clin Pharmacol Toxicol*. 2014;114(2):168–173. https://doi.org/10.1111/bcpt.12149

118. Zellers SM, Ross JM, Saunders GRB, et al. Impacts of recreational cannabis legalization on cannabis use: a longitudinal discordant twin study. *Addiction*. 2023;118(1):110–118. https://doi.org/10.1111/add.16016
119. Ryan S, Ammerman S, O'Connor M; Committee on Substance Use and Prevention, Section on Breastfeeding. Marijuana use during pregnancy and breastfeeding: implications for neonatal and childhood outcomes. *Pediatrics*. 2018;142 (3): e20181889. https://doi.org/10.1542/peds.2018-1889
120. Perez-Reyes M, Wall ME. Presence of delta9-tetrahydrocannabinol in human milk. *N Engl J Med*. 1982;307(13):819–820. https://doi.org/10.1056/nejm198209233071311
121. Marchei E, Escuder D, Pallas CR, et al. Simultaneous analysis of frequently used licit and illicit psychoactive drugs in breast milk by liquid chromatography tandem mass spectrometry. *J Pharm Biomed Anal*. 2011;55(2):309–316. https://doi.org/10.1016/j.jpba.2011.01.028
122. Contraindications to breastfeeding or feeding expressed breast milk to infants. Centers for Disease Control and Prevention. Accessed February 26, 2023. https://www.cdc.gov/breastfeeding/breastfeeding-special-circumstances/contraindications-to-breastfeeding.html
123. Clinical considerations for Mpox in people who are pregnant and breastfeeding. Centers for Disease Control and Prevention. Accessed February 26, 2023. http://www.cdc.gov/poxvirus/monkeypox/clinicians/pregnancy.html
124. Fenton TR, Nasser R, Eliasziw M, Kim JH, Bilan D, Sauve R. Validating the weight gain of preterm infants between the reference growth curve of the fetus and the term infant. *BMC Pediatr*. 2013;13:92. https://doi.org/10.1186/1471-2431-13-92
125. WHO growth standards are recommended for use in the U.S. for infants and children 0 to 2 years of age. Centers for Disease Control and Prevention, National Center for Health Statistics. Accessed September 5, 2023. https://www.cdc.gov/growthcharts/who_charts.htm#The%20WHO%20Growth%20Charts

Test Your Knowledge Questions Answers

1. The correct answer is **D**. Delays in lactogenesis II can be the result of hormonal, surgical augmentation, stress, hormonal contraception, or lack of breast emptying.
2. The correct answer is **C**. The most compelling components translating to human studies have included specifically lactoferrin, sIgA, lysozyme, and HMOs.
3. The correct answer is **B**. Milk donors tend to be in a later lactation stage, thus the DHM is less nutrient-dense than MOM. DHM has less abundant HMOs compared to MOM. Despite being primarily late-lactational-stage milk, DHM maintains some of the human milk's bioactivity and anti-infective properties that are not found in currently marketed preterm formulas. Protein concentration in DHM is 0.8–1 g/dL compared to 2.1–2.2 g/dL in early preterm MOM, and 1.5–1.6 g/dL in mature preterm MOM.

12

Infant Formulas and Complementary Feeding

Kelly Green Corkins, MS, RD, LDN, CNSC, FAND, FASPEN, and
Lindsey Lee, MS, RD, LDN, CSP

Learning Objectives

1. Explain the basic composition of infant formulas and their regulation.
2. Discuss the reasons for functional ingredients in infant formulas.
3. Differentiate the types of infant formulas and their appropriate use.
4. Describe how to increase calorie concentrations.
5. Summarize the reasoning behind current guidelines for introducing complementary foods to an infant's diet.

Introduction

Nutrition during infancy is the foundation of growth and development. Human milk is considered the gold standard base for infant nutrition in the first 12 months of life. When human milk cannot provide the needed nutrients to promote growth and development or if a family decides not to use human milk, infant formulas are appropriate alternatives. This chapter

reviews the types of infant formulas available in the United States and their proper usage.

Background

Breastfeeding is considered to be the best as well as the standard nutrition for an infant.[1,2] Breastfeeding or human milk provides benefits to infants that formula cannot. The unique composition and bioactive agents in human milk contribute to the developing gastrointestinal tract, immune system, and brain.[3] A mother might not always be able to breastfeed or pump or may choose not to breastfeed because of cultural, social, or health reasons. Iron-fortified infant formulas are appropriate substitutes for human milk. A mother should be encouraged to breastfeed—or provide as much expressed human milk as possible—even when choosing to supplement with formula or needs to supplement for medical reasons.[4]

Because human milk is the optimal source of infant nutrition, the first infant formulas were developed to be similar to human milk in composition.[5] Even with the latest functional ingredients added (docosahexaenoic acid [DHA] and arachidonic acid [ARA], nucleotides, probiotics, prebiotics), infant formulas still cannot provide the hormones, immunoglobulins, enzymes, and live cells that are in human milk.[4] Standard term infant formulas and those modified for symptoms of intolerance are formulated using cow's milk or soy as a base. Infant formula manufacturers may never be able to completely replicate the composition of human milk, so modifications and research continue with the emphasis on promoting growth and development similar to that of the breastfed infant.[6]

While 83% of infants in the United States receive some human milk, 75% of infants receive some infant formula.[1] There are many choices of infant formula, so healthcare professionals need to be familiar with the indications and benefits of each formula category, especially specialty formulas and those for perceived symptoms of intolerance as most of those are more expensive.[1,7]

Formula Regulation

Infant formula is defined by the Federal Food, Drug, and Cosmetic Act (FDCA) as "a food which purports to be or is represented for special dietary use solely as a food for infants by reason of its simulation of human milk or its suitability as a complete or partial substitute for human milk."[8] Infant formulas designed to meet a specific medical need (eg, preterm birth) are considered "exempt" from the FDCA because the nutrition requirements differ from those of healthy infants. These formulas are not exempt from monitoring or regulation, however, and they need to meet certain criteria developed for those products. All infant formula manufacturers must begin with safe ingredients that are approved for use in infant formulas or are generally recognized as safe.[8]

The Infant Formula Act of 1980 (revised in 1986), an amendment to the FDCA, was developed because of an incident involving inadequate chloride in a soy-based formula that resulted in hypochloremic metabolic alkalosis in several infants.[9] The U.S. Food and Drug Administration (FDA) is responsible for monitoring infant formula manufacturers and regulating quality control, labeling, nutrient levels, recalls, new product notifications, and exempt products. Minimum levels for 29 nutrients and maximum levels for 9 nutrients have been established. Manufacturers are required to declare on the product label the minimum levels of each nutrient provided, and they must analyze each batch of formula to ensure they contain the declared levels of all essential nutrients. The FDA reviews analysis records and performs tests on formulas to monitor manufacturers.[6] The concentration of nutrients in infant formula is higher than in human milk because of the decreased bioavailability in infant formula. Specifically, the protein content of infant formula is 50% higher than in human milk, and the iron content is 2 to 4 times higher than in human milk because of the increased absorption of iron in human milk (20%–50%) compared to infant formula (4%–7%).[10]

Claims purported on infant formula labels regarding structure and functionality must be truthful and not misleading, but there is no legal standard. Although manufacturers are required to have data supporting the claims, they are not required to share this data.[11] These claims may confuse

parents, especially those who feel guilty for using infant formula, prompting them to choose a more expensive formula based on a claim.[12]

Types of Infant Formulas

Manufacturers are continually changing and updating product names and composition, so no specific product information will be provided in this chapter. For the most current information, please visit the manufacturers' websites (see Table 12-1).

TABLE 12-1. Infant Formula Manufacturer Websites

Manufacturer	Product Line	Web Site
Abbott Nutritionals	Similac and Elecare	www.abbottnutrition.com
Mead Johnson	Enfamil	www.meadjohnson.com
Nutricia	Neocate and other products	www.nutricia-na.com
Perrigo Nutritionals	Gerber Good Start Parent's Choice	https://medical.gerber.com www.perrigonutritionals.com
Vitaflo	Some modulars	www.vitaflousa.com

Standard Milk-Based Term Infant Formulas

Standard milk-based infant formulas are designed to meet the needs of healthy, term infants from birth to 1 year of age. These formulas are cow's milk–based and iron-fortified. The whey-to-casein ratio of cow's milk (20:80) is adapted to be more similar to human milk (70:30) with most standard infant formulas being 60:40 whey to casein.[10] Standard infant formula contains more protein compared to human milk (~2.2–2.4 g protein/100 kcal vs 1.35 g protein/100 kcal) to better match the protein quality of human milk.[10] Formula composition, both micronutrient and macronutrient components, varies among manufacturers, although all provide 20 cal/oz based on standard mixing instructions. Most formula-fed

infants will consume one of these products. There is also a subgroup of standard milk-based term infant formulas that is organic.

Organic Formulas

Organic formulas are milk-based and meet all the same guidelines as standard infant formulas. To be labeled organic, the formula's ingredients must be certified organic and meet U.S. Department of Agriculture regulations under the Organic Foods Production Act. Ingredients must be produced without added growth hormones or antibiotics. Pesticides used during the growing of the ingredients or in the plants used to feed animals that produce the ingredients must meet specific guidelines.[13] There are no evidence-based advantages of organic formulas and they are more expensive than standard term infant formulas.[1]

Term Formulas for Symptoms of Intolerance

Formulas designed for symptoms of intolerance are cow's milk–based or soy-based and are appropriate for full-term infants. Modifications include partial hydrolysis of the protein, reduced lactose, probiotics, and added rice starch.

Formulas with Partially Hydrolyzed Protein

Formulas containing partially hydrolyzed protein are not considered hypoallergenic and are not intended to be used for the treatment of any allergic condition or disease. Partially hydrolyzed protein formulas contain reduced or no lactose, and each product differs by the type of protein hydrolyzed and the degree of hydrolysis; therefore, it cannot be assumed that all partially hydrolyzed protein formulas offer identical benefits.[14] Even if the products contain the same type of partially hydrolyzed protein, the processes used to hydrolyze the protein may vary, resulting in different end products.

The benefits of a specific partially hydrolyzed 100% whey protein have been studied, and research indicates that it may decrease atopic dermatitis risk in infants with a family history of allergic disease.[14,15] A product with

partially hydrolyzed whey and casein has been shown to decrease fussiness, gas, and crying.[16]

Reduced-Lactose/Lactose-Free Formulas

Lactose is universally present in mammalian milk and is the predominant carbohydrate in human milk. Reduced-lactose formulas have similar calories, protein, fat, and micronutrient content as standard milk-based formulas. In some products, the lactose is reduced to compensate for the increased osmolality due to the hydrolyzed protein. Polysaccharides such as maltodextrin are used instead of disaccharide lactose. Currently, there is also a low-lactose product containing a probiotic.

Parents with lactose intolerance often assume their infants are also lactose intolerant, however, most babies make adequate amounts of lactase, and congenital lactase deficiency is extremely rare.[7] In addition, there is no significant evidence that these formulas decrease symptoms of colic.[7] Milk-based lactose-free formulas are not indicated in galactosemia because they still may contain small amounts of lactose or galactose.

Formulas With Added Rice Starch

Formulas with added rice starch are standard milk-based infant formulas designed to thicken in the acidic environment of the stomach to decrease spitting-up.[13] These formulas have not been shown to decrease episodes of gastroesophageal reflux (GER) and therefore are not indicated as medical treatment for GER.[17] Rice starch is added as part of the carbohydrate content; therefore, the macronutrient distribution remains consistent with standard milk-based infant formulas. Rice cereal may be added to standard infant formula to achieve a similar effect; however, it increases the caloric density and carbohydrate concentration (altering the macronutrient distribution), and may result in clogged bottle nipples. Formulas with added rice starch are not substitutes for thickened formulas indicated for aspiration risk.

Currently, 2 products with added rice starch are on the market; one of the products is lactose-free, and the other has reduced lactose. Each product has

studies supporting that the added rice starch decreases episodes of spitting up and supports normal growth in healthy term infants.[18,19]

Soy-Based Formulas

Soy-based formulas are designed to meet the needs of healthy term infants from birth to 1 year of age. The protein source is soy, supplemented with L-methionine, taurine, and L-carnitine.[10]

Soy formulas are fortified with iron and are lactose-free. It is estimated that about 25% of infants consuming formula will consume a soy-based formula. Soy-based infant formulas have higher concentrations of calcium and phosphorus than standard cow's milk–based formulas because of reduced bioavailability secondary to phytates.[20] Phytates and soy fiber oligosaccharides also interfere with the absorption of zinc and iron, so these are added in higher amounts to compensate.[10] Soy-based formulas offer no advantage over cow's milk–based formulas, except for a few indications such as infants with galactosemia or hereditary lactase deficiency (rare), or a request for vegetarian human milk substitute.[21]

Soy-based formulas are not recommended for preterm infants because they do not meet preterm infants' increased need for calcium and phosphorus.[10] Soy milk protein is no less allergenic than cow's milk protein.[4] Infants with documented cow's milk allergy should not be given a soy formula because 10% to 14% of these babies will also have a sensitivity to soy protein.[22,23]

Specialized Infant Formulas

Preterm or Low-Birth-Weight Formulas

Preterm or low-birth-weight formulas come in ready-to-feed nurser bottles that are available for hospital use only. These formulas are milk-based and designed to meet the special nutrition needs of preterm infants (those born at <37 weeks gestation or weighing <1500 g) while in the hospital if human milk is not available. The unique characteristics of this group of formulas include increased protein, carbohydrate blends of lactose and glucose polymers, fat blends containing a higher portion of fat as medium-chain triglycerides to promote fat absorption, and increased calcium and

phosphate to promote net mineral retention and bone mineralization.[24,25] Preterm infant formulas are available with low iron or with iron fortification. They are also available in a variety of caloric concentrations (ie, 24 kcal/oz, 30 kcal/oz), and there is a higher protein option. These products contain lactose due to the prebiotic effect on the developing gastrointestinal tract and because lactose has been shown to enhance calcium absorption, though the significance of this has not been demonstrated.[10]

Preterm Transitional Formulas

Preterm transitional formulas are designed to meet the nutritional needs of infants born prematurely or those with low birth weight who are transitioning home. Typically, these infants transition from preterm formulas to preterm transitional formulas at a weight of 1800−2000 g or a gestational age of 34 weeks, and they continue on these formulas until 6 to 9 months of age. These formulas can achieve vitamin and mineral goal requirements without additional supplementation.[10] They are milk-based with higher levels of calcium and phosphorus than standard term infant formulas. They provide a nutrient intake that is between a preterm and term formula, and the caloric concentration at standard dilution is 22 kcal/oz, which is higher than standard term infant formulas. Protein is 2.8 g/100 kcal.

A 2012 Cochrane Review concluded that there is insufficient evidence for current recommendations for preterm transitional formula use.[26] Preterm transitional formulas are still commonly recommended, however. Manufacturers' studies indicate that these formulas support appropriate growth for preterm or low birth weight infants after discharge from the hospital.

Extensively Hydrolyzed Protein Formulas

Formulas containing extensively hydrolyzed protein are considered hypoallergenic according to American Academy of Pediatrics (AAP) and FDA standards, meaning that 90% of infants or children with a confirmed allergy to cow's milk protein will not react to the formula.[10] The standard

dilution is 20 kcal/oz. The protein in these formulas is casein extensively hydrolyzed by heat or enzymes, resulting in free amino acids and small peptides. The fat content is made up of long-chain triglycerides from polyunsaturated vegetable oil to supply essential fatty acids (EFAs) and varying amounts of medium-chain triglycerides. These formulas are lactose-free, and because of the hydrolyzed protein, they have a higher osmolarity.

Protein hydrolysates are recommended for infants who are intolerant of cow's milk and soy proteins and those with significant malabsorption due to gastrointestinal or hepatobiliary disease.[4,27] These products are safe for the general population, but they cost significantly more than standard term infant formulas and should only be used with medical advice.

Amino-Acid-Based Formulas

Amino-acid-based infant formulas are considered hypoallergenic and are indicated in extreme protein hypersensitivity or when intolerance symptoms persist on an extensively hydrolyzed formula.[28] Approximately 2% to 10% of infants with an allergy to cow's milk protein develop persistent symptoms despite therapy with extensively hydrolyzed protein formula and thus require an amino-acid-based formula.[29] Using an amino-acid-based formula has no additional benefit if an extensively hydrolyzed protein formula is effective. Other indications for the amino-acid-based formulas include eosinophilic gastrointestinal disorders, transitioning from parenteral to enteral feedings, and short bowel syndrome.[29] These formulas should only be used with medical advice and under medical supervision.

Carbohydrate-Free Formulas

Carbohydrate-free formulas are designed for the management of carbohydrate metabolism disorders and carbohydrate malabsorption issues (eg, glucose-galactose malabsorption).[30] These formulas require a carbohydrate source. The physician or healthcare professional prescribes a carbohydrate to be added to the formula, and it is usually titrated up to make the formula 20 kcal/oz.[31]

Reduced-Fat/Modified-Fat Formulas

Reduced-fat or modified-fat formulas can be used in conditions of decreased bile salts, fat malabsorption, defective lymphatic transport of fat, chylothorax, or long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency. Because of the risk of EFA deficiency (EFAD), these formulas should only be used under the supervision of a physician and dietitian. Patients on these formulas for an extended period need to be evaluated for signs and symptoms of EFAD. The addition of EFAs at a volume of 3% to 5% of total kilocalories may be indicated with some of the formulas with lower levels of the long-chain fatty acids to meet EFA needs and prevent deficiency.

Reduced-Mineral Formulas

The mineral content of reduced-mineral formula is close to that of human milk and is designed to treat calcium disorders.[31] This formula may also be used for infants with impaired renal function. An additional iron source may need to be considered. Infants should be monitored by a medical professional when consuming this formula.

Infant Formula Shortage in the United States

In February 2022, a nationwide recall of multiple lines of formula shut down the largest infant formula manufacturing plant in the country. This along with supply chain issues resulting from the COVID-19 pandemic and import restrictions critically incapacitated the entire US formula distribution system, leaving parents and caregivers scrambling to find formula.[32] As previously discussed, infants should only have human milk or infant formula in the first 6 months. Anything other than human milk or infant formula is nutritionally incomplete. A shortage of infant formula puts infants at risk for a range of health problems affecting their growth and development. In addition, using unsafe alternatives, such as watering down formula or making homemade infant formula, puts infants at greater risk for electrolyte disturbances and nutrient deficiencies.[33]

The FDA does not regulate recipes for homemade formulas and advises against them because of serious health and safety concerns. Infant formula can be the sole source of nutrition for infants and therefore is strictly

regulated by the FDA. The potential problems with homemade formulas include contamination and the absence of or inadequate amounts of critical nutrients that can result in life-threatening, severe nutritional imbalances as well as foodborne illnesses.[33] Homemade formulas from ingredients using regular dairy products like cow's milk or other milk substitutes such as hemp, soy, or almond milk do not have the right amounts of protein, iron, calcium, and vitamins. Because of infants' immature gastrointestinal tract, they may not readily absorb the chemical forms of the nutrients used in the ingredients. Excessive amounts of some nutrients, such as protein and sodium, can also negatively affect the infant's kidneys and liver, whereas inadequate amounts of minerals such as calcium or sodium can lead to serious health issues.[34] Insufficient iron intake can cause deficiencies with lasting neurodevelopmental effects.[35]

Three specific cases reported to the FDA involved infants who consumed nutritionally deficient homemade formula based on alkaline diet recipes for a month or longer, resulting in hospitalization for hypocalcemia and vitamin D–deficient rickets. Several variations of recipes associated with this diet have been deficient in vitamins and micronutrients such as calcium, vitamin D, and iodine. These deficiencies can result in lasting harm, with long-lasting developmental consequences and possibly death. Hypocalcemia can lead to cardiorespiratory failure. Hypovitaminosis D can result in diffuse bone demineralization consistent with rickets during a time of exponential growth.[36]

Foreign Infant Formula

Industry and federal efforts to alleviate the formula shortage in the United States included the importation of foreign brands to supplement the increased domestic production of formulas from US manufacturers unaffected by the recall.[32] Some caregivers report choosing European brands because they offer certain formula options, such as those made from goat's milk or milk from pasture-raised cows, which are uncommon or (in the case of goat's milk) nonexistent in the United States. There is also the perception that the European formulas are of higher quality and that regulations are stricter.[35] There is no scientific evidence indicating that

these formulas are superior to commercial infant formulas sold in the United States. The FDA reviews all foreign infant formulas sold legally in the United States to make sure they meet minimum nutrition and safety requirements, including that the water used to make formulas meets safety standards set by the U.S. Environmental Protection Agency. The AAP advises against using formulas that are imported and sold illegally. The FDA has not reviewed these formulas, and there is also no guarantee they have been stored or shipped properly.[37]

There are some important differences between commercial infant formulas sold in the United States and legally imported formulas. One difference is labeling. Formulas from Europe, Australia, and Mexico are labeled as "stage 1" for newborns up to 6 months and "stage 2" for infants over 6 months up to 12 months. Additionally, mixing instructions may differ in units and powder-to-water ratios. For example, Europe and Australia use milliliters instead of ounces. Mixing instructions for commercial infant formula sold in the United States typically include a standard powder-to-water ratio of 1 scoop of infant formula powder to 2 ounces of water. Anyone preparing imported formula will need to pay close attention to the mixing instructions as adding too little or too much water will overconcentrate or overdilute the formula, respectively.[32]

Lastly, in the United States, all animal-based infant formula contains cow's milk, and the use of goat's milk protein is uncommon. However, goat's milk is commonly used in other parts of the world and in some imported formula brands from Australia and the United Kingdom. European and other international authorities have thoroughly reviewed the nutritional content of goat's milk and found that when it is adapted for formula, the milk protein supports normal growth and development in infants. There is even some scientific evidence suggesting that goat's milk protein is more easily digested by infants than cow's milk protein.[38]

It is important to note that parents who buy European or foreign formulas can pay a higher price. A study analyzing popular brands of European formulas found that European formulas generally meet most of the FDA nutritional guidelines even if the foreign formulas are not FDA-approved.[39] The European Commission does have additional regulations on formula that the FDA does not; therefore, the opposite is not always true.

The most notable difference is that the European Union (EU) bans certain added sugars (such as corn syrup) from milk-based formulas, requiring that at least 30% of carbohydrates come from lactose. It should be noted that it is not difficult to find formulas in the United States that meet the EU's carbohydrate requirement. Despite requiring similar vitamins and minerals in infant formula, many American formulas contain more iron than European formulas (1.8 mg/100 kcal vs 1.3 mg/100 kcal, respectively), because the AAP recommends a higher iron level to prevent iron deficiency.[40] In contrast, the EU has recently begun requiring higher levels of DHA than is found in most American formulas. Of note, the FDA does not require DHA, but most American formulas have it. Higher amounts of DHA are safe, and human milk contains a wide range of DHA; however, research does not conclusively support the benefits of the higher level of DHA found in European formulas.[35,39]

Functional Ingredients in Infant Formulas

DHA and ARA

Long-chain polyunsaturated fatty acids (LCPUFAs) have been shown to play an important role in the neurodevelopment of infants. DHA and ARA are the most abundant LCPUFAs in the brain; DHA is also found in retinal cells.[41–43] DHA and ARA can be obtained from dietary sources or by the endogenous conversion of their precursors, α-linolenic acid (18:3 ω3) and linoleic acid (18:2 ω6).[42,43] DHA and ARA occur naturally in human milk, with levels varying based on maternal diet.

During pregnancy, DHA and ARA are transported across the placenta to the fetus. Fetuses can synthesize DHA and ARA after 26 weeks of gestation, though the amount produced is highly variable.[43] After birth, DHA and ARA are provided via human milk or infant formula supplemented with DHA and/or ARA. Infants fed formula without supplementation have been shown to have lower levels of DHA in the brain.[43]

Nucleotides

Dietary nucleotides are nonprotein, nitrogenous compounds found in high concentrations in human milk.[45] They play key roles in many biological processes and are sometimes described as being "conditionally essential" in infancy. Nucleotides serve as nucleic acid precursors and coenzyme constituents as well as physiologic mediators.[44–46]

Some research suggests that nucleotide supplementation enhances growth and maturation of the gut and enhances mucosal recovery after intestinal injury. Nucleotides also play an important role in immune function by stimulating lymphocyte differentiation and proliferation.[44–46] Nucleotide-supplemented formula has been shown to support normal growth in infants.[44,45]

Prebiotics and Probiotics

Prebiotics are fermentable carbohydrates that are not fully digested in the small intestine. Prebiotics promote growth of normal gut flora, thus preventing the proliferation of pathogenic bacteria.[48,49] Fermentation of prebiotics produces short-chain fatty acids that can be used by colonocytes for energy. Fructo-oligosaccharides and galacto-oligosaccharides are the main prebiotics found in human milk and infant formula.[47]

Probiotics are nonpathogenic bacteria that alter the microflora of the host. They can help interfere with the adherence of pathogenic bacteria, increase the immunological barrier function of the intestine, and modulate the inflammatory response.[47–49]

Bifidobacteria are the predominant species of bacteria found in the intestines of breastfed infants. Some studies have shown *Bifidobacterium lactis* to be protective against necrotizing enterocolitis because of its effect on gut barrier function.[47–49] *Lactobacillus rhamnosus* GG is also found in the intestine of infants. It has been shown in numerous studies to reduce the duration of diarrhea in infants and may also be protective against necrotizing enterocolitis.[49] Infant formula with prebiotics and/or probiotics may be beneficial for infants experiencing gastrointestinal distress during and after illness or use of antibiotics.[47]

Forms of Infant Formula and Mixing Guidelines

Infant formula is available in 3 forms: ready-to-feed, liquid concentrate, and powder, although not all formulas are available in all 3 forms. All forms are nutritionally complete and regulated, but small differences exist among them because of processing.[50] Liquid concentrate and powder forms require the addition of potable water to reconstitute and can be mixed according to various caloric dilutions depending on the special need of the infant.

Ready-to-feed formula is the form most commonly used in hospitals because it is considered commercially sterile, is convenient, and the possibility of contamination is minimal. Manufacturers provide many different formulas in standard caloric dilution and some formulas at higher caloric concentrations in convenient ready-to-feed nurser bottles. Consumers can purchase ready-to-feed formula at standard dilution in quart-sized bottles or single-serving nurser bottles. Ready-to-feed formula is the most expensive form because the consumer is paying for the convenience.

Liquid concentrate is also considered commercially sterile, but because it needs to be mixed with water to make a standard dilution, there is more potential for contamination than in ready-to-feed form. Liquid concentrate is the second choice in hospitals and can be used to make higher-caloric concentrations. It is easy for consumers to mix and offers some financial savings over ready-to-feed formula.

Powder is not sterile and must be mixed with water. Therefore, it may contain pathogenic bacteria.[51] *Cronobacter sakazakii* is a bacteria that is naturally found in the environment and can live in dry foods, such as powder infant formula. Infant formula can be contaminated by germs on surfaces in homes, in processing facilities, or in water. Although *Cronobacter* infections are rare, infants younger than 2 months, preterm, or those who have weakened immune systems are at a higher risk for infection.[52] Powder formula has been associated with *Cronobacter sakazakii* contamination and infection in immunocompromised neonates in healthcare facilities.[53] Because of the population that they serve, hospitals should only use powder if no other option is available.[54,55]

Reconstituted powder formulas have been safely consumed by millions of infants worldwide over the past half-century, so parents of healthy newborns should continue to feel comfortable using powder infant formulas. Consumers choose it because it is the least expensive form and can be quickly mixed at any location when needed. The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition recommends that in the home, powder infant formulas should be freshly prepared for each feeding and any remaining formula should be discarded to minimize potential risk of contamination.[55,56] Prepared formula should be used within 1 hour of starting to feed and within 2 hours of preparation.[52] If larger quantities are mixed, no more than a 24-hour supply should be mixed and refrigerated.[55]

Formula Preparation

Parents and caregivers can decrease risk and even prevent infection and illness during formula preparation by cleaning and sanitizing feeding items, such as bottles, nipples, caps, rings, and other objects like pacifiers and teething toys that may enter an infant's mouth. Once clean, these items should also be stored safely. Hands should be washed before preparing bottles, feeding an infant, and touching an infant's mouth or items that go in an infant's mouth, as well as after using the bathroom or changing diapers. Washing hands with soap and water for 20 seconds is preferred. However, if that is not possible, hand sanitizer with at least 60% alcohol content will kill *Cronobacter.*[52]

Water

Water from the tap is usually adequate to use for preparing formula at home for infants with a normal immune system and who are fed orally.[55] If tap water is chemically softened or is well water, it is not appropriate for use to make infant formula. Chemically softened water uses chemicals that bind calcium and magnesium, increasing the sodium in the water.[58] Well water can be contaminated by dirt and may contain high levels of minerals.[59]

When tap water is not available or usable, bottled water should be used. Municipal tap water is fluoridated, whereas bottled water is not. Regardless of whether tap or bottled water is used, boiling the water is still

recommended to kill any bacteria.[59] The only exception is "infant water" or "nursery water" specifically made for making infant formula. This water is sterilized before bottling.

Infants consuming either human milk or infant formula exclusively do not need additional water in their diets. Human milk or infant formula mixed to standard dilution provides adequate free water for hydration in hot or dry climates and if the infant is febrile.

Standard Dilution

The standard dilution of most term infant formulas is 20 kcal/oz and preterm discharge formulas are 22 kcal/oz. When mixing formulas, parents should read the manufacturer's instructions on the container because they may vary by manufacturer and product. When mixing powdered formulas, only use the scoop that comes with that particular product because scoop sizes are different for each formula. In addition, to ensure accuracy, it is important to note whether the instructions indicate a packed scoop or a heaping scoop.

Increasing Caloric Concentration

For special feeding situations in which fluid volume may be limited and/or calorie needs are higher, many of which are discussed in detail in this book, both powder infant formula or infant formula concentrate can be reconstituted (see Tables 12-2 and 12-3) to provide formula with more concentrated calories than the standard dilution (20 cal/oz).[31] This maintains caloric intake within less volume or increases caloric intake within the same volume. Concentrated liquids from all manufacturers contain 40 kcal/oz, but not all manufacturers have the same size container for the concentrated formula (13 oz or 12.1 oz). The number of calories per gram per household measure varies among powdered formulas. Also, some powder formulas may need to be a packed measure. Therefore, it is important to concentrate the formula specifically for each product.[55]

TABLE 12-2. Increasing Caloric Concentration With Formula Concentrate

Caloric concentration	Formula Brand	Amount Concentrate (oz)	Water to Add (oz)	Approx. Yield (oz)
20 kcal/oz (0.67 kcal/mL)	Enfamil/Similac	13	13	26
	Good Start	12.1	12	24
22 kcal/oz (0.73 kcal/mL)	Enfamil/Similac	13	11	24
	Good Start	12.1	10	22
24 kcal/oz (0.8 kcal/mL)	Enfamil/Similac	13	9	22
	Good Start	12.1	8	20
27 kcal/oz (0.9 kcal/mL)	Enfamil/Similac	13	6	19
	Good Start	12.1	6	18

All concentrates are standard 40 kcal/oz or 1.33 kcal/mL.

TABLE 12-3. Increasing Caloric Concentration With Powder Infant Formula—Standard Dilution 20 kcal/oz

Caloric Concentration	Amount of Powder to Add[a]	Water to Add (oz)	Approx. Yield (oz)
20 kcal/oz (0.67 kcal/mL)	4 scoops	8	9
22 kcal/oz (0.73 kcal/mL)	4 scoops	7	8
24 kcal/oz (0.8 kcal/mL)	5 scoops	8	9
27 kcal/oz (0.9 kcal/mL)	5 scoops	7	8

[a] Only use the scoop provided for the specific formula. Scoop sizes vary from product to product even within the same manufacturer.

When calories are being concentrated to >24 kcal/oz using only concentrate or powdered infant formula and less water, potential renal solute load (PRSL) must be considered. Protein, sodium, chloride, potassium, and phosphorus all contribute to PRSL, and a higher PRSL can contribute to more rapid dehydration.[60] In certain medical conditions, the increase in caloric concentration may be indicated but should only be done under close monitoring by medical professionals. Increasing the

concentration of formula also increases the osmolarity of the formula, so tolerance and fluid status should be monitored by a medical professional when the formula is mixed to provide increased calorie concentration.

When increasing caloric concentration, many nutrition professionals limit the increase to no more than 4 kcal/oz at a time. If the infant has perfusion issues or dysmotility, smaller increments of 2 kcal/oz may be recommended to prevent intolerance. Maintain the caloric concentration for 48 to 72 hours before increasing concentration further. It is not recommended to advance caloric concentration if there are any significant changes in medical status or medications that might affect gastrointestinal motility or perfusion.

Modular Macronutrients

Modular macronutrients can be used to increase caloric concentration. Modulars are available as protein, carbohydrate, fat, and combinations of macronutrients. The fat and/or carbohydrate modulars may not add as significantly to the PRSL and osmolality as concentrating the formula with less water, and fat and/or carbohydrate modulars should be considered for concentrating calories >24 cal/oz.

Modular macronutrients will not increase the concentration of micronutrients like concentrating only the formula powder or concentrate. This may be desirable in some situations (eg, renal insufficiency) and not desirable in other situations (eg, increased calcium and phosphorus needs in prematurity). Another consideration is that the modular products will alter the macronutrient distribution. Modulars can be used to customize the formula to meet specific patient needs.

Modulars can be added to the formula when mixing, or they can be mixed with water and delivered as a bolus through the tube separate from the formula. To boost caloric intake of formula, some common food products or ingredients may also be used (eg, vegetable oil, corn starch). These ingredients may not be ideal, but they are much less expensive and easier to purchase than the manufactured modulars.

Increasing Concentration of Human Milk

Preterm infants often have caloric and nutrient deficits, even at discharge, and although human milk is the best choice for these infants, it may not meet all of the caloric and nutrient needs of an infant with significant comorbidities.[61] Expert opinions and studies indicate that preterm infants discharged from the hospital at suboptimal weight who are being fed human milk should continue to be supplemented to ensure adequate nutrient intake.[62,63] Some healthcare professionals suggest adding preterm or term infant formula concentrate or powder to human milk to increase caloric and nutrient density.[4,55,64] Remember that powder is not commercially sterile.[55] Close medical monitoring is suggested when adding formula to human milk because evidence for or against this practice is lacking, and a potential exists for error.

Introducing Complementary Foods to the Infant's Diet

The AAP recommends exclusive human milk feeding for up to 6 months of age.[3] No nutrition indication exists for starting complementary foods any earlier than 4 to 6 months of age but starting solids as early as 4 months has not shown any adverse effects on growth.[4] There may be a link to earlier introduction of solids (within the 4–6 month range) and overweight in adulthood.[65]

Due to the varying rates of growth and development among infants, they are usually ready for solid foods when birth weight has doubled, truncal stability permits sitting with support, and neuromuscular maturation has been achieved.[4] Other signs may include frequently putting things in their mouth or leaning forward and opening their mouth to indicate a desire for food.[4]

There is no supporting evidence for introducing foods in any certain order, but the first food is usually iron-fortified cereal. Consideration should be given to introducing meats early in the process because they are good sources of iron. The general rule is to add 1 "single-ingredient" food at a time and wait 3 to 5 days before introducing a new food, watching for

possible intolerances or allergic reactions.[4] Some parents make their own baby food. The food should be cooked until soft and put in a baby food grinder or blender until the desired consistency is reached. For infants just starting on solid foods, the consistency should be a smooth puree. Older infants can tolerate small consistent-sized bits in their food. Avoid adding salt or sugar.[4]

Some parents may choose to let their infant self-feed using "baby-led weaning." The basic idea behind baby-led weaning is to watch the infant for signs of developmental readiness and, when they are ready, allow them to self-feed. Infants are ready when they demonstrate the ability to sit upright with minimal/no support, reach for an object, pick it up, and bring it to their mouth with a diminishing tongue-thrust reflex. This typically happens around 6 months. This method often skips traditional baby foods such as purees. Instead, infants get the same meal as the family with modifications as needed, saving time and money. Baby-led weaning can also increase an infant's exposure to a greater variety of foods and, therefore, tastes and textures. It also promotes self-regulation by allowing infants to gauge their hunger and fullness. Lastly, when infants pick up a piece of food, bring it to their mouth, manipulate getting it into their mouth, chew, and then swallow, they are practicing tasks that require fine motor and oral motor skills.

A good time to advance textures to minced or diced foods and other finger foods is when the infant starts teething. Parents should be aware that "rub on" teething medications can interfere with chewing and swallowing because muscles in the throat can become numb. Careful observation is advised.

Juice

After 1 year of age, fruit juice can be introduced in a cup and should be limited to 4 oz daily.[66] Only 100% fruit juice should be offered. Juice is not a nutritionally necessary addition to the diet of an infant. Fruit juice displaces the more nutrient-dense human milk or infant formula; therefore, if juice is introduced, it should be in limited amounts. Infants should not be given juice in a bottle or cup that can be carried around, and they should not consume juice right before bed because of the increased risk of dental

caries. Overconsumption of juice can lead to osmotic diarrhea due to the high fructose and sorbitol content.[4]

Milk

Cow's milk (whole, 2%, 1%, skim), goat or any other animal milk, or any plant-based beverage (soy, almond, coconut, rice) other than infant formula should be avoided during the first year of life. These milk types and plant-based beverages are not fortified with vitamins and minerals at the levels recommended for infants and have been associated with protein-calorie malnutrition.[4]

Foods to Avoid the First Year

Foods that are difficult to chew or can easily choke a child or be aspirated should be avoided until about 4 years of age. Foods to avoid include, but are not limited to:

- hot dogs
- nuts
- grapes
- raisins
- raw carrots
- popcorn
- round candies[4]

Honey is another food to avoid during the first year of life. Honey can contain a bacterium that produces the toxin that results in botulism. Botulism is potentially very serious and can result in death if not diagnosed and treated properly in the infected infant.[4]

With the increasing prevalence of obesity and research supporting the claim that healthy eating habits are established early in life, high-fat or high-sugar foods are unnecessary in an infant's diet. These foods are high in calories and offer limited nutritional value, and therefore, should be avoided during the first year of life.[67]

Toddler Formulas

Toddlers consuming adequate amounts of nutrients, especially iron, from solid foods do not need a toddler formula. Whole cow's milk is adequate and appropriate after 1 year of age. If nutrient intake is a concern, toddler formulas are an option because they contain higher amounts of iron, vitamin C, and vitamin E than cow's milk, and they contain nutrients such as zinc that cow's milk does not contain but that a toddler usually gets in a varied, healthy diet. The calcium and phosphorus levels of toddler formulas are higher than infant formulas to match the needs of the growing toddler. Toddler formulas contain DHA and ARA, and the standard dilution for these products is 0.67 kcal/mL (20 kcal/oz).

Conclusion

Nutrition during infancy is the foundation of growth and development. Human milk is considered the gold standard base for infant nutrition in the first 12 months of life; 75% of infants will receive some infant formula. There are many choices of infant formula, so healthcare professionals working with infants need to be familiar with the indications and benefits of each formula to guide parents on appropriate use and ensure adequate nutrition.

Test Your Knowledge Questions

1. Which infant formula is indicated for an allergy to cow's milk protein?
   A. Partially hydrolyzed protein infant formula
   B. Extensively hydrolyzed protein infant formula
   C. Organic infant formula
   D. Goat's milk with added vitamins and minerals
2. What is the standard dilution of preterm discharge formulas?
   A. 19 kcal/oz
   B. 20 kcal/oz
   C. 22 kcal/oz
   D. 24 kcal/oz

3. According to the Federal Food, Drug, and Cosmetic Act, infant formulas that meet a specific medical need are considered to be which of the following?
   A. Exempt
   B. Generally recognized as safe
   C. Specialized
   D. Medical foods
4. Which of the following are prebiotics?
   A. Oligosaccharides
   B. Complex dietary carbohydrates that are not digestible by humans
   C. The fuel for beneficial bacteria in the gut
   D. All of the above

References

1. Abrams SA, Daniels SR. Protecting vulnerable infants by ensuring safe infant formula use. *J Pediatr*. 2019;211:201–206. https://doi.org/10.1016/j.jpeds.2019.04.032
2. Meek JY, Noble L. American Academy of Pediatrics, Section on Breastfeeding. Breastfeeding and the use of human milk. *Pediatrics*. 2022;150(1): e2022057988. https://doi.org/10.1542/peds.2022-057988
3. Martin CR, Ling P, Blackburn GL. Review of infant feeding: key features of breast milk and infant formula. *Nutrients*. 2016;8:279–290. https://doi.org/10.3390/nu8050279
4. Kleinman RE, Greer FR, eds. *Pediatric Nutrition*. 8th ed. American Academy of Pediatrics; 2019.
5. Schulman AJ. A concise history of infant formula (twists and turns included). *Contemp Ped.* 2003;20(2):91–103.
6. Aggett PJ, Agostini C, Goulet O, et al; European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition. The nutritional and safety assessment of breast milk substitutes and other dietary products for infants: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr*. 2001; 32:256–258. https://doi.org/10.1097/00005176-200103000-00004

7. Milbrandt TP. Specialized infant formulas. *Pediatr Rev*. 2017;38(5):241–242. https://doi.org/10.1542/pir.2016-0212
8. Federal Food, Drug, and Cosmetic Act, § 412, Title 21 Code of Federal Regulations 106, 107. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-B
9. Centers for Disease Control and Prevention. Infant metabolic alkalosis and soy-based formula—United States. *MMWR Morb Mortal Wkly Rep.* 1996;45(45):985–988. Accessed May 30, 2023. https://www.cdc.gov/mmwr/preview/mmwrhtml/00044475.htm
10. Martinez JA, Ballew MP. Infant Formulas. *Pediatr Rev*. 2011;32(5):179–189. https://doi.org/10.1542/pir.32-5-179
11. Wallingford JC. Perspective: structure-function claims on infant formula. *Am Society Nutr*. 2018;9:183–192. https://doi.org/10.1093/advances/nmy006
12. Hughes HK, Landa MM, Sharfstein JM. Marketing claims for infant formula: the need for evidence. *JAMA Pediatr* 2017;171(2):105–106. https://doi.org/10.1001/jamapediatrics.2016.3837
13. Organic production. U.S. Department of Agriculture, National Agricultural Library. Accessed January 24, 2024. https://www.nal.usda.gov/afsic/pubs/ofp/ofp.shtml
14. von Berg A, Koletzko S, Filipiak B, et al; German Infant Nutritional Intervention Study Group. Certain hydrolyzed formulas reduce the incidence of atopic dermatitis but not that of asthma; three-year results of the German Infant Nutrition Intervention Study. *J Allergy Clin Immunol*. 2007;119(3):7118–7125. https://doi.org/10.1016/j.jaci.2006.11.017
15. Vandenplas Y, De Greef E, Devreker T. Treatment of cow's milk protein allergy. *Pediatr Gastroenterol Hepatol Nutr.* 2014;17(1):1–5. https://doi.org/10.5223/pghn.2014.17.1.1
16. Berseth CL, Johnston WH, Stolz SI, Harris CL, Mitmesser SH. Clinical response to two commonly used switch formulas occurs in 1 day. *Clin Pediatr.* 2009;48(1):58–65. https://doi.org/10.1177/0009922808321897
17. Horvath A, Dziechciarz P, Szajewska H. The effect of thickened-feed interventions on gastroesophageal reflux in infants: systematic review and meta-analysis of randomized, controlled trials. *Pediatrics*. 2008;122(6):e1268–e1277. https://doi.org/10.1542/peds.2008-1900

18. Vanderhoof JA, Moran JR, Harris CL, Merkel KL, Orenstein SR. Efficacy of a pre-thickened infant formula: a multicenter, double-blind, randomized, placebo-controlled parallel group trial in 104 infants with symptomatic gastroesophageal reflux. *Clin Pediatr*. 2003; 41:483–495. https://doi.org/10.1177/000992280304200602
19. Lasekan JB, Linke HK, Oliver JS, et al. Milk-based infant formula containing rice starch and low lactose reduced common regurgitation in healthy term infants: a randomized, blinded and prospective trial. *J Am Coll Nutr.* 2014;33(2):136–146. https://doi.org/10.1080/07315724.2013.828578
20. Mimouni F, Campaigne B, Naylan M, Tsang RC. Bone mineralization in the first year of life in infants fed human milk, cow-milk formula or soy-based formula. *J Pediatr*. 1993;122(3):348–354. https://doi.org/10.1016/s0022-3476(05)83415-8
21. Bhatia J, Greer F; American Academy of Pediatrics Committee on Nutrition. Use of soy protein-based formulas in infant feeding. *Pediatrics*. 2008;121;1062–1068. https://doi.org/10.1542/peds.2008-0564
22. Zeigler RS, Sampson HA, Bock SA, et al. Soy allergy in infants and children with IgE-associated cow's milk allergy. *J Pediatr*. 1999;134(5):614–622. https://doi.org/10.1016/s0022-3476(99)70249-0
23. Klemola T, Vanto T, Juntunen-Blackman K, Kalimo K, Korpela R, Verjonen E. Allergy to soy formula and to extensively hydrolyzed whey formula in infants with cow's milk allergy: a prospective, randomized study with a follow-up to the age of 2 years. *J Pediatr*. 2002;140(2):219–224. https://doi.org/10.1067/mpd.2002.121935
24. Picaud JC, Decullier E, Plan O, et al. Growth and bone mineralization in preterm infants fed preterm formula or standard term formula after discharge. *J Pediatr*. 2008; 153:616–621.
25. Klein CJ. Nutrient requirements for preterm infant formulas. *J Nutr*. 2002;132(suppl 16-I):1395S-1577S. https://doi.org/10.1016/j.jpeds.2008.05.042
26. Young L, Embleton ND, McCormick FM, McGuire W. Multinutrient fortification of human breast milk for premature infants following hospital discharge. *Cochran Database Syst Rev.* 2013;2:CD004866. https://doi.org/10.1002/14651858.cd004866.pub4

27. American Academy of Pediatrics Committee on Nutrition. Hypoallergenic infant formulas. *Pediatrics*. 2000;106:346–349. https://doi.org/10.1542/peds.106.2.346
28. Sicherer SH, Noone SA, Koerner CB, Christie L, Burks AW, Sampson HA. Hypoallergenicity and efficacy of an amino acid-based formula in children with cow's milk and multiple food hypersensitivities. *J Pediatrics*. 2001; 138:688–693. https://doi.org/10.1067/mpd.2001.113007
29. Hill DJ, Murch SH, Rafferty K, Wallis P, Green CJ. The efficacy of amino acid-based formulas in relieving symptoms of cow's milk allergy: a systematic review. *Clin Exp Allergy*. 2007; 37:808–822. https://doi.org/10.1111/j.1365-2222.2007.02724.x
30. Wright EM. Glucose galactose malabsorption. *Am J Physiol*. 1998;275(5): G879–G882. https://doi.org/10.1152/ajpgi.1998.275.5.g879
31. Joeckel RJ, Phillips SK. Overview of infant and pediatric formulas. *Nutr Clin Prac*. 2009; 24:356–362. https://doi.org/10.1177/0884533609335309
32. The US is importing baby formula to help end supply shortage—what parents need to know. The Conversation. Accessed January 24, 2024. https://theconversation.com/the-us-is-importing-baby-formula-to-help-end-supply-shortage-what-parents-need-to-know-184408
33. U.S. Food & Drug Administration. FDA advises parents and caregivers to not make or feed homemade infant formula to infants. Published February 24, 2021. Accessed January 24, 2024. https://www.fda.gov/food/alerts-advisories-safety-information/fda-advises-parents-and-caregivers-not-make-or-feed-homemade-infant-formula-infants
34. Abrams SA. Why are we seeing baby formula brands on the shelves from companies I haven't heard of before? Healthychildren.org. American Academy of Pediatrics. Updated November 27, 2023. Accessed January 24, 2024. https://healthychildren.org/English/tips-tools/ask-the-pediatrician/Pages/why-are-we-seeing-baby-formula-brands-on-the-shelves-from-companies-i-havent-heard-about-before.aspx

35. Szalinski C. Why US parents are choosing European baby formula. *The New York Times Wirecutter*. Published March 12, 2021. Accessed January 24, 2024. https://www.nytimes.com/wirecutter/blog/us-parents-european-baby-formula/
36. Calello DP, Jefri M, Yu M, Zarraga J, Bergamo D, Hamilton R. Notes from the field: vitamin D–deficient rickets and severe hypocalcemia in infants fed homemade alkaline diet formula—three states, August 2020–February 2021. *Morb Mortal Wkly Rep*. 2021;70(33);1124–1125. https://doi.org/10.15585/mmwr.mm7033a4
37. Choosing an infant formula. Centers for Disease Control and Prevention. Reviewed June 29, 2023. Accessed January 24, 2024. https://www.cdc.gov/nutrition/infantandtoddlernutrition/formula-feeding/choosing-an-infant-formula.html
38. Abrams S. Is homemade baby formula safe? Healthychildren.org. American Academy of Pediatics. Updated March 5, 2021. Accessed January 24, 2024. https://www.healthychildren.org/English/ages-stages/baby/formula-feeding/Pages/Is-Homemade-Baby-Formula-Safe.aspx
39. DiMaggio DM, Du N, Scherer C, et al. Comparison of imported european and US infant formulas: labeling, nutrient and safety concerns. *J Pediatr Gastroenterol Nutr*. 2019;69(4):480–486. https://doi.org/10.1097/MPG.0000000000002395
40. Strazlkowski A, Black G, Young BE. Iron and DHA in infant formula purchased in the US fails to meet European nutrition requirements. *Nutrients*. 2023;15(8):1812. https://doi.org/10.3390/nu15081812
41. Agostoni C, Riva E. Role and function of long-chain polyunsaturated fatty acids in infant nutrition. In: Raiha NC, Rubaltelli FF, eds. *Infant Formula: Closer to the Reference*. Nestle Nutrition Workshop Series. Pediatric Program. Vol 47 Suppl. Lippincott Williams & Wilkins; 2002.
42. Hadders-Algra M. Effect of long-chain polyunsaturated fatty acid supplementation on neurodevelopmental outcome in full-term infants. *Nutrients*. 2010;2:790–804. https://doi.org/10.3390/nu2080790
43. Qawasmi A, Landeros-Weisenberger A, Leckman JF, Bloch MH. Meta-analysis of long-chain polyunsaturated fatty acid supplementation of formula and infant cognition. *Pediatrics* 2012;129:1141–1149. https://doi.org/10.1542/peds.2011-2127

44. Singhal A, Kennedy K, Lanigan J, et al. Dietary nucleotides and early growth in formula-fed infants: a randomized controlled trial. *Pediatrics.* 2010;126: e946–e953. https://doi.org/10.1542/peds.2009-2609
45. Carver JD. Advances in nutritional modifications of infant formulas. *Am J Clin Nutr*. 2003;77:1550S-1554S. https://doi.org/10.1093/ajcn/77.6.1550s
46. Hess JR, Greenberg NA. The role of nucleotides in the immune and gastrointestinal systems: potential clinical applications. *Nutr Clin Pract.* 2012; 27:281–294. https://doi.org/10.1177/0884533611434933
47. Patel RM, Denning PW. Therapeutic use of prebiotics, probiotics and postbiotics to prevent necrotizing enterocolitis: what is the current evidence? *Clin Perinatol.* 2013;40(1):11–25. https://doi.org/10.1016/j.clp.2012.12.002
48. Murguia-Peniche T, Mihatsch WA, Zegarra J, Supapannachart S, Ding ZY, Neu J. Intestinal mucosal defense system, part 2: probiotics and prebiotics. *J Pediatr.* 2013;162: S64–S71. https://doi.org/10.1016/j.jpeds.2012.11.055
49. Wall, R, Ross, RP, Ryan CA, et al. Role of gut microbiota in early infant development. *Clin Med Pediatr.* 2009; 3:45–54. https://doi.org/10.4137/cmped.s2008
50. Borschel MW, Baggs GE, Barrett-Reis B. Growth of healthy term infants fed ready-to-feed and powdered forms of an extensively hydrolyzed casein-based infant formula: a randomized, blinded, control trial. *Clin Pediatr.* 2014;53(6):585–592. https://doi.org/10.1177/0009922814528036
51. Drudy D, Mullane NR, Quinn T, Wall PG, Fanning F. *Enterobacter sakazakii*: an emerging pathogen in powdered infant formula. *Clin Infect Dis*. 2006; 42:996–1002. https://doi.org/10.1086/501019
52. Cronobacter infection and infants. Centers for Disease Control and Prevention. Accessed January 24, 2024. https://www.cdc.gov/cronobacter/infection-and-infants.html
53. *Enterobacter sakazakii* infections associated with the use of a powdered infant formula—Tennessee 2001. *MMWR Morb Mortal Wkly Rep*. 2002;51(14):298–300.

54. Whaley T, Robbins S. Strategies for implementing the guidelines for handling of infant feeding. *Building Block for Life.* 2004:27(3).
55. Robbins ST, Meyers R, eds. *Infant Feedings: Guidelines for Preparation of Human Milk and Formula in Health Care Facilities.* Academy of Nutrition and Dietetics; 2011.
56. Agostoni C, Axelsson I, Goulet O, et al; ESPGHAN Committee on Nutrition. Preparation and handling of powdered infant formula: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr.* 2004;39(4):320–322. https://doi.org/10.1097/00005176-200410000-00002
57. Mueller C, Nestle M. Regulation of medical foods: toward a rational policy. *Nutr Clin Pract.* 1995;10:8–15. https://doi.org/10.1177/011542659501000108
58. Steele C, Collins E, eds. *Infant and Pediatric Feeding: Guidelines for Preparation of Human Milk and Formula in Health Care Facilities*. 3rd ed. Pediatric Nutrition Practice Group and the Academy of Nutrition and Dietetics; 2019.
59. Water for formula: which type should you use? Healthline. Accessed January 24, 2024. https://www.healthline.com/health/baby/water-for-formula
60. Ziegler EE, Fomon SJ. Potential renal solute load of infant formulas. *J Nutr.* 1989;119:1785–1788. https://doi.org/10.1093/jn/119.suppl_12.1785
61. Groh-Wargo S, Sapsford A. Enteral nutrition support of the preterm infant in the neonatal intensive care unit. *Nutr Clin Pract.* 2009;24(3):363–376. https://doi.org/10.1177/0884533609335310
62. ESPGHAN Committee on Nutrition; Aggett PJ, Agostoni C, Axelsson I, et al. Feeding preterm infants after hospital discharge: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr*. 2006;42(5):596–603. https://doi.org/10.1097/01.mpg.0000221915.73264.c7
63. O'Connor DL, Khan S, Weishuhn K, et al. Growth and nutrient intakes of human milk fed preterm infants provided with extra energy and nutrients after hospital discharge. *Pediatrics*. 2008;121:766–776. https://doi.org/10.1542/peds.2007-0054

64. Noble LM, Okogbule-Wonodi AC, Young MA, Academy of Breastfeeding Medicine. ABM clinical protocol #12: Transitioning the breastfeeding preterm infant from the neonatal intensive care unit to home, revised 2018. *Breastfeeding Med*. 2018;13(4):230–236. https://doi.org/10.1089/bfm.2018.29090.ljn
65. Schack-Nielsen L, Sorensen TI, Mortensen EL, Michealsen KF. Late introduction of complementary feeding, rather than duration of breastfeeding, may protect against adult overweight. *Am J Clin Nutr.* 2010;91:619–627. https://doi.org/10.3945/ajcn.2008.27078
66. Heyman MB, Abrams SA. Fruit juice in infants, children, and adolescents: current recommendations. *Pediatrics*. 2017;139(6):1–8. https://doi.org/10.1542/peds.2017-0967
67. Grummer-Strawn LM, Scanlon KS, Fern SB. Infant feeding and feeding transitions during the first year of life. *Pediatrics.* 2008;122:S36–S42. https://doi.org/10.1542/peds.2008-1315D

Test Your Knowledge Answers

1. The correct answer is **B**. The protein in these formulas is casein extensively hydrolyzed by heat or enzymes, resulting in free amino acids and small peptides. Formulas containing extensively hydrolyzed protein are considered hypoallergenic according to AAP and FDA standards, meaning that 90% of infants or children with a confirmed allergy to cow's milk protein will not react to the formula.
2. The correct answer is **C**. Preterm discharge formulas have a standard dilution of 22 kcal/oz.
3. The correct answer is **A**. Infant formulas designed to meet a specific medical need are considered "exempt" from the FDCA because the nutrition requirements differ from those of healthy infants. These formulas are not exempt from monitoring or regulation, however, and they need to meet certain criteria developed for those products.
4. The correct answer is **D**. Prebiotics are fermentable carbohydrates that are not fully digested in the small intestine. Fermentation of prebiotics produces short-chain fatty acids that can be used by colonocytes for

energy. Fructo-oligosaccharides and galacto-oligosaccharides are the main prebiotics found in human milk and infant formula.

The authors of this chapter wish to thank Timothy Sentongo, MD, for his contributions to the first edition of this text.

13

Enteral Formulas

Kelly Green Corkins, MS, RD, LDN, CNSC, FAND, FASPEN

Learning Objectives

1. Explain the regulation of pediatric and adult formulas.
2. Describe the target populations for each formula category and what to monitor when using products with children that are intended for adults.
3. Differentiate the benefits of and contraindications for a blenderized diet administered through a gastrostomy tube.
4. Evaluate the clinical basis for the use of functional ingredients in enteral formulas.
5. Weigh the advantages and disadvantages of both open and closed systems for enteral formula administration.

Introduction

This chapter reviews enteral formulas and their application in pediatric nutrition support. Enteral nutrition (EN) is nourishment administered into the gastrointestinal tract through a feeding tube, and it is a critical part of nutrition support. Enteral feeding is preferred over parenteral nutrition when the patient's gastrointestinal tract is functioning and accessible and it is medically appropriate for safe enteral feeding.[1–3] EN helps support gut integrity, which is important to protect against gut atrophy and support

immune function.[4] An enteral formula is liquid nutrition designed to be administered via an enteral access device.[5] The selected enteral formula should be based on a complete nutrition assessment that includes individualized estimation of fluid, protein, and energy needs. The patient's specific diagnoses and comorbidities should also be considered; for example, potassium and phosphorous needs for renal disease or remnant intestinal length in patients with short bowel syndrome.[6] For information on different categories of enteral formulas and their uses, see Table 13-1.

TABLE 13-1. Enteral Formulas

Formula Category	Uses	Potential Populations
Oral supplements	Limited diet variety, limited diet volume, inability to take solid foods, increased calorie needs that are difficult to meet with food alone	Autism, overly picky eater, gastrointestinal disorders, cystic fibrosis; hypermetabolism
Polymeric enteral formulas	Normal functioning gastrointestinal tract, inability to consume adequate calories orally	Dysphagia, neurologic disorders, cerebral palsy
Semi-elemental formulas	Malabsorption issues, malfunctioning gastrointestinal tract, inability to take adequate calories from foods	Crohn's flare, cystic fibrosis, dysmotility, short bowel syndrome
Elemental formulas	Allergic responses, malfunctioning gastrointestinal tract, malabsorption issues	Multiple food allergies, dysmotility, short bowel syndrome
Specialized formulas	See product labels/handbooks for each product	—
Adult formulas	Higher protein percentage needs	Cerebral palsy, neuromuscular disorders
Modulars	Special needs of a patient requiring modified macronutrient content of foods or formula	—
	Meet protein needs with low-calorie expenditure	Cerebral palsy, neuromuscular disorders, catabolic state
	Carbohydrate/fat: Meet high-calorie needs without excessive protein	Congenital heart disease, renal disease

Regulation of Enteral Products

Enteral formulas for both adult and pediatric patients fall under the category of "medical foods," defined in the Orphan Drug Amendments of 1988 as "a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by

medical evaluation."[7] The definition was incorporated into the Federal Food, Drug, and Cosmetic Act, and the following 5 criteria are listed to qualify the characteristics of medical foods:[8]

1. Specially formulated and processed product for the partial or exclusive feeding of a patient via oral intake or an enteral feeding tube;
2. Intended for dietary management of a patient who has a limited or impaired capacity to digest or absorb ordinary foodstuffs or certain nutrients or who has other special medically determined nutrient requirements that cannot be achieved by the modification of the normal diet alone;
3. Provides nutrition support that is specifically modified to manage the unique needs resulting from a specific disease or condition, as determined by appropriate medical evaluation;
4. Intended for use under medical supervision; and
5. Intended only for a patient who requires medical care and is receiving active and ongoing medical supervision, including instruction on the use of medical food.

Although infant formulas are regulated by the U.S. Food and Drug Administration, medical foods are not. Congress passed the Infant Formula Act of 1980, making infant formulas distinct from other formulations for special dietary use. While infant formulas are subject to regulations regarding quality control, labeling, nutrient requirements, recalls, new product notifications, and exempt products, medical foods are minimally regulated, only according to Good Manufacturing Practices for conventional foods. This makes the veracity of enteral formula labeling and product claims dependent on the specific vendor. Thus, the American Society for Parenteral and Enteral Nutrition recommends that medical professionals interpret the content and health claims of enteral formulas with caution until more specific regulations are in place.[9] It is important to note that efficacy studies are not required for enteral products,[10] and the available research is not always good quality and may provide conflicting data, so healthcare professionals should carefully evaluate the quality and usefulness of the research.[10,11]

Enteral Formula Selection

Enteral formula selection starts with a complete nutrition assessment that includes current medical status and treatment plans.[3,6,12] For infants <12 months, infant formula is the most appropriate choice in the absence of human milk.[5] For more information on infant formulas, see Chapter 12, "Infant Formulas and Complementary Feeding." Pediatric formulas are designed for children ages 1 to 13 years,[2] and adult formulas are more nutritionally appropriate for adolescents older than age 14 years.[5] For children ages 1 to 13 years, adult formulas should be considered when disease-specific pediatric formulas are not available. Adult enteral formulas are commonly used for pediatric patients because of their higher protein content (up to 25% of calories from protein compared with 10%−15% in pediatric enteral formulas) and ability to meet pediatric protein needs without the use of modular protein and without exceeding calorie requirements. When using adult products for children, special attention should be given to prevent excessive or inadequate intake of specific micronutrients, especially if they are used as sole-source nutrition. Manufacturer information on caloric density, macronutrient caloric distribution, and micronutrients to meet the dietary reference intake (DRI) is important, and ingredients in enteral formulas must be carefully evaluated.[3] It is also important to monitor the manufacturer information because products change, and these changes may impact tolerance and efficacy for individual patients.[11] For a list of manufacturer websites, see Table 13-2. When selecting the most appropriate enteral formula, it is important to consider family or caregiver culture, religion, insurance, and financial abilities.[5]

TABLE 13-2. Enteral Formula Manufacturer Websites

Manufacturer	Product/Product Lines	Website
Abbott Nutrition	Elecare Pediasure Vital	www.abbottnutrition.com
Kate Farms	Pediatric Standard 1.2 Pediatric Peptide 1.5 Pediatric Peptide31.0	www.katefarms.com
Nestle	Boost Compleat Nutren Peptamen	www.nestle-nutrition.com
Nutricia	Neocate Ketocal Pepdite Jr. Monogen	www.nutricia-na.com
Vitaflo	Lipistart Renastart Renastep	www.vitaflousa.com

Oral Supplements

Oral supplements are usually polymeric (intact proteins) and have additional sucrose for enhanced taste. They are available in a variety of flavors. As the name implies, these formulas are intended to supplement a limited oral diet and may not be indicated for sole-source nutrition, whereas others are also indicated for tube feeding and sole-source nutrition.

Pediatric Polymeric Enteral Formulas

Polymeric formulas are the most commonly used enteral formulas[11] and are designed for long-term sole-source nutrition.[2] These products are usually

milk-based and lactose-free, available with and without fiber, and come in different caloric densities (0.6−1.5 kcal/mL). The macronutrient distribution generally ranges from 12% to 20% of calories from protein (milk, soy proteins), 25% to 45% of calories from fat (vegetable oils), and 44% to 55% of calories from carbohydrates (maltodextrin). Some products have soy proteins in addition to milk proteins (casein, whey). One plant-based product line uses pea protein. These products are indicated for tube-fed pediatric patients with normal gastrointestinal function whose nutrition needs cannot be met orally.[6] Some are available flavored, making them appropriate for sole-source oral nutrition.

Pediatric Peptide-Based Enteral Formulas

Polymeric formulas are usually considered the first choice for EN. If the polymeric formula is not tolerated, switching to a semi-elemental formula can improve tolerance.[13] Peptide-based formulas are designed to meet the needs of pediatric patients with gastrointestinal conditions resulting from malabsorption or maldigestion because the hydrolyzed protein is easier to absorb.[4] These formulas also can be used for impaired motility.[14] They are given as supplemental or sole-source nutrition, and some are flavored for oral consumption. The protein content is dipeptides and tripeptides made from heat-hydrolyzed or enzymatically hydrolyzed casein, whey, soy, or pea protein, and these products usually contain a percentage of the fat as medium-chain triglycerides for better absorption.[13] Cow's milk−protein-based peptides are not appropriate for cow's milk–protein allergy.[14] The proportion of macronutrients in peptide-based formulas is similar to that of polymeric formulas. Semi-elemental products are lactose-free, gluten-free, and kosher, and may contain milk and soy ingredients. Caloric formulations are available in 1.0, 1.2, and 1.5 kcal/mL.

Pediatric Elemental Enteral Formulas

Elemental products (or amino-acid-based formulas) are also used in pediatric patients with malabsorption resulting from a compromised gastrointestinal tract or with multiple food protein allergies. The protein

source of elemental formulas is 100% free amino acids, with the caloric distribution from protein ranging from 10% to 15%. Carbohydrates provide 42% to 63% of calories, and fats provide 25% to 45%.[4] This wide range allows for individual tailoring for various conditions. Most elemental formulas have a higher osmolarity than semi-elemental formulas because of the smaller particles (amino acids vs peptides). Many of these products are only available in powder form and must be reconstituted with water. Healthcare professionals often choose a peptide-based or elemental formula first for feeding into the jejunum, yet there is no strong evidence to support this practice. Formula choice should be based on the patient's condition and tolerance, not on the type of feeding tube.[15]

Pediatric Specialized Enteral Formulas

A limited number of products are designed to meet the disease-specific needs of pediatric patients. There are pediatric specialty products for inborn errors of metabolism, and the ketogenic diet for seizures, renal diseases, and fat malabsorption. In some cases, an adult product may be the best choice. If an adult product is chosen, pay special attention to the micronutrient intake to ensure that the needs of the growing child are met.[3,6]

Blenderized or Pureed Diets Through Feeding Tubes

Blenderized (or pureed) tube feedings are simply a variety of foods pureed in a blender to be fed through a gastrostomy tube. The first tube feedings were pureed hospital foods.[11] Even with the wide variety of products available for different diseases and conditions as well as commercially prepared blenderized formulas, parents are choosing homemade blenderized tube feedings.[16]

Blenderized tube feedings can be designed to meet individual macronutrient needs, and food choices can be based on cultural, religious, and ethical desires as well as medical issues such as allergies.[12] This individualized design requires open communication between the caregiver

and healthcare professionals, especially a registered dietitian. This communication is key to preventing many of the potential diet complications, such as bacterial contamination and nutrient deficiencies or toxicities.[17]

Parents may be interested in blenderized tube feedings because of the changing healthcare environment and increasing number of insurance companies not paying for enteral formulas because they are considered "food." Manufactured tube-feeding products are more expensive than preparing meals for a child, however, a blenderized diet requires the initial investment in a high-quality blender to meet the daily demands of pureeing large volumes of food to the desired consistency to avoid clogging the enteral tube. Another reason why caregivers may select a blenderized diet is because food is nurturing and parents want to be involved with their child's care.[17] The benefits of blenderized tube feeding may include improved feeding tolerance and growth trends, however, careful consideration must be given before it is initiated.[11,16]

Blenderized tube feeding is not appropriate for all patients, even if the parent or caregiver is motivated and desires to use this type of feeding. Because of the variable viscosity of home-prepared blenderized tube feedings, smaller bore (<14 Fr) tubes can easily clog.[18,19] Feedings should be given as a bolus within 2 hours of preparation and not given continuously because of the increased risk for bacterial growth when at room temperature over longer periods. During inpatient stays, a backup commercial blenderized tube feeding may be needed if hospital policy does not allow homemade blenderized tube feedings. Concerns related to blenderized tube feeding include foodborne illness from improper preparation or handling of the food items, inconsistent or uncertain nutrient content, and increased risk of clogging the tube.[10,17]

Pediatric Food-Based Enteral Formulas

Commercially prepared pediatric food-based enteral formula is a new subcategory of polymeric and semi-elemental pediatric formulas that manufacturers began developing and marketing to meet the demand of consumers wanting more natural food options for tube feeding.[13] Food-

based products offer an alternative to standard polymeric formulas and can be used to supplement homemade blenderized tube feeding.[20]

Because these products are made with real foods, many of the perceived benefits are similar to homemade blenderized tube feedings, such as decreased diarrhea, nausea, vomiting, constipation, abdominal distention,[20] and gastroesophageal reflux.[18] The composition of each formula varies with each manufacturer.[12] Protein sources include beef, poultry, fish, legumes, rice, and dairy.[5,16] The products may contain soluble or insoluble fiber, prebiotics, antioxidants, or phytonutrients from the whole foods used to make the products.[12] It's important to consider that there may be additional drug–nutrient interactions compared with other commercially prepared formulas.[12]

The increased viscosity of the commercially prepared blenderized formulas may require additional water to pass through the smaller nasogastric or j-tubes.[19] It is important to follow the manufacturer's recommended tube size and hang times.[5,12]

Modular Macronutrients

Modular products are available as protein (intact or extensively hydrolyzed), carbohydrate (modified starch), fat (medium-chain or long-chain triglycerides), or combinations of macronutrients. Modular macronutrients can be used to increase the caloric concentration of liquid ready-to-use enteral formulas. Modular macronutrients will not increase the concentration of micronutrients but will alter the macronutrient distribution of the product. Modular protein and carbohydrate may significantly alter the osmolarity of the formula and may result in intolerance. Specific macronutrients may be used to modify a formula to meet disease-specific needs. It is important to follow manufacturer guidelines to administer modulars because they can increase the risk of tube occlusion if not adequately dissolved.[10]

Functional Ingredients in Enteral Formulas

Fiber and Prebiotics

Fibers are structural and storage plant-derived carbohydrate compounds that are not broken down by intestinal digestive enzymes.[21,22] Traditionally grouped into soluble and insoluble forms, dietary fiber provides many benefits including normalization of colonic motility and regularity of bowel movements, promotion of normal colonic cell proliferation, and maintenance of the colonic microbiome balance with overall effects on immune function, digestion, and absorption.[23] Historically, enteral formulas did not contain additional fiber because of concerns about its viscous nature and the possibility of clogging feeding tubes.[22] The American Health Foundation recommends 5 to 10 g of fiber plus the child's age to promote adequate laxation.[24] A fiber-free enteral formula should be considered in patients at risk for bowel obstruction or ischemia.[22]

A prebiotic is a nondigestible component in food that exerts beneficial effects by stimulating growth and activity of select bacteria in the colon.[25] Because prebiotic consumption results in better gastrointestinal and immune health, much research has been done on these food components, which include oligosaccharides and polysaccharides. Roberfroid detailed the following specific criteria for an ingredient to be named a prebiotic[26]:

1. Resistance to digestion and modification by gastric acid, hydrolysis of intestinal enzymes, and gastrointestinal digestion
2. Fermentation by microflora in the intestines
3. Selective stimulation of the growth and/or activity of intestinal bacteria that contribute to health and well-being

Among the most extensively studied prebiotics are inulin, oligofructose, trans-galactooligosaccharides, and lactulose. Since the discovery of prebiotics a little over a decade ago, they have been included in commercially available infant and pediatric formulas. The addition of prebiotics to infant formulas arose from previous studies characterizing the substantial prebiotic content of human milk.[27] Limited data examine the effects of prebiotics in the pediatric population, but it has been suggested

that prebiotics can prevent the development of atopic eczema and infections.

EN formulas usually contain a mixture of dietary fibers from various sources. Examples of fiber sources are soy polysaccharides, partially hydrolyzed guar gum, acacia gum, resistance starch, cellulose, and outer pea fiber. A group of fibers—inulin, oligofructose, and fructo-oligosaccharides—are categorized as inulin-type fructans and are the most studied prebiotic fibers.[23,29] The Fiber Consensus Panel recommends that patients receiving EN be provided with a mixture of bulking and fermentable fibers to conceptually promote a balanced intake of fiber similar to a regular diet.[23,25] Consumption of a fiber blend provides advantages such as continued production of short-chain fatty acids for colon health and increased tolerance of different fibers and for the enteral formula itself by minimizing gastrointestinal symptoms such as bloating, flatulence, and abdominal pain.[23]

Forms and Administration of Enteral Formulas

Pediatric formulas are available in 2 forms: ready-to-use liquid and powder. Ready-to-use liquid is the most commonly used form in hospitals because it is considered commercially sterile, but some of the specialty formulas only come in powder. Powder is not sterile and must be mixed with water. Because it is not sterile, it may contain pathogenic bacteria.[30] The use of powdered infant formula has been associated with *Enterobacter sakazakii* infection in immunocompromised neonates.[31] Because of bacteria/infection risk, hospitals should only use powder when no other option is available.[32] For more information on mixing powdered formulas, see Chapter 12, "Infant Formulas and Complementary Feeding."

Open Versus Closed Systems

Ready-to-use liquid formula in cans or bottles can be poured into a tube-feeding bag (open system), or prefilled sterile containers can be spiked and infused through the tube (closed system). A closed system for delivery of

enteral formulas offers some advantages over an open system. With a closed system, less manipulation is needed, and labor and labor costs are decreased.[33–35] The cost savings of the closed system are primarily in the labor. Cost comparisons of the products, including waste, indicate the closed system is more expensive.[33] Another advantage of decreased manipulations is an increased time that the product is infused, resulting in an increased volume of tube feeding received by the patient.[34–36]

Older research studies indicated that the closed system was safer for patients because less manipulation meant less risk of contamination and infection.[35] A recent study in a pediatric hospital indicated that when recommended enteral feeding practices are followed, ready-to-use liquid formula in an open system has a lower-than-expected rate of bacterial growth.[37] An aseptic technique must be used when spiking the closed system because it can cause bacterial contamination.[34]

One significant limitation of closed systems is limited product selection, particularly in pediatric specialty products. The product in the closed system cannot be manipulated to meet specific needs or disease states.[38] Given that the main advantage of the open system is that the product can be modified for individual needs, many hospitals have both open and closed systems available.

Enteral feedings can be administered as continuous, bolus, or intermittent feedings. Continuous feedings are given with a pump. They are used when there is some gastric or intestinal dysmotility or if the terminal end of the feeding tube is postpyloric. The disadvantage to this type of feeding administration is that the patient is tethered to the feeding pump. Bolus feedings are preferred when administered into the stomach. These feedings can be given via gravity or can be pushed using a syringe and are given over a relatively short time. Intermittent feedings offer the advantage of the patient being off the pump for a short period while the feeding occurs over a longer period. Sometimes a combination of feedings is given; for example, continuous feedings may be given for 8 hours overnight while the patient and family are sleeping, and then 2 to 3 bolus feedings are given during the day after some oral feedings are offered.[4]

Conclusion

Enteral formula selection should be based on the patient's individual needs. Formulas are designed for age-specific and disease-specific needs and gastrointestinal tract function. Products are only regulated for Good Manufacturing Practices, so it is recommended that medical professionals review them and interpret their health claims with caution.

Test Your Knowledge Questions

1. Enteral formulas are regulated on which of the following parameters?
   A. Nutrient requirements
   B. Health claims
   C. Good Manufacturing Practices
   D. All of the above
2. Which is the least concerning factor of using an adult product in a pediatric patient?
   A. Calorie concentration
   B. Micronutrient levels
   C. Electrolyte levels
   D. Macronutrient distribution, specifically the amount of protein
3. What is the most significant advantage of an open system for tube feeding?
   A. Decreased manipulation of the product
   B. Increased cost of labor
   C. Ability to modify the formula
   D. Ability to spike more easily without contaminating the product
4. Prebiotics are which of the following?
   A. Oligosaccharides
   B. Complex dietary carbohydrates that are not digestible by humans
   C. The fuel for beneficial bacteria in the gut
   D. All of the above

References

1. Kleinman RE, Greer FR. Enteral feeding for nutrition support. In: Kleinman RE, Greer FR, eds. *Pediatric Nutrition*. 8th ed. American Academy of Pediatrics; 2019:703–720.
2. Axelrod D, Kazmerski K, Iyer K. Pediatric enteral nutrition. *JPEN J Parenter Enteral Nutr*. 2006;30(1):S21–S26. https://doi.org/10.1177/01486071060300S1S21
3. Savino P. Knowledge of constituent ingredients in enteral nutrition formulas can make a difference in patient response to enteral feeding. *Nutr Clin Prac.* 2018;33(1):90–98. https://doi.org/10.1177/0884533617724759
4. Doley J. Enteral nutrition overview. *Nutrients.* 2022;14(11):2180. https://doi.org/10.3390/nu14112180
5. Klepper CM, Moore J, Gabel ME, Fleet SE, Kassel R. Pediatric formulas: categories, composition and considerations. *Nutr Clin Prac.* 2023;38(2):302–317. https://doi.org/10.1002/ncp.10954
6. Joeckel RJ, Phillips SK. Overview of infant and pediatric formulas. *Nutr Clin Prac*. 2009;24:356–362. https://doi.org/10.1177/0884533609335309
7. Grants and contracts for development of drugs for rare diseases and conditions. Federal Food, Drug, and Cosmetic Act, 21 USC §360ee(b)(3). Accessed November 20, 2023. https://uscode.house.gov/view.xhtml?req=(title:21%20section:360ee%20edition:prelim)
8. Nutrition labeling of food. Federal Food, Drug, and Cosmetic Act, 21 CFR 101.9(j)(8). Accessed November 20, 2023. https://uscode.house.gov/view.xhtml?req=(title:21%20section:360ee%20edition:prelim)
9. Bankhead R, Boullata J, Brantley S, et al; A.S.P.E.N. Board of Directors. Enteral nutrition practice recommendations. *JPEN J Parenter Enteral Nutr.* 2009;33:122–167. https://doi.org/10.1177/0148607108330314
10. Escuro AA, Hummel AC. Enteral formulas in nutrition support practice: is there a better choice for our patient? *Nutr Clin Prac*. 2020;35(3):417–431. https://doi.org/10.1177/0884533616668492

11. Brown B, Roehl K, Betz M. Enteral nutrition formula selection. *Nutr Clin Prac*. 2015;30(1):72–85. https://doi.org/10.1177/0884533614561791
12. Church A, Zoeller S. Enteral nutrition product formulations: a review of available products and indications for use. *Nutr Clin Prac*. 2023;38(2):277–300. https://doi.org/10.1002/ncp.10960
13. Elfadil OM, Shah RN, Hurt RT, Mundi MS. Peptide-based formula: clinical applications and benefits. *Nutr Clin Prac*. 2023;38(2):318–328. https://doi.org/10.1002/ncp.10961
14. Verduci E, Salvatore S, Bresesti I, et al. Semi-elemental and elemental formulas for enteral nutrition in infants and children with medical complexity—thinking about cow's milk allergy and beyond. *Nutrient.* 2021;13(12):4230. https://doi.org/10.3390/nu13124230
15. Zoeller S, Bechtold ML, Burns B, et al. Dispelling myths and unfounded practices about enteral nutrition. *Nutr Clin Prac*. 2020;35(2):196–204. https://doi.org/10.1002/ncp.10456
16. Bennett K, Hjelmgren B, Piazza J. Blenderized tube feeding: health outcomes and review of homemade and commercially prepared products. *Nutr Clin Prac*. 2020;35(3):417–431. https://doi.org/10.1002/ncp.10493
17. Bobo E. Reemergence of blenderized tube feedings. *Nutr Clin Prac.* 2016;31(6):730–735. https://doi.org/10.1177/0884533616669703
18. Hron B, Rosen R. Viscosity of commercial food-based formulas and home-prepared blenderized feeds. *J Pediatr Gastroenterol Nutr*. 2020;70(6):e124–e128. https://doi.org/10.1097/mpg.0000000000002657
19. Weston SC, Crespo A, Harwin C. Stir, shake, or blend: a comparison of methods used to reduce viscosity of blenderized tube feedings. *J Pediatr Gastroenterol Nutr*. 2022;75(1):110–112. https://doi.org/10.1097/mpg.0000000000003479
20. Steel C, Wile H, Li O, Yedulla S. Understanding the use and tolerance of a pediatric and an adult commercial blenderized enteral formula through real world data. *Nutr Clin Prac*. 2023;38(2):449–457. https://doi.org/10.1002/ncp.10905
21. Khoshoo V, Sun S, Storm H. Tolerance of an enteral formula with insoluble and prebiotic fiber in children with compromised

gastrointestinal function. *J Am Diet Assoc.* 2010;110:1728–1733. https://doi.org/10.1016/j.jada.2010.08.011
22. Malone A. Enteral formula selection: a review of selected product categories. *Prac Gastroenterol.* 2005;June:44–74. https://med.virginia.edu/ginutrition/wp-content/uploads/sites/199/2015/11/MaloneArticle-June-05.pdf
23. Klosterbuer A, Roughead ZF, Slavin J. Benefits of dietary fiber in clinical nutrition. *Nutr Clin Pract.* 2011;26:625–635. https://doi.org/10.1177/0884533611416126
24. Williams CL, Bollella M, Wynder EL. A new recommendation for dietary fiber in childhood. *Pediatrics* 1995;96(5):985–988. https://doi.org/10.1542/peds.96.5.985
25. Meier R, Gassull MA. Consensus recommendations on the effects and benefits of fibre in clinical practice. *Clin Nut Suppl.* 2004;1:73–80. https://doi.org/10.1016/j.clnu.2004.09.011
26. Roberfroid M. Prebiotics: the concept revisited. *J Nutr*. 2007;137:830S-837S.
27. Thomas DW, Greer FR; Committee on Nutrition, Section of Gastroenterology, Hepatology and Nutrition of the American Academy of Pediatrics. Clinical report probiotics and prebiotics in pediatrics. *Pediatrics*. 2010;126:1217–1231. https://doi.org/10.1542/peds.2010-2548
28. Lee HY, Navin KV, Thirumaran T. Prebiotics in atopic dermatitis prevention and management. *J Functional Foods*. 2021;78:104352. https://doi.org/10.1016/j.jff.2021.104352
29. Van de Wiele T, Boon N, Possemiers S, Jacos H, Vestrate W. Inulin-type fructans of longer degree of polymerization exert more pronounced in vitro prebiotic effects. *J Appl Microbiol.* 2007;102:452–460. https://doi.org/10.1111/j.1365-2672.2006.03084.x
30. DrAZudy D, Mullane NR, Quinn T, Wall PG, Fanning F. *Enterobacter sakazakii*: an emerging pathogen in powdered infant formula. *Clin Infect Dis*. 2006;42:996–1002. https://doi.org/10.1086/501019
31. Centers for Disease Control and Prevention. *Enterobacter sakazakii* infections associated with the use of a powdered infant formula—Tennessee 2001. *MMWR Morb Mortal Wkly Rep*. 2002;51(14):298–300. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5114a1.htm

32. Whaley T, Robbins S. Strategies for implementing the guidelines for handling of infant feeding. *Building Block for Life.* 2004:27(3).
33. Phillips W, Roman B, Glassman K. Economic impact of switching from an open to closed enteral nutrition feeding system in an acute setting. *Nutr Clin Prac.* 2013;28(4):510–514. https://doi.org/10.1177/0884533613489712
34. Storm H. Closed-system enteral feedings: point-counterpoint. *Nutr Clin Prac.* 2000;15:193–197. https://doi.org/10.1177/088453360001500408
35. Wagner DR, Elmore MF, Knoll DM. Evaluation of "closed" vs "open" systems for the delivery of peptide-based enteral diets. *JPEN J Parenter Enteral Nutr.* 1994;18(5):453–457. https://doi.org/10.1148607194018005453
36. Vanek VW. Closed versus open eternal delivery system: a quality improvement study. *Nutr Clin Prac.* 2000;15(5):234–243. https://doi.org/10.1177/088453360001500506
37. Lyman B, Gebhards S, Hensley C, Roberts C, San Pablo W. Safety of decanted enteral formula hung for 12 hours in a pediatric setting. *Nutr Clin Prac.* 2011;26(4):451–456. https://doi.org/10.1177/0884533611413891
38. Skipper A. Closed systems: counterpoint. *Nutr Clin Prac.* 2000;15:197–200. https://doi.org/10.1177/088453360001500409

Test Your Knowledge Answers

1. The correct answer is **C**. Enteral formulas are considered "medical foods" under the Federal Food, Drug, and Cosmetic Act. Unlike infant formula, enteral formula is minimally regulated according to Good Manufacturing Practices for conventional foods.
2. The correct answer is **A**. Adult products are designed with the specific micronutrient and macronutrient needs of adolescents >14 years of age so special consideration is needed to prevent deficiencies and toxicities in younger children. Calorie concentration can be chosen or adapted as needed.
3. The correct answer is **C**. An open system is when cans of formula or prepared powder are added to the feeding bag allowing for

manipulation if needed. A closed system does not allow manipulation of the product.

4. The correct answer is **D**. Prebiotics is defined as a "non-digestible component in food that exerts beneficial effects by stimulating growth and activity of select bacteria in the colon."[25]

14

Childhood Overweight and Obesity: Efficacy and Safety of Popular Diets and Weight-Control Programs

David Freestone, DO

Learning Objectives

1. Describe the importance of weight maintenance versus weight-loss recommendations for children and adolescents.
2. Critique one of the popular diets discussed for use with children.
3. Devise a weight-loss plan for adolescents with at least 3 positive characteristics.
4. Assess the efficacy of a balanced macronutrient low-kilocalorie diet for use with children.

Introduction

Overweight and obesity in the pediatric population has been an escalating issue for many years. This worldwide disease is a combination of both medical and socioeconomic issues. Because of the documented increase in the incidence of pediatric overweight and obesity, there has been an increase in studies on etiology and interventions. It is important to

understand that this disease connects to socioeconomic issues; children of Hispanic and non-Hispanic Black ethnicity are in the highest risk groups for obesity, as are children from low-income households. The multifaceted nature of obesity, which is linked to immediate and long-term health risks as well as mental health problems, emphasizes the need for early recognition and tailored treatment plans directed by a multidisciplinary team. While primary obesity management focuses on sustainable lifestyle modifications, severe cases may require more significant interventions. This chapter focuses on practical nutrition support, understanding of the issues underlying overweight and obesity, and current approaches for prevention and management.

Background

Obesity is a complex medical condition with systemic metabolic changes.[1] The incidence and prevalence of childhood overweight and obesity has increased worldwide.[2] In the United States, obesity has more than tripled in children and quadrupled in adolescents in the last 30 years.[1,3] Between 2017 and 2020, the prevalence of obesity in those between ages 2 and 19 years was 19.7%, affecting 14.7 million children and adolescents.[1] These numbers have continued to rise over the last decade, since this text was last updated.[3] In a study comparing children starting kindergarten and followed over 5 years showed children at a younger age had more severe levels and a higher incidence of obesity in the 2000s compared with the 1990s.[4] Worldwide obesity has tripled since 1975 with an estimated 39 million children <5 years old and 340 million children between ages 5 and 19 years, increasing in percentage from 4% in 1975 to 18% in 2016.[5]

The groups with the highest risk for prevalent obesity are those with Hispanic ethnicity (26.2%) and non-Hispanic Black (24.8%), compared with non-Hispanic White (16.6%) and non-Hispanic Asian (9%). Obesity is more prevalent in low-income households than in high-income households.[1]

Childhood and adolescent obesity are associated with multiple health risks and adverse effects during childhood as well as later in life, including the following:

- sleep problems
- bone and joint problems
- metabolic and endocrine disorders
- respiratory problems
- gastrointestinal problems
- skin conditions
- diabetes
- dyslipidemia
- nonalcoholic fatty liver disease and other cardiovascular disease risk factors
- social and psychological problems[6–13]

Thus, it is key to include a mental health professional on the treatment care team.[14]

Increased risks for certain types of cancers have been linked to conditions of overweight and obesity, including breast, colon, endometrium, esophagus, kidney, pancreas, gall bladder, thyroid, ovary, cervix, and prostate, as well as multiple myeloma and Hodgkin's lymphoma.[15]

There is no single cause for obesity, but rather a combination of many individual factors as well as environmental and societal influences.[16,17] The complex nature of obesity makes it challenging to manage. Early recognition and development of a treatment or prevention plan are important parts of pediatric obesity management.[18] Children and adolescents who have obesity are also likely to have it as adults[15,19–22] and are therefore more at risk for adult health problems such as heart disease, type 2 diabetes mellitus (DM), stroke, and osteoarthritis.[22] The connection between these health problems—obesity, hypertension, hyperlipidemia, and type 2 DM and the increased risk for cardiovascular disease (CVD)—is referred to as metabolic syndrome.[2]

Management strategies are usually focused on making healthy diet and lifestyle modifications to achieve lasting lifelong goals of healthy living. When lifestyle modifications are not effective or when cases are more severe, multidisciplinary weight-management programs should be considered. Additional strategies may include pharmacologic and bariatric surgery options.[23–29]

Definition

Obesity is diagnosed when the body mass index (BMI) is greater than or equal to the 95th percentile based on sex-specific and age-specific reference data from the Centers for Disease Control and Prevention growth charts, and if the BMI is between the 85th and 94th percentiles for sex and age, the diagnosis is "overweight" (see Table 14-1). Children <2 years old have obesity when their weight-for-length is ≥ 97th percentile.[24] Severe obesity is defined as BMI ≥ 35 or ≥ 120th percent of the 95th percentile for age and sex.[30]

TABLE 14-1. Weight Recommendations According to Age and BMI Percentile

Age	Target
2–5 y	
BMI of 85th–94th percentile	Weight maintenance until BMI of <85th percentile or slowing of weight gain, as indicated by downward deflection of BMI curve.
BMI of ≥ 95th percentile	Weight maintenance until BMI of <85th percentile; however, if weight loss occurs with healthy, adequate-energy diet, then it should not exceed 1 lb/mo. If greater loss is noted, then patient should be monitored for causes of excessive weight loss.
6–11 y	
BMI of 85th–94th percentile	Weight maintenance until BMI of <85th percentile or slowing of weight gain, as indicated by downward deflection of BMI curve.
BMI of 95th–98th percentile	Weight maintenance until BMI of <85th percentile or gradual weight loss of ~1 lb/mo. If greater loss is noted, then patient should be monitored for causes of excessive weight loss.
BMI of ≥ 99th percentile	Weight loss not to exceed an average of 2 lb/wk. If greater loss is noted, then patient should be monitored for causes of excessive weight loss.
12–18 y	
BMI of 85th–94th percentile	Weight maintenance until BMI of <85th percentile or slowing of weight gain, as indicated by downward deflection of BMI curve.
BMI of 95th–98th percentile	Weight loss until BMI of <85th percentile, no more than an average of 2 lb/wk. If greater loss is noted, then patient should be monitored for causes of excessive weight loss.
BMI of ≥ 99th percentile	Weight loss not to exceed an average of 2 lb/wk. If greater loss is noted, then patient should be monitored for causes of excessive weight loss.

Abbreviation: BMI, body mass index.

Reproduced with permission from Spear et al.[26]

Pathogenesis of Obesity

Obesity is a complex process resulting from multiple factors including a combination of calorie excess, insufficient activity, and genetic predisposition, with environmental and social factors playing contributing roles.[16] The complex regulation control of taste, smell, and hunger impacts eating behaviors individually. Many hormones influence satiety. The hypothalamus is the main center of the brain that controls appetite, and orexigenic and anorexigenic messages are relayed to it to stimulate hunger and satiety.[6] Regulation of this system can be impacted by multiple factors, resulting in altered satiety sensations. Psychological disorders can alter appetite regulation, causing increased appetite and emotional eating.[6,31] Poor sleep is associated with obesity for various reasons, including a lack of structure associated with poor diet and higher screen-time exposure, and sleep deprivation is linked with growth hormone deficiency and raised cortisol levels, which both contribute to obesity.[32,33]

Obesity is a contributing factor to metabolic syndrome. Metabolic syndrome describes how environmental and genetic factors work together to produce a constellation of chronic metabolic disorders resulting in a connection to obesity, hypertension, hyperlipidemia, and type 2 DM with increased CVD risk.[2] Insulin resistance and increased inflammation are key characteristics of metabolic syndrome. Identification of metabolic syndrome and its component disorders among adults and children offers useful information about patients' metabolic risk, particularly that associated with future cardiovascular morbidity and mortality.[34,35]

Visceral fat is far more inflammatory than peripheral fat, which explains why waist circumference (as a proxy for visceral fat) is such a key sign when assessing risk in patients with obesity.[36,37] Adipokines released from metabolically active adipose tissue include tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), and interleukin (IL)-6, all of which have been implicated in accelerating the atherosclerotic process.[38,39] Obesity and the subsequent proinflammatory state are suspected as the underlying mechanisms responsible for the progression of insulin resistance. Consequently, the triad of obesity, inflammation, and insulin resistance is associated with metabolic syndrome in children. Children and adolescents

who have morbid obesity are more insulin-resistant and present with higher levels of inflammatory biomarkers, including IL-6, intracellular adhesion molecule-1, and E-selectin, compared with lean counterparts.[36,40]

Insults to the cardiovascular system are associated with obesity and insulin resistance in childhood and adolescence, and the formation of plaques and fatty streaks deposited in the blood vessel walls, are associated with abnormal lipids and high blood pressure. These abnormalities have all been found among children and adolescents with obesity. For example, excess body weight drives metabolic change resulting in insulin resistance and vascular dysfunction, and over time, anatomical changes to the arterial wall begin to develop, which are thought to be the earliest indicators of CVD risk.[41,42] The interconnected process of obesity and inflammation promotes CVD and stroke by promoting platelet adhesion, which is a critical step in the formation of atherosclerotic plaques.[43] These changes may be reversed through interventions such as physical activity and proper nutrition.[44–46]

Metabolic Syndrome

Unifying criteria for the diagnosis of metabolic syndrome in adults was proposed in 2009 by the International Diabetes Federation; National Heart, Lung, and Blood Institute; American Heart Association (AHA); World Health Federation; International Atherosclerosis Society; and International Association for the Study of Obesity.[28,47–50] The same criteria are used for diagnosing pediatric metabolic syndrome. Table 14-2 summarizes diagnosis features based on a compilation of 8 sets of diagnostic criteria. The presence of 3 out of 5 risk factors classifies an individual as having metabolic syndrome. Each of the 5 risk factors, except waist circumference, was assigned a single set of cutoff points. The committee recommended the use of population-specific and country-specific definitions to measure waist circumference until new data emerge.

TABLE 14-2. Diagnostic Criteria for the Metabolic Syndrome in Pediatrics

Group/Study	Criteria	Obesity	Triglyceride	HDL-C	Blood Pressure (mm Hg)	Glucose
IDF (2007)[27] 10–16 y	Abdominal obesity and any 2 risk factors	WC ≥ 90th percentile	≥ 150 mg/dL	<40 mg/dL	Systolic ≥ 130 Diastolic ≥ 85	Fasting ≥ 100 mg/dL or known type 2 DM
Modified NCEP ATP III (2007)[28]	3 or more of the following conditions	WC ≥ 90th percentile	>95th percentile	<5th percentile	>95th percentile of either SBP/DBP	Impaired glucose tolerance
Goodman (2005)[29]	Insulin resistance or DM and 2 additional risk factors	BMI ≥ 95th percentile	≥ 150 mg/dL	≤ 35 mg/dL (male) or ≤39 mg/dL (female)	≥ 130/85	Fasting ≥ 110 mg/dL or DM
Ford (2005)[30]	3 or more of the following conditions	WC ≥ 90th percentile	≥ 110 mg/dL	≤ 40 mg/dL	≥ 90th percentile	Fasting ≥ 110 mg/dL
de Ferranti (2004)[31]	3 or more of the following conditions	WC >75th percentile	≥ 1.1 mmol/L (100 mg/dL)	<1.3 mmol/L (50 mg/dL)	>90th percentile	Fasting ≥ 6.1 mmol/L (110 mg/dL)
Weiss (2004)[32]	3 or more of the following conditions	BMI > 97 or BMI Z score > −2	> 95th percentile	<5th percentile	>95th percentile	Impaired glucose tolerance (2 h, >140 mg/dL)
Cruz (2004)[33]	3 or more of the following conditions	WC ≥ 90th percentile	≥ 90th percentile	≤ 10th percentile	> 90th percentile	Impaired glucose tolerance
Cook (2003)[34]	3 or more of the following conditions	WC ≥ 90th percentile	≥ 110 mg/dL	≤ 40 mg/dL	≥ 90th percentile	Fasting ≥ 110 mg/dL

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; IDF, International Diabetes Federation; NCEP ATP III, National Cholesterol Education Program, Adult Treatment Panel III; SBP, systolic blood pressure; WC, waist circumference.

Currently, there is no established diagnosis for metabolic syndrome in children and adolescents, however, many have tried to develop guidelines because of the known adverse health consequences. There are too many physiologic changes between different ages, genders, and ethnicities of children and adolescents during growth and development extending through

puberty to devise a unifying set of diagnostic standards for metabolic syndrome.[51] Defining metabolic syndrome in pediatrics with a set value for a potential risk factor is even more challenging than in an adult population. A scientific statement from the AHA was released in 2009 that provides a more comprehensive synopsis of the advancements, challenges, and limitations of metabolic syndrome diagnosis in children and adolescents.[52]

Various studies reported changes in insulin resistance, lipid profile, body fat, and blood pressure as participants grew from late childhood to adolescence.[53–57] With the constant changes in these factors, more than set values are needed to define metabolic syndrome in the pediatric population. Also, wide variations in pediatric-specific cutoff points have been found across studies,[58] with many assigning arbitrary threshold values with no proven basis to predict future health risk.[59]

For example, the value of waist circumference is arbitrary because no standardized protocol has been accepted for obtaining its measurement in clinical practice.[60] Some argue that measurements of waist circumference as a representation of visceral fat is the single most predictive anthropometric value of the metabolic syndrome.[61] However, in children, percentile values for waist circumference are poorly established across age groups, and most guidelines result from studies conducted in White, European descendants, which questions the utility for other ethnic populations.[62]

Normal physiologic changes that occur during puberty complicate the diagnosis of metabolic syndrome. The combined metabolic effects of growth hormone and insulinlike growth factor 1 (IGF-1) are associated with a normal state of mild insulin resistance, which follows the onset of puberty.[63] Furthermore, this phenomenon appears to be independent of body fat.[64] Thus, puberty-induced insulin resistance complicates the task of attributing insulin resistance to normal pubertal changes versus the metabolic consequences of overweight and obesity.[24,30]

Risk Factors for Obesity

Dietary Habits

Sugar-sweetened beverage intake is associated with insulin resistance, obesity (including truncal obesity), dyslipidemia, and increased inflammatory markers.[65–68] These beverages contribute to obesity because of high sugar content, low satiety, high glycemic load, an abundance of excess energy storage, and incomplete compensation for total energy.[69,70] Several studies have shown that consuming low-sugar-sweetened beverages combined with increased physical activity decreases insulin resistance and triglycerides and increases HDL cholesterol.[65–68] Evidence suggests that fruit and vegetable consumption may be protective against the development of childhood obesity.[71]

Increased Weight and Adiposity

The pediatric population has had a higher rate of increase in adiposity compared with the adult population.[56] Increased truncal obesity correlates with abnormal blood pressure and increased low-density lipoprotein (LDL) cholesterol, triglycerides, lipoproteins, and insulin as well as decreased HDL cholesterol.[72–75] Similarly, an increased waist-to-height ratio is associated with increased metabolic and cardiovascular risk.[74,75]

Physical Inactivity

Sedentary lifestyle behaviors have been implicated as potential causes of pediatric overweight and obesity. Increased screen-time usage is associated with less physical activity and a higher tendency for overweight. One study showed that 35% of boys and 25% of girls watch 4 or more hours of television each day.[76] Children who watch more television regardless of socioeconomic status are less physically active and are more overweight.[77] Television watching can influence appetite. A study of Saturday morning television broadcasts targeted at children may have more than 50% of advertisements promoting food items with over 90% featuring high-sugar, high-salt, and high-fat foods.[78] As Halford et al found, children with overweight and obesity respond to such advertisements by choosing more-calorie-dense foods.[79,80] Schmitz et al showed that physical inactivity is

associated with metabolic syndrome traits in pediatrics,[81] which was further strengthened by observation in clinical trials that exercise improved insulin sensitivity in adults.[82,83] Studies in children who had regular physical activity showed improvement in all facets of metabolic syndrome, including improved insulin sensitivity, dyslipidemia, obesity, cardiorespiratory fitness, and blood pressure.[65,68,81,84] Balducci et al and Rubin et al found a reduction in inflammatory markers (independent of weight loss) in patients with metabolic syndrome who were engaged in exercise.[85,86]

Genetic Factors

Genetics plays an important role in obesity and metabolic syndrome.[87–89] There are single gene mutations that impact satiety centers in the hypothalamus and appetite-regulating hormones, resulting in hyperphagia.[90] Some of these single genetic mutations include Prader-Willi syndrome (PWS), Alström syndrome, and Bardet Biedl syndrome, which often include developmental delay and dysmorphic features and should prompt genetic evaluation.[91]

Genetic factors influence metabolic syndrome–related traits such as central obesity, insulin resistance, dyslipidemia, hypertension, and endothelial dysfunction.[92–95] Having a first-degree relative with type 2 DM doubled a child's risk for developing metabolic syndrome.[96] In a study of the pediatric population, the presence of metabolic syndrome in parents was a risk factor for adolescent obesity and insulin resistance. In some individuals, multiple gene abnormalities may result in a combination of risk factors; for example, diminished satiety combined with decreased physical activity and a tendency for adiposity results in a much higher propensity for obesity.[6] Epigenetic factors are another way gene expression may result in a higher tendency for obesity. Chemical modifications occurring in times of stress (ie, aging, socioeconomic challenges, and/or starvation) can enhance or suppress gene function. Critical phases of development are the most vulnerable, but these alterations can also have a generational impact.[97,98]

Endocrinopathy

Endocrine abnormalities resulting in obesity are uncommon. Hypothyroidism and Cushing's disease are both associated with impaired linear growth. It is unlikely to see normal growth velocity with an underlying endocrine etiology for weight gain.[99] Rapid-onset obesity with hypoventilation and hypothalamic dysfunction (ROHHAD) syndrome is a relatively recent diagnosis of rapidly developing obesity in young children associated with multiple endocrinopathies and autonomic dysregulation. Neuroendocrine tumors are associated with about half of these cases, but there is not a clear etiology.[100]

Neurologic and Psychiatric Conditions

Head injury, stroke, and brain lesions that impact the hypothalamus can alter satiety control. Many medications, especially atypical antipsychotics and mood stabilizers, may also lead to excessive weight gain.[99]

Tobacco Exposure

Smoking and smoke exposure is a known risk factor for obesity. This includes the use of e-cigarettes.[101] The use of e-cigarettes has increased, with 35% of 12th graders reporting use in the last year, 25% in the past 30 days, and 1 in 9 using daily.[102] The smoke exposure could be active and/or passive. Maternal smoking during pregnancy and early childhood increases the risk of overweight and obesity extending into adolescent years.[103]

Race and Ethnicity

Mexican-American populations have the highest prevalence of obesity (26%) followed by non-Hispanic Black (25%) and non-Hispanic White populations (17%).[1] This difference is less in girls compared with boys.[104] However, the adiposity increase rate is higher in Black populations compared to White populations, but only among females, and is independent of baseline adiposity.[56] Mexican-American adolescent males have less hypertension than non-Hispanic adolescent males.[104] Non-Hispanic Black girls have less hypertriglyceridemia compared with others.[105]

Socioeconomic Status

Low socioeconomic status is strongly associated with the development of overweight and obesity among American children.[1] Furthermore, when socioeconomic status is a factor along with race and ethnicity, the risk for obesity is even greater. For example, children from Hispanic and Black lower socioeconomic groups are at significantly greater risk for obesity than their White counterparts.[77]

Obesity-Related Comorbidities

Evaluation of children or adolescents with overweight or obesity should include searching for underlying medical conditions that may cause weight gain and recognizing associated comorbidities that need independent treatment. This is accomplished with a detailed history, including family history of obesity.[99] Accurate weight and height/length are necessary to calculate BMI, which is a key component for the diagnosis of overweight and obesity. Every evaluation should include a blood pressure measurement (using the correct cuff size) and a comparison to normal values for age, height, and sex.[106] Single data points are helpful, but follow-up data points should be used to monitor progress.

Because BMI is an indirect measurement of body fat based on the proportion of weight and height or length, it does not account for body features that will alter proportion (ie, head size, muscular development, torso-to-leg ratio). Alternative methods to measure body fat include a dual x-ray absorptiometry (DEXA) scan, a fat displacement plethysmograph (water and air technique), skin-fold measurements, and circumference body measurements from the waist, arm, leg, and neck. DEXA scan and plethysmography testing is expensive, and the measurements lack adequate standards for pediatrics. Although there are some limitations to using BMI, it is inexpensive and should be considered a first-line screening tool for obesity rather than a diagnostic modality.[107]

Risk factors should be reviewed to identify modifiable changes. When genetic conditions are identified, modifying the home environment can minimize food exposure. Behavior assessment (nutrition and physical activity), medication history, family health history, and a thorough system

review should be part of the evaluation to help identify causes of weight gain and associated comorbidities.[99]

Insulin Resistance

Insulin resistance leads to compensatory hyperinsulinemia, impaired fasting glucose level, impaired glucose tolerance, and subsequent type 2 DM.[108,109] The exact etiology for developing insulin resistance is unclear, however, the following hypotheses are proposed[110–114]:

1. Increased free fatty acid influx from abdominal fat in patients with obesity induces hepatic insulin resistance.
2. Intracellular fatty acyl interferes with the insulin signaling pathway.
3. Release of proinflammatory cytokines in patients with obesity (TNF-α and IL-6) promotes insulin resistance.
4. Reduced adiponectin levels occur in patients with obesity.
5. Excess glucocorticoid levels impact insulin resistance.

Children experience a transient physiological insulin-resistance state during pubertal growth. This is secondary to physiological increases in growth hormone, IGF-1, and sex hormones during puberty.[115,116] However, long-term insulin resistance is associated with elevated blood pressure, increased weight gain, and the development of cardiovascular risk factors.[117–119] Twenty-four percent of adolescents with obesity with impaired glucose tolerance developed type 2 DM over a 12-month follow-up.[120,121] Laboratory monitoring guidelines for fasting blood glucose are summarized in Table 14-3.

TABLE 14-3. Laboratory Testing Guidelines Based on Age, BMI Percentile, and Risk Factors Present

Laboratory Testing Parameters[a]	Fasting Lipid Profile (Cholesterol, HDL, LDL, Triglycerides)	Fasting Glucose (every 2 y)	Hepatic Function (ALT and AST; every 2 y)
Age 2–9 y			
BMI percentile 85th–95th (with no additional risk factors)	X		
BMI percentile ≥ 85th–95th (with additional risk factors)	X		
BMI percentile ≥ 95th–99th (with or without additional risk factors)	X		
BMI percentile ≥ 99th (with or without additional risk factors)	X		
Age 10–18 y			
BMI percentile 85th–95th (with no additional risk factors)	X		
BMI percentile ≥ 85th–95th (with additional risk factors)	X	X	X
BMI percentile ≥ 95th–99th (with or without additional risk factors)	X	X	X
BMI percentile ≥ 99th (with or without additional risk factors)	X	X	X

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[a] Risk factors refer to those risks found during the assessment of family history and physical examination. The laboratory guidelines recommended by the Expert Committee[145] are merely baseline recommendations. Any concerns found during the assessment of the family history and/or physical examination should be evaluated and monitored.

Inflammation

Obesity is considered to be a low-grade proinflammatory condition, with liver and visceral adipose tissue playing a role in the induction of inflammation.[120,121] The adipose tissue releases proinflammatory cytokines (IL-6, IL-8, monocyte chemoattractant protein-1, and TNF-α),[122,123] which induce lipolysis and hepatic synthesis of free fatty acids.[124] These cytokines also decrease insulin receptor signaling, resulting in insulin resistance. The hepatic insulin resistance initiates an innate immune response resulting in the production of CRP, fibrinogen, and clotting factors,[123] which (if unchecked) can induce thrombogenesis.

Various inflammatory markers, including CRP, TNF-α, IL-18, IL-6, and adipocytokines, are associated with metabolic syndrome.[122,125,126] Elevated CRP is associated with obesity, insulin resistance, dyslipidemia, and elevated blood pressure in children.[127,128] CRP is also associated with atherosclerotic plaques and poor cardiovascular outcomes.[129–135] Adiponectin is an anti-inflammatory agent, and its production is attenuated in patients with obesity,[136] leading to an inverse correlation between adiponectin and metabolic syndrome.[137,138] Despite the strong evidence of ongoing inflammation in metabolic syndrome, inflammatory markers are currently not part of metabolic syndrome diagnostic criteria.

CVD and Hypertension

Hypertension is an essential component of pediatric metabolic syndrome,[139] and its development is likely multifactorial. Insulin resistance and subsequent development of hyperinsulinemia are critical for the development of hypertension through a variety of mechanisms including the following:

- renal sodium retention
- vascular smooth muscle growth

- endothelial dysfunction
- increased sympathetic tone
- impaired vasodilation resulting in hypertension[140–143]

Other mechanisms include reduced bioavailability of nitric oxide due to increased oxidative stress, excess glucocorticoid, increased free fatty acids, and increased leptin levels.[144–148] Sinaiko et al indicated that blood pressure level was associated with cluster features of metabolic syndrome but not with individual components (insulin level, triglycerides, HDL, BMI).[149]

Acanthosis Nigricans

Acanthosis nigricans is characterized by hyperpigmented velvety plaques on body folds, seen mainly on the neck. Several studies indicate that acanthosis nigricans is relatively common among children and adolescents, particularly those with obesity. National directives have recognized acanthosis nigricans screening as a noninvasive tool to identify burgeoning changes in metabolism that are associated with numerous risk factors for CVD, including abnormal lipid and glucose metabolism.[150–153] Pediatricians are urged to obtain laboratory tests on children with overweight and obesity who present with acanthosis nigricans, including a complete fasting lipid profile, fasting glucose, and markers of liver function.[26] Unlike family history, ethnicity, lifestyle, behavior, and BMI, which predict future health burdens, the skin sign of acanthosis nigricans represents a physical manifestation of existing metabolic change.

Dyslipidemia

Dyslipidemia, specifically hypertriglyceridemia and low HDL cholesterol, are strongly associated with insulin resistance.[73,119,154] Hyperinsulinemia causes increased hepatic lipogenesis due to increased flux of free fatty acid into the liver.[155,156] This causes increased triglyceride production as very low-density lipoprotein, leading to hyperlipidemia. An inverse relationship exists between the plasma insulin level and the HDL level.[157] Also, hyperinsulinemia causes increased clearance of HDL, resulting in a low HDL level.[158,159]

Dyslipidemia is an integral feature of metabolic syndrome. Dyslipidemia is associated with visceral fat and abdominal obesity. The abnormal lipid profile has the potential to cause premature atherosclerotic changes. Ethnicity variability is one of the limitations of using cutoff values for triglycerides. For example, individuals in Black populations have less frequent hypertriglyceridemia.[105,160] Thus, there is a need to integrate this variability when diagnosing individuals with metabolic syndrome using current diagnostic criteria.

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) has also been implicated as an adverse consequence of carrying excess weight in childhood. In general, it is estimated that 38% of children with obesity have NAFLD.[161] The relationship between NAFLD and the presence or development of metabolic syndrome is less understood, particularly in the pediatric population. However, evidence shows a positive correlation between increased levels of aminotransferases and the number of metabolic syndrome risk factors present among children diagnosed with NAFLD.[162] Schwimmer et al indicated that children with NAFLD have significantly more CVD risk factors associated with metabolic syndrome than children without NAFLD.[163] Although more studies are needed to determine the pathophysiology, natural history, and treatment of NAFLD,[164] an expert committee recognized that biomarkers for liver function, alanine aminotransferase, and aspartate aminotransferase are reasonable markers for NAFLD and are an important part of the laboratory assessment for children with obesity.[10,24]

Polycystic Ovarian Syndrome

Polycystic ovarian syndrome (PCOS) is a clinical disorder characterized by menstrual dysfunction, hyperandrogenism, and polycystic ovaries.[165] Females with PCOS have an increased risk of metabolic syndrome, type 2 DM, and CVD.[166,167] Adolescents with PCOS were 4.5 times as likely to have metabolic syndrome compared with age-matched controls despite adjusting for BMI. Childhood PCOS predicts adulthood metabolic

syndrome.[168] In females, excess visceral adiposity increases androgen precursor synthesis, resulting in hyperandrogenism. Excess visceral adiposity also causes defective insulin receptor signal transduction, resulting in insulin resistance. In a cross-sectional study, Rossi et al found that adolescent girls with PCOS had higher glucose intolerance and increased plasminogen activator inhibitor compared with BMI-matched controls.[169] Stuckey et al reported the clustering of cardiovascular and metabolic risk factors in women with PCOS.[170]

Respiratory Disorders

Asthma and obstructive sleep apnea are more common in individuals with overweight and obesity. Obstructive sleep apnea is present in many children with obesity and increases with more severe cases of obesity.[29,171] Poor sleep quality from sleep apnea may have a negative impact on cognitive functioning.[172]

Psychological Disorders

Psychological disorders including poor self-esteem, mood disorders/depression, disordered eating, body dysmorphia, negative relationship with food, social isolation, and anxiety have been observed in children with overweight and obesity.[14,173] They are also more likely to be bullied in school, which can have a lifelong impact on emotional well-being and quality of life.[14,174] Childhood abuse may play a role in the development of obesity.[175,176] Those who have been victims of sexual assault may develop food addiction as an emotional coping mechanism while also unconsciously benefiting from weight gain to avoid future unwanted attention.

Evaluation and Management of Obesity

Past medical history and physical exam are key components of obesity evaluation. Detailed dietary history, ideally by a registered dietitian, should be a focus of the interview. Medication use may identify appetite-stimulant medications. Questions about fatigue can identify concerns for sleep apnea,

vitamin D deficiency, and depression. Type 2 DM screening should be performed by asking about polyuria, polydipsia, and nocturia. Gastroesophageal reflux disease (GERD) and gallbladder disease are common comorbidities of obesity. Mobility can be limited by slipped capital femoral epiphysis (SCFE) and can impact the ability to participate in physical activity. Physical changes noted in the previous section should direct physical examination.[18]

Laboratory analysis is required for children with overweight and obesity to identify health risks that may be otherwise hidden. Expert committee guidelines on further laboratory testing mirror most of the components of the metabolic syndrome.[24] Table 14-3 lists the tests that should be drawn for different degrees of obesity and at different ages. Physicians should also explore concerns raised during the history and physical exam, which should be investigated fully along with the testing recommended for all children with overweight. Initial management relies on the early identification of children with overweight and obesity and the initiation of lifestyle changes to decrease energy consumption and increase activity. Although this is necessary, prompt involvement with behavioral health, pharmacotherapy, and metabolic surgery is vital, especially in more severe cases of obesity.[18]

Preventative measures should include school-based education to help improve lifestyle changes, including appropriate food choices and regular physical activity, which can lower the risk of obesity and the concomitant risk of chronic diseases.[18,20] The dietary and physical activity behaviors of children and adolescents are influenced by many sectors of society, including families, communities, schools, childcare settings, medical care providers, faith-based institutions, government agencies, the media, and the food and beverage and entertainment industries. Schools play a particularly critical role by establishing a safe and supportive environment with policies and practices that support healthy behaviors. Schools also provide opportunities for students to learn about and practice healthy eating and physical activity behaviors.

Dietary intake data are also of concern. The Total Healthy Eating Index—2020 score is a measure of overall diet quality.[177,178] Diet quality decreased by age group, with a low for ages 14 to 18 years. The age groups 5−8 years, 9−13 years, and 14−18 years were all below the national

average, indicating that the diet quality of children and adolescents fell short of dietary recommendations.[177,178] For children ages 2 to 18 years, the limited intake of vegetables, greens, and beans contributed to lower scores. Total protein intake is insufficient with higher-than-recommended intake of carbohydrates and fats.[178] Additional nutrition-related information is available from the Youth Risk Behavior Survey.[177] Comparing behaviors among high school students indicated positive dietary changes in the past decade (2009–2019) with an impressive decrease in sugar-sweetened beverages from nearly 30% in 2009 down to 15% in 2019. However, there was no difference in the intake of whole fruits and vegetables during that same period. Physical activity showed an overall decreasing trend, though not considered significant in any group between 2011 and 2019 (≥60 min/d on all 7 days, 28.7%−23.2%; attending physical activity class, 31.5% −25.9%; meeting guidelines for aerobic and muscle-strengthening activities, 21.9%−16.5%).[179]

Successful, scientifically sound weight-loss measures with dietary, physical activity, and social support components are needed to assist youth. According to the Youth Risk Behavior Survey in 2011, many adolescents use unhealthy methods to lose or maintain weight, evidenced by the finding that during the 30 days preceding the survey, 12.2% of students went without eating for 24 hours or more, 4.3% had vomited or taken laxatives, and 5.1% had taken diet pills, powders, or liquids without a doctor's advice.[177] Multiple systematic reviews of childhood obesity and expert committee recommendations[18,23–26,29] all agree that child and adolescent obesity treatment should accomplish the following:

- Be directed at motivated families in which the child and/or parents perceive obesity to be a problem and are willing to make lifestyle changes
- Be directed at the entire family rather than just the child with overweight or obesity
- Aim for weight maintenance in children unless BMI is >99th percentile
- Be more intensive and comprehensive than the norm
- Combine changes in diet with changes in physical activity and/or the reduction in sedentary behavior

Clinical Approach for Children or Adolescents With Overweight or Obesity

The evidence-based analysis by the Academy of Nutrition and Dietetics of pediatric overweight literature on intervention programs reports strong evidence for multicomponent, family-based programs for children between the ages of 5 and 12 years and limited evidence for multicomponent, family-based programs for adolescents. Formats may vary with adolescents and parents together or separated. The components included diet, physical activity, nutrition counseling, and parent or caregiver participation.[180,181] These recommendations are reaffirmed by the Endocrine Society's clinical practice guidelines.[18] Individual focus is insufficient for obesity mitigation. A community-wide effort to promote healthier behaviors is more likely to have lasting effects.[182]

Lifestyle Modification With Nutrition and Physical Activity

Interventions should be based on the family's readiness to change.[14,18] Parents and family members should be counseled regarding the following behaviors that have been associated with an increased risk of childhood and adolescent obesity:

- Restriction of highly palatable foods
- Consumption of high-calorie foods at meals and snacks consumed at and away from home
- Larger portion sizes of meals
- Skipping breakfast

Nutrition

Optimal nutrition, particularly a diet rich in fruits, vegetables, and low-fat dairy (as described in the Dietary Approaches to Stop Hypertension [DASH] diet), has been shown to prevent increases in blood pressure during early childhood.[183] The DASH diet significantly improved measures of systolic and diastolic blood pressure among adolescents with documented hypertension.[184]

Mounting evidence in support of optimal nutrition, physical activity, and weight maintenance to ameliorate obesity and therefore lessen CVD risk has prompted an expert committee to establish 9 core messages for pediatricians to reinforce as preventive and treatment strategies, applicable for both low-risk and high-risk children.[24] Evidence-informed prevention and treatment goals should focus on the following:

1. Limiting sugar-sweetened beverages
2. Encouraging a healthful diet with at least 9 servings of fruits and vegetables daily
3. Limiting television and screen time to 2 hours or less per day
4. Eating breakfast daily
5. Limiting eating away from home
6. Encouraging family meals
7. Limiting portion sizes
8. Engaging in 1 hour or more of moderate to vigorous physical activity each day
9. Breastfeeding exclusively until 6 months of age

For some high-risk children, optimal nutrition, physical activity, and weight maintenance efforts are ineffective at controlling weight and reducing the burden of comorbidities, and a more aggressive intervention is required.

Because of the many variables that contribute to the development of obesity, a multidisciplinary team approach including a physician, dietitian, behavioral health specialist, and nurses should be incorporated into the management of patients with obesity. There is also a need for early recognition in cases when more aggressive therapy options should be considered. Multidisciplinary team clinics with formal programs for intensive lifestyle modification should follow patients closely, monitoring adherence while giving positive encouragement for maintaining compliance.[18,185]

Pharmacotherapy

If intensive lifestyle modifications have not been successful in improving weight management and identified comorbidities, pharmacologic therapy

for weight loss should then be considered as an adjunct to lifestyle modification.[18,29] Orlistat is the only medication that is FDA-approved for weight loss in pediatrics (ages 12–18 y). Although metformin is used to treat obesity in children, it is only approved for the management of type 2 DM. Studies assessing weight-loss medications for long-term pediatric safety and success are not available.[29] The Endocrine Society's assessment, treatment, and prevention guidelines for pediatric obesity recommend discontinuing pharmacologic therapy if BMI has not improved by >4% by 12 weeks after starting therapy.[18]

Vitamin E may have a role in treating some comorbidities (diabetes, dyslipidemia, nonalcoholic steatohepatitis [NASH], and CVD).[186] Antioxidant properties of vitamin E may help minimize inflammatory changes from obesity, however, studies do not show consistent benefits.[6] Lipid-lowering drug therapies, particularly statins, have been approved for use in children as young as 8 years of age at the highest risk.[187]

Metabolic and Bariatric Surgery

The American Society for Metabolic and Bariatric Surgery has published guidelines for selecting patients for bariatric surgery. Indications include a BMI ≥35 kg/m^2 or 120% of the 95th percentile with clinically significant comorbidities such as obstructive sleep apnea (OSA; AHI >5), type 2 DM, idiopathic intracranial hypertension, NASH, Blount's disease, SCFE, GERD, hypertension, or a BMI ≥40 kg/m^2 or 140% of the 95th percentile (whichever is lower). Patients need to show an ability to be compliant with recommendations through an evaluation by a multidisciplinary team. Bariatric surgery is contraindicated when obesity is caused by medically correctable etiology, known substance abuse, or pregnancy or when compliance to postsurgical management may be in question because of medical, psychiatric, psychosocial, or cognitive impairment.[29] Additional recommendations from the Endocrine Society guidelines indicate that patients should attain a Sexual Maturity Rating (Tanner Stage) 4 or 5 and be at final or near-final height.[18]

Surgical options include laparoscopic adjustable gastric banding, Roux-en-Y gastric bypass (RYGB), and vertical sleeve gastrectomy. The FABS-

5+ study has demonstrated with an average of 8-year follow-up, that there was a 29% reduction in BMI following RYGB with an associated improvement in blood pressure, type 2 DM, and dyslipidemia.[188] Comparison studies show an average increase in BMI in adolescents who participated in lifestyle modification programs compared with RYGB.[27,189,190]

Lifelong Weight Management

Individuals with overweight and obesity can lose weight by following lower-calorie diets that vary widely in macronutrient composition. Although caloric composition has been used to promote various diets over the years, caloric restriction is the key determinant of weight loss rather than macronutrient composition. Weight-loss management is focused on minimizing weight gain while allowing for continued growth (see Table 14-1). Further research is needed to determine the optimal dietary macronutrient composition for improving specific comorbid conditions, such as impaired glycemic control, hypertension, and/or CVD risk.[191]

The choice of diet therapy should focus on ease of adherence.[192,193] A successful reducing diet is one that an individual can adhere to for several months to lose 5% to 10% of the initial weight. Greater weight loss is desirable because it is associated, in a linear manner, with greater improvements in CVD disease risk factors, including hemoglobin A1c (HbA1c), blood pressure, triglycerides, and HDL cholesterol.[194] Although dietary interventions for hypertension and other comorbid conditions have shifted to the prescription of dietary patterns, such as the DASH diet,[191,195] such approaches must be combined with caloric restriction to induce clinically meaningful weight loss (as they have in some recent trials).[196,197]

To achieve long-term weight loss, most individuals with obesity must consciously restrict their energy intake, whether by reducing portion sizes, decreasing the energy density of the diet, counting calories (or specific macronutrients), or combining these approaches in some way.[198] Behavioral modification is also an important component of weight-management

programs. If no behavioral or lifestyle changes are instituted, weight lost will likely be regained over time.[199]

Use of Popular Diets

Parents of children with overweight or obesity may have overweight themselves and often look to popular diets as a means of losing weight. Because these diets are often adopted by the family and modified for children or adolescents, a discussion of the use of popular diets for pediatric patients is warranted.

Family-friendly popular diets include elements of healthy eating that are applicable or can be easily modified to safely include children. Popular diets can be effective in reducing weight regardless of the plan or claim because the principal goal is to create a calorie deficit. The more extreme the plan, the more difficult it is to follow over the long term, however. The key for lifelong weight management is following a plan individualized to each person's needs.

According to the Weight Control Registry, adults who are successful at losing weight and keeping it off individualize their lifestyle changes to include eating and exercise behaviors that they can sustain for a lifetime.[200] Therefore, when considering any change in eating behavior, individuals should consider nutrition, food variety, moderate portions, ease of including these into their lifestyle, ways to continue them for an extended time, and opportunities to add physical activity and reduce sitting time. For many, the term "diet" evokes thoughts of something temporary. The resultant "on-off" mindset produces short-term change only and does not address the underlying behaviors that created the need to change eating behaviors in the first place.

Successful weight-reduction programs reduce body weight and body fat gradually by decreasing caloric intake and increasing caloric expenditure. Individual plans may also include healthful foods such as fruits and vegetables in the diet. An increase in physical activity builds or maintains muscle mass and, together with aerobic activity, determines the use of body fat reserves and thus the metabolic rate or the rate of kilocalories being burned. Diets that promise immediate or fast weight loss are not

recommended as they defy the scientific basis for metabolism, particularly in children because their normal growth and development may be inhibited. Such claims are at best misleading and at worst potentially harmful. The mathematics of energy balance estimates that fat loss occurs at the rate of 1 to 2 pounds per week, even when a person severely restricts caloric intake. Weight loss greater than the recommended 1 to 2 pounds per week can only occur by losing muscle mass and water in addition to fat.[201]

Before undertaking a diet, families should set reasonable and reachable goals for weight loss with their health care provider and a registered dietitian. A plan for changing the diet for the family should first be evaluated to ensure that it is compatible with lifestyle and health needs. The family should be able to foresee continuing the plan indefinitely. A lifestyle change is required to prevent periods of on-and-off dieting and regression to the previous habits that initially caused weight gain. On-and-off dieting contributes to weight regain and could negatively impact health and affect chronic disease progression.

Types of Popular Diets

Although a myriad of popular diets exist, most share common claims or principles that enable them to be grouped into a few categories.

Behavioral Weight-Management Plans

Behavioral weight management focuses on changing behaviors related to food intake rather than focusing solely on the foods themselves. This approach promotes the following behaviors:

- Plan what to eat in advance.
- Make physical activity an integral part of the day.
- Eat 3 daily meals that include carbohydrates, proteins, and fats.
- Enjoy fresh foods and flavorful fruits and vegetables in season.
- Focus on smaller portions of high-quality foods.
- Do not skip meals or induce feelings of deprivation.
- Avoid obsessing about eating and dieting.
- Eat without stuffing yourself or feeling guilty.

- Change your environment to avoid overeating or eating foods you do not really want.
- Simply get back on track following a relapse.
- Incorporate mindfulness training.

Behavioral plans emphasize the importance of assessing and creating an environment that increases cues for healthy eating and activity behaviors and minimizes the cues for unhealthy eating and activity behaviors. Helping participants create personal food environments that encourage healthy food-related decisions and/or exposure may be very helpful for long-term weight loss and maintenance. Mindfulness helps develop more awareness of eating habits by recognizing hunger and satiety cues as well as emotional triggers for overeating. Eat Right Now is a mobile phone app using mindfulness training that shows a 40% improvement in the craving of more-calorie-dense foods.[202] That study reports short-term results and does not show long-term lifestyle changes, but it does demonstrate the potential for the app to be a valuable tool for those who have the maturity to include mindfulness in their approach to obesity management.

Behavioral approaches are part of a multidisciplinary approach to weight loss that includes portion control, regular physical activity, self-efficacy, and self-regulation, and the monitoring of eating and weight has been shown to be effective for successful long-term weight management in adults.[181] These principles are also recommended for children and adolescents.[26] Behavioral strategies to help children with overweight and their families include establishing a regular meal and snack pattern; eating smaller portions at meals and snacks; limiting second helpings to fresh fruit and nonstarchy vegetables; selecting lower-calorie dairy products; eating more foods that are baked, broiled, grilled, or boiled instead of fried to reduce calories; selecting healthful snacks that include leaner protein along with fresh fruit, vegetables, or whole grain bread and cereals; and when eating out, selecting more healthful options or splitting larger servings to share with other family members or peers.[25,185]

The focus of behavioral change programs may also influence outcomes. A 2008 study by Epstein et al looked at increasing healthy eating versus reducing more-energy-dense foods to treat pediatric obesity.[203] After a 24-

month family-based behavioral treatment that focused on increasing fruits and vegetables and low-fat dairy versus reducing intake of more-energy-dense foods, children in the group that increase health foods showed a greater reduction in BMI compared with children in the group that reduced more-energy-dense foods at 12 and 24 months. The change in parents followed the same pattern as the change in the children and was significantly correlated ($P < .001$).[203]

Reduced Macronutrient Content Plans

The best known of the low-carbohydrate plans may be the Atkins Diet, followed by the South Beach Diet.[204,205] The Atkins diet relies on a high consumption of protein, high consumption of fiber, substantial vitamin and mineral intake, and low amounts of sugar. Although physical activity is encouraged with the diet plan, the main focus is on high-protein, low-carbohydrate eating. Short-term research studies tracking the progress of adults on the diet have reported high levels of satiety, a temporary improvement in blood lipids and glucose levels, some loss of body fat, and the sparing of muscle protein.[206,207]

Diet plans that focus on healthier fats may produce better health outcomes. For example, in a 2-year trial, researchers concluded that Mediterranean-style diets that are not necessarily lower in fat but focus on healthier fats and lower-carbohydrate diets may be more effective alternatives to low-fat diets.[208] The more positive effects on lipids with the low-carbohydrate diet and on glycemic control seem to hold up over time with the Mediterranean-style diet, and these are recognized as favorable lasting lifestyle changes.[208,209] Whereas reducing the intake of simple sugars may be appropriate for children and adolescents, low-carbohydrate plans should not be universally recommended due to the potential low intake of fiber, nutrients, and kilocalories to support growth and development.

The South Beach Diet, a variation of the carbohydrate-restricted diet, is divided into 3 phases.[205] Phase I allows lean meats, chicken, egg or egg substitutes, fish, olive oil, vegetables, salads, nuts, and some low-fat milk. Phase II introduces lower-glycemic-index carbohydrates in limited amounts. Fruits are recommended for lunch or dinner, but not breakfast.

Whole grain bread, sweet potatoes, and brown or wild rice in modest portions replace white bread, white potatoes, and white rice. Mashed, steamed cauliflower replaces mashed potatoes. Sandwiches are replaced by filled lettuce wraps. This second phase lasts for 2 weeks or until the desired weight is lost. If overindulgence occurs during this phase, the recommendation is to return to phase I for 1 week. Phase III is a lifelong maintenance phase that emphasizes the consumption of "good" carbohydrates and fats with the restriction of "bad" carbohydrates and fats. This low-kilocalorie, high-protein, lower-carbohydrate plan allows healthy fats, high-fiber foods, and selected carbohydrates in moderate amounts. Evidence suggests that a moderate intake of carbohydrates, proteins, and healthy fats facilitates weight management in adults.[210,211] This plan is adaptable for use with children, particularly in phase III. However, the entire family should be committed to adapting these changes into a healthy lifestyle.

The Dean Ornish Diet is one of the most well-known low-fat diets still being used and was originally developed for the prevention and treatment of heart disease, though it became popular for weight loss.[212] The Dean Ornish Diet allows only 10% of kilocalories from fat. It also limits sugar and honey. The restriction on fat and simple sugars prevents individuals from consuming excess kilocalories, and the high fiber content contributes to a feeling of fullness. In addition, the diet promotes whole foods and a high intake of phytochemicals from plant-based foods and forbids meat, nuts, seeds, avocados, white flour, white rice, and fried foods. The diet also advocates for a comprehensive lifestyle change including stress-management training, smoking cessation, meditation, and moderate exercise. Strong scientific evidence supports the plan's claim to reverse the risk of heart disease in adults, and the resulting weight loss is due to the caloric restriction.[211] However, no studies have evaluated the use of this diet in children or adolescents.

The Paleo Diet by Loren Cordain, PhD, is a high-protein, high-fiber eating plan that allows fresh lean meats, eggs, fish, fruits and vegetables, nuts and seeds, and "healthier" fats such as olive oil and coconut oil.[213] The diet claims that by changing eating habits to resemble those of cavemen or Stone Age humans, weight can be lost and chronic diseases such as

diabetes, heart disease, and cancer can be avoided. Foods that are not allowed on the diet include processed foods, wheat and other grains and legumes, dairy, potatoes, salt, refined sugar, and refined vegetable oils such as canola. No large randomized clinical trials have been conducted on this diet, but short-term studies with very small sample sizes comparing the Paleo diet to other eating plans have reported decreases in caloric intake, weight, and HbA_{1c} after 12 weeks.[214–218] More recent studies do not show that the Paleo diet is superior to other diets in regards to glucose and insulin homeostasis.[218] These studies were all done in adults, and this plan would not be recommended for children or adolescents because of the potential for nutrient deficiencies due to the restriction of dairy, grains, and legumes.

Food Group Guides and Exchange Systems

One example of a food group or exchange plan is the Volumetrics Weight-Control Plan.[219] Food choices in this plan are based on kilocalorie density. The fat, fiber, protein, and water content of foods all affect energy or kilocalorie density. By eating predominantly filling, less-kilocalorie-dense foods, smaller portions of a few more-kilocalorie-dense foods can be included, and the person will still lose weight due to the overall kilocaloric restriction. Less-kilocalorie-dense (or less-energy-dense) foods include fruits and vegetables, skim milk, broth-based soups, fat-free salad dressings, pasta, cooked high-fiber grains, potatoes, legumes, low-fat meats, salads, low-fat soups, low-fat cheeses, cottage cheese, frozen yogurt, and kilocalorie-free beverages. This diet is complemented by regular exercise and behavior management, which includes keeping a food and exercise log, not skipping meals, identifying and managing cues to overeating, managing stress, and planning to handle setbacks. No foods are forbidden, and treats are allowed if the predominant eating style has a low kilocalorie density.

No studies have evaluated the use of this diet in children or adolescents. However, it does contain many of the elements recommended, including focusing on consuming more than 5 fruits and vegetables per day, minimizing sweetened beverages, increasing physical activity, and reducing sedentary behaviors, as well as eating breakfast daily, limiting meals outside the home (including at fast-food venues and other restaurants),

allowing the child to self-regulate his or her meals, and avoiding overly restrictive behaviors.[18,29,185]

Food Timing

Intermittent fasting has become popular. It is an eating pattern that involves periods of fasting, typically lasting 16 hours, allowing 8 hours for eating during the day. Other patterns may be used. Fasting often limits oral intake because of caloric restriction and associated weight management. Other potential health benefits include improved insulin sensitivity, reduced inflammation, cellular repair, and the optimization of brain health. However, further research is needed to fully understand the long-term effects and mechanisms behind these potential benefits.[220]

Intermittent fasting is not recommended for children, because of the need for regular meals and snacks that provide a variety of nutrients, including carbohydrates, proteins, fats, vitamins, and minerals. Restricting calorie intake through intermittent fasting may lead to disordered eating and nutrient deficiencies.

Commercial Meal and Snack Replacements

One of the largest commercial weight-loss programs is Weight Watchers (WW).[221] WW was one of the first programs to incorporate a walking program and emphasize physical activity as a necessary part of dieting. The POINTS Weight-Loss System assigns a point value to activities and food that is determined by the number of kilocalories, total fat, and dietary fiber in a defined serving. Each person is given a daily POINTS target that will lead to a caloric deficit that translates into 1 to 2 pounds per week of weight loss. A second plan, called the Core Plan, focuses on choosing foods with low energy density. By routinely monitoring hunger cues and with an allowance for periodic “indulgences,” the Core Plan has been shown to produce weight losses equal to the POINTS system. Strong evidence supports a lifestyle plan that includes regular monitoring and support systems using commonly available foods. The emphasis on portion control and low-energy–density foods can be translated to many food settings, and the recipes help teach dieters to prepare dishes that are lower in kilocalories. Members do pay a fee for the weight-loss services (including those online)

and for Weight Watchers–branded food items.[221] WW does not recommend its plan for children and instead discusses children's needs in terms of 2 goals: ensuring the child grows and develops normally and helping the child reach a healthy weight. WW did have a child-focused mobile phone app called kurbo, but it is no longer available.

Nutrisystem is another commercially available weight-loss program that offers home delivered prepackaged meals and snacks. The goal of this program is to help with weight management by providing portion-controlled, nutritionally balanced meals and snacks designed to promote weight loss and healthy eating habits. There is some evidence suggesting participation in a portion-controlled diet program like Nutrisystem may be more effective than a self-directed approach.[222] Nutrisystem has no products intended for children or adolescents.

Noom is a popular app-based program that uses a cognitive behavioral approach with coaching and nutrition education. The user can log in to the mobile phone app for personalized coaching, food tracking, and community support from other users. The app offers nutrition guidance to help make informed decisions on foods regarding caloric density, nutrient density, portion control, and strategies for incorporating healthier choices into meals and snacks. Limited data are available to demonstrate the efficacy of this program; studies currently are limited to retrospective review but show success with weight management.[223]

Other Plans

Eat Right for Your Type was on the *New York Times* bestseller list and remains a popular diet plan today. The book provides 4 diets based on the blood types O, A, B, and AB. The book has a list of protein sources for each blood type, as well as a long list of forbidden foods including specific meats and poultry, seafood, dairy, eggs, oils and fats, nuts and seeds, beans, legumes, cereals, breads, muffins, grains, pasta, vegetables, fruit, juices, fluids, spices, condiments, herbal teas, and other beverages. Each of the blood-type diets consists of whole, unprocessed foods, and all of these diets recommend the consumption of vegetables, which provide fiber, health-promoting nutrients, and phytochemicals. Physical activity, stress management, and reduction of health risks in the environment are integrated

into each plan. However, no scientific evidence validates the claim that a diet should be defined by blood type. By limiting specific foods and sometimes food groups, those who follow one of these diets can lose weight, but the elimination of specific foods and groups is based on a premise without adequate scientific evidence.[199] A recent systematic review of the evidence by Cusack et al concluded, "no evidence currently exists to validate the purported health benefits of blood type diets."[224] This diet plan is not recommended for children or adolescents.

Diets Designed for Use With Children and Adolescents

School-Based Programs

School-based programs play an important role in the prevention and management of childhood obesity through promoting healthy habits, nutrition education, and physical activities.[225] Education focused on healthy nutrition has been the most effective mechanism for prevention[226] whereas programs combining nutrition education and promoting physical activity have been more impactful for weight loss.[227] School-based programs provide a setting where high-impact behavioral changes can be emphasized through participation in physical education, the promotion of water consumption over sugary drinks, the availability of nutritious meal options in cafeterias, and the discouragement of unhealthy snacks and vending machines. Programs working with children ages 15 to 19 years old were most effective ($r = 0.133$), and programs working with boys and girls were more effective ($r = 0.110$) than those working with girls alone ($r = 0.073$). Program effectiveness was higher with older children in programs including physical activity and nutrition education combined with parental involvement and lasting at least 1 year. [227]

Balanced-Macronutrient Low-Kilocalorie Diets

Evidence suggests that short-term and long-term reduced energy (900–1200 kcal) may be an effective part of a multicomponent weight-management program in children ages 6 to 12 years.[18] In the adolescent population, the

use of reduced energy (not less than 1200 kcal) is generally effective for short-term weight loss, but without a continued dietary intervention, weight is regained.[18]

Traffic Light Diet

The Traffic Light Diet was designed to promote weight loss, provide adequate kilocalories and nutrients for growth and development, and be easy to follow.[228] The diet divides foods into 5 categories, with the foods in each category separated into 3 color groups: green, yellow, and red. These colors correspond to the colors of a traffic light and signify GO (green), meaning eat as much as you like of these foods; approach with CAUTION (yellow), meaning eat in moderate amounts; and STOP (red), meaning rarely or occasionally eat. Green foods are those foods that contain <20 kcal per average serving and are found only in the vegetable and "free foods" categories. Yellow foods are staple foods that provide most of the nutrition from the protein, grain, fruit, vegetable, and milk and dairy food groups; a child should eat these foods in recommended amounts to obtain adequate nutrition. Red foods are foods that are high in calories from sugar or fat and that exceed the caloric value of yellow food, thereby providing low nutrient density. Initially, participants were limited to 4 red foods per week and 900 to 1200 calories, with some later studies using 1200 to 1500 calories.[228,229] Traffic Light labeling of foods can be an effective tool because it works within the developmental aspects of children of early elementary school age. There is some debate on how foods should be labeled; however, positive outcomes have been seen when traffic light methodology is followed. Long-term efficacy is not established.[229]

Results from a study by Epstein et al showed that a parent and child intervention with diet and self-monitoring by both parent and child (group I) was clearly superior to diet and self-monitoring by the child alone (group II) and no diet or self-monitoring (group III, the control group).[230] After 8 months and 21 months of treatment, the results for children in the 3 treatment groups were similar. Children's weight decreased by 16.6%, 18.6%, and 16.1% in groups I, II, and III, respectively. However, after 5 years, the children in group I maintained their relative weight change (–

13.6%), while children in group II were at baseline (+3.3%) and the children in group III were heavier (+7%).[230]

MyPlate

MyPlate was designed by the U.S. Department of Agriculture to replace the Food Guide Pyramid and is a general online guide for diet and exercise primarily for adults; however, it also includes a plan for preschool children.[231] MyPlate is also part of a larger initiative based on the *2020–2025 Dietary Guidelines for Americans* to help consumers and their families make healthier food choices.[231,232] MyPlate illustrates the 5 food groups using the image of a plate, which is familiar to most, and it shows relational portions of various food groups.

The following nutrition messages are emphasized in the online material:

- Balance calories
  - Enjoy your food, but eat less.
  - Avoid oversized portions.
- Foods to increase
  - Make half of your plate fruits and vegetables.
  - Make at least half of your grains whole grains.
  - Switch to fat-free or low-fat (1%) milk.
- Foods to reduce
  - Limit high-sodium-containing foods (eg, soup, bread, and frozen meals) and choose foods with lower sodium content.
  - Drink water instead of sugary drinks.

MyPlate's area of emphasis has been improving awareness of portion sizes and total daily calorie limits to help consumer efforts to achieve and maintain a healthy weight.[178,231] Studies evaluating the use of MyPlate materials are limited[233]; however, at least one comparative study has shown that MyPlate can be used for weight management.[234]

Multidisciplinary Behavior-Change Programs

There are various multidisciplinary behavior-modification programs for children with overweight and their families, including the following:

- New Moves
- Keep ME Healthy
- Strong People-Healthy Weight
- Trim Kids
- Smart Moves and Bright Bodies
- SHAPEDOWN
- KidShape[235,236]

Most successful programs often include the disciplines of nutrition, exercise physiology, endocrinology, psychology, family therapy, adolescent medicine, family medicine, and/or behavioral and developmental pediatrics. Each program is designed for a target group: New Moves is for girls only whereas the Smart Moves and Bright Bodies programs (https://www.smartmovesforkids.com/) are for adolescent children living in inner city or urban locations.

Conclusion

Obesity and associated metabolic disturbances are a public health crisis. Obesity causes changes to metabolism resulting in insulin resistance and inflammation that can result in systemic comorbidities with negative health consequences (CVD, type 2 DM, NASH, OSA). These changes in the pediatric population suggest that a shift in metabolism is fueled by excess body weight. Further, the presence of risk factors in early childhood means that damage to the cardiovascular system has begun. When metabolic risk factors present in a cluster, the clinical course and health outcomes for that child are compromised, unless interventions are undertaken.

A comprehensive approach to the assessment of metabolic syndrome and its components allows the pediatrician to observe the development of metabolic risk at its earliest stages and to intervene to arrest the prospect of lifelong CVD risk. Mounting evidence in support of optimal nutrition, physical activity, and weight maintenance to ameliorate obesity and therefore lessen CVD risk has prompted expert guidelines.[18,24,27,29]

Many diets will result in weight loss or weight maintenance in adults and children because they lower and control caloric intake. Scientific evidence indicates that a successful weight-loss or weight-maintenance plan for

children and adolescents should include reduced kilocalorie intake through the consumption of ≥ 5 servings of fruits and vegetables per day and the minimization or elimination of sugar-sweetened beverages (both of these elements are present in a balanced-macronutrient reduced-kilocalorie diet and the Traffic Light Diet), as well as behavioral components (eg, eating breakfast daily, limiting meals outside the home [including at fast-food venues and other restaurants], eating family meals at least 5 or 6 times per week, allowing the child to self-regulate his or her meals, and avoiding overly restrictive behaviors). Long-term weight management happens when a plan is individualized to a family's needs and preferences. Kilocalorie-controlled and portion-controlled diets such as the balanced-macronutrient low-calorie diets and the Traffic Light Diet have been studied over time and may be more conducive to long-term compliance than low-fat and carbohydrate-restricted diets.

Research indicates that popular and fad diets have the potential to result in weight loss in adults, however, they have not been studied for weight loss in children and adolescents. These diets are not recommended for growing children and adolescents because of the elimination of key food groups, greater-than-recommended caloric restriction, adverse behavioral patterns of eating, and/or a lack of scientific evidence for the basis of the diet's recommendations. The key requirement for the dietary treatment of children and adolescents with overweight is to initiate and maintain lifelong healthy eating habits that focus on unhealthy weight in the short term and foster improved health outcomes in the long term. Family involvement—particularly from parents or caregivers—in weight control, weight maintenance, and weight-loss interventions promotes weight loss in children, and the use of behavior-modification techniques as an integral part of the program improves outcomes for both children and parents.[237]

Key prevention strategies include encouraging multidisciplinary management (ie, a school-based education or hospital-centered program), discouraging high-calorie, nonnutritious foods (eg, sugar-sweetened beverages), encouraging whole fruits, and increasing physical activity to at least 20 minutes but optimally 60 minutes per day for at least 5 days a week.[18]

For children presenting with substantial health risks associated with metabolic syndrome, pediatricians should focus on a comprehensive intervention strategy, including optimal nutrition, physical activity, weight maintenance, and (when appropriate) pharmacological and/or surgical intervention.

Test Your Knowledge Questions

1. According to the Academy of Nutrition and Dietetics Evidence Analysis Library, which of the following clinical approaches had positive effects when working with children ages 5 to 12 years with overweight and obesity?
   A. Multicomponent, school-based
   B. Behavioral, family-based
   C. Multicomponent, family-based
   D. Diet, family-based
2. The parents of an 8-year-old child have decided to implement changes that will promote healthier lifestyle habits among all the family members. Which one of the following is recommended when there is readiness to change?
   A. Adding a salad or vegetable to lunch and dinner meals
   B. Substituting the dinner soda with a caffeine-free beverage
   C. Limiting family television viewing time to 3 hours a day
   D. Taking the family for a 30-minute walk after dinner
3. Which of the following diets have been studied for use with children or adolescents?
   A. MyPlate and the (Children's) Atkins Plan
   B. The Traffic Light Diet and Behavior Change
   C. The Traffic Light Diet and the Pritikin Plan
   D. The Volumetrics and the Exchange Plans
4. Which of the following is NOT a reason why popular/fad diets commonly used by adults are not recommended for children?
   A. Potential negative growth risks resulting from eliminating/decreasing a key food group
   B. Caloric restriction that is higher than recommended

C. Promotion of an adverse eating pattern
D. Adequate scientific data for use in children for the diet/plan

References

1. Stierman B, Afful J, Carroll MD, et al. National Health and Nutrition Examination Survey 2017—March 2020 prepandemic data files—development of files and prevalence estimates for selected health outcomes. *Natl Health Stat Reports*. 2021;158. https://doi.org/10.15620/cdc:106273
2. Leslie BR. Metabolic syndrome: historical perspectives. A*m J Med Sciences*. 2005;330(6):264–268. https://doi.org/10.1097/00000441-200512000-00002
3. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. *JAMA*. 2014;311(8):806–814. https://doi.org/10.1001/jama.2014.732
4. Cunningham S, Hardy S, Jones R, et al. Changes in the incidence of childhood obesity. *Pediatrics*. 2022;150(2):1. https://doi.org/10.1542/peds.2021-053708
5. World Health Organization obesity and overweight fact sheet. World Health Organization. Updated 2021. Accessed Oct 2, 2023. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
6. Kansra AR, Lakkunarajah S, Jay MS. Childhood and adolescent obesity: a review. *Front Pediatr*. 2021;8:581461. https://doi.org/10.3389/fped.2020.581461
7. American Diabetes Association. 2. classification and diagnosis of diabetes: Standards of medical care in diabetes—2021. *Diabetes Care*. 2021;44(suppl 1):S15–S33. https://doi.org/10.2337/dc21-S002
8. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents—National Heart, Lung. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: summary report. *Pediatrics*. 2011;128(suppl 5):213. https://doi.org/10.1542/peds.2009-2107C

9. Flynn JT, Falkner BE. New clinical practice guideline for the management of high blood pressure in children and adolescents. *Hypertension*. 2017;70(4):683–686. https://doi.org/10.1161/HYPERTENSIONAHA.117.10050
10. Vos MB, Abrams SH, Barlow S, et al. NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children: recommendations from the expert committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). *J Pediatr Gastroenterol Nutr*. 2017;64(2):319–334. https://doi.org/10.1097/MPG.0000000000001482
11. Legro RS, Arslanian SA, Ehrmann DA, et al. Diagnosis and treatment of polycystic ovary syndrome: an endocrine society clinical practice guideline. *J Clin Endocrinol Metabol*. 2013;98(12):4565–4592. https://doi.org/10.1210/jc.2013-2350
12. Wise MS, Nichols CD, Grigg-Damberger MM, et al. Executive summary of respiratory indications for polysomnography in children: an evidence-based review. *Sleep*. 2011;34(3):389–98AW. https://doi.org/10.1093/sleep/34.3.389
13. Zametkin AJ, Zoon CK, Klein HW, Munson S. Psychiatric aspects of child and adolescent obesity: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry*. 2004;43(2):134–150. https://doi.org/10.1097/00004583-200402000-00008
14. Rankin J, Matthews L, Cobley S, et al. Psychological consequences of childhood obesity: psychiatric comorbidity and prevention. *Adolesc Health Med Ther*. 2016;7:125–146. https://doi.org/10.2147/ahmt.s101631
15. Rock CL, Thomson C, Gansler T, et al. American Cancer Society guideline for diet and physical activity for cancer prevention. *CA Cancer J Clin*. 2020;70(4):245–271. https://doi.org/10.3322/caac.21591
16. Qasim A, Turcotte M, Souza RJ, et al. On the origin of obesity: identifying the biological, environmental and cultural drivers of genetic risk among human populations. *Obesity Rev*. 2018;19(2):121–149. https://doi.org/10.1111/obr.12625

17. Upadhyay J, Farr O, Perakakis N, et al. Obesity as a disease. *Med Clinics North Am*. 2018;102(1):13–33. https://doi.org/10.1016/j.mcna.2017.08.004
18. Styne DM, Arslanian SA, Connor EL, et al. Pediatric obesity—assessment, treatment, and prevention: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metabol*. 2017;102(3):709–757. https://doi.org/10.1210/jc.2016-2573
19. Guo SS, Chumlea WC. Tracking of body mass index in children in relation to overweight in adulthood. *AmJ Clin Nutr*. 1999;70(1):145–148. https://doi.org/10.1093/ajcn/70.1.145s
20. Freedman DS, Khan LK, Serdula MK, et al. The relation of childhood BMI to adult adiposity: the bogalusa heart study. *Pediatrics*. 2005;115(1):22–27. https://doi.org/10.1542/peds.2004-0220
21. Freedman DS, Wang J, Thornton JC, et al. Classification of body fatness by body mass index–for-age categories among children. *Arch Pediatr Adolesc Med*. 2009;163(9):805–811. https://doi.org/10.1001/archpediatrics.2009.104
22. Freedman DS, Khan LK, Dietz WH, et al. Relationship of childhood obesity to coronary heart disease risk factors in adulthood: the Bogalusa heart study. *Pediatrics*. 2001;108(3):712–718. https://doi.org/10.1542/peds.108.3.712
23. Washington R. Overview of the expert: recommendations for the assessment, prevention, and treatment of child and adolescent overweight and obesity. *Obes Management*. 2008;4(1):2–23. https://doi.org/10.1089/obe.2008.0116
24. Barlow SE, Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: Summary report. *Pediatrics*. 2007;120(suppl):S164–S192. https://doi.org/10.1542/peds.2007-2329C
25. Kirk S, Scott BJ, Daniels SR. Pediatric obesity epidemic: treatment options. *J Am Dietetic Assoc*. 2005;105(5):44–51. https://doi.org/10.1016/j.jada.2005.02.013
26. Spear BA, Barlow SE, Ervin C, et al. Recommendations for treatment of child and adolescent overweight and obesity. *Pediatrics*.

2007;120(suppl):S254–S288. https://doi.org/10.1542/peds.2007-2329F
27. Armstrong SC, Bolling CF, Michalsky MP, Reichard KW. Pediatric metabolic and bariatric surgery: evidence, barriers, and best practices. *Pediatrics*. 2019;144(6):e20193223. https://doi.org/10.1542/peds.2019-3223
28. Einhorn D, Reaven GM, Cobin RH, et al. American College of Endocrinology position statement on the insulin resistance syndrome. *Endocr Pract*. 2003;9(3):237–252. https://doi.org/10.4158/EP.9.S2.5
29. Pratt JSA, Browne A, Browne NT, et al. ASMBS pediatric metabolic and bariatric surgery guidelines, 2018. *Surg Obesity Rel Dis*. 2018;14(7):882–901. https://doi.org/10.1016/j.soard.2018.03.019
30. Skinner AC, Ravanbakht SN, Skelton JA, et al. Prevalence of obesity and severe obesity in US children, 1999–2016. *Pediatrics*. 2018;141(3):e20173459. https://doi.org/10.1542/peds.2017-3459
31. Labarthe A, Fiquet O, Hassouna R, et al. Ghrelin-derived peptides: a link between appetite/reward, GH axis, and psychiatric disorders? *Front Endocrinol*. 2014;5:163. https://doi.org/10.3389/fendo.2014.00163
32. Androutsos O, Moschonis G, Mavrogianni C, et al. Identification of lifestyle patterns, including sleep deprivation, associated with insulin resistance in children: the healthy growth study. *Eur J Clin Nutr*. 2014;68(3):344–349. https://doi.org/10.1038/ejcn.2013.280
33. Chaput J. Is sleep deprivation a contributor to obesity in children? *Eat Weight Disord*. 2016;21(1):5–11. https://doi.org/10.1007/s40519-015-0233-9
34. Blaha MJ, Bansal S, Rouf R, et al. A practical "ABCDE" approach to the metabolic syndrome. *Mayo Clinic Proceed*. 2008;83(8):932–943. https://doi.org/10.1016/S0025-6196(11)60770–2
35. Huang TT, Morrison JA, Aronson Friedman L, et al. Metabolic syndrome in childhood predicts adult metabolic syndrome and type 2 diabetes mellitus 25 to 30 years later. commentary. *J Pediatr*. 2008;152(2). https://doi.org/10.1016/j.jpeds.2007.09.010
36. Fox CS, Massaro JM, Hoffmann U, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham heart study. *Circulation*.

2007;116(1):39–48. https://doi.org/10.1161/CIRCULATIONAHA.106.675355
37. Pou KM, Massaro JM, Hoffmann U, et al. Visceral and subcutaneous adipose tissue volumes are cross-sectionally related to markers of inflammation and oxidative stress: the Framingham heart study. *Circulation*. 2007;116(11):1234–1241. https://doi.org/10.1161/CIRCULATIONAHA.107.710509
38. Wozniak SE, Gee LL, Wachtel MS, Frezza EE. Adipose tissue: the new endocrine organ? a review article. *Dig Dis Sci*. 2009;54(9):1847–1856. https://doi.org/10.1007/s10620-008-0585-3
39. Antuna-Puente B, Feve B, Fellahi S, Bastard J. Adipokines: the missing link between insulin resistance and obesity. *Diab Metabol*. 2007;34(1):2–11. https://doi.org/10.1016/j.diabet.2007.09.004
40. Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. *Arteriosclerosis, Thrombos Vasc Biol*. 2006;26(5):968–976. https://doi.org/10.1161/01.ATV.0000216787.85457.f3
41. Groner JA, Joshi M, Bauer JA. Pediatric precursors of adult cardiovascular disease: noninvasive assessment of early vascular changes in children and adolescents. *Pediatrics*. 2006;118(4):1683–1691. https://doi.org/10.1542/peds.2005-2992
42. Woo KS, Chook P, Yu CW, et al. Overweight in children is associated with arterial endothelial dysfunction and intima-media thickening. *Int J Obes*. 2004;28(7):852–857. https://doi.org/10.1038/sj.ijo.0802539
43. Pai JK, Pischon T, Ma J, et al. Inflammatory markers and the risk of coronary heart disease in men and women. *New Engl J Med*. 2004;351(25):2599–2610. https://doi.org/10.1056/NEJMoa040967
44. Meyer AA, Kundt G, Lenschow U, et al. Improvement of early vascular changes and cardiovascular risk factors in obese children after a six-month exercise program. *J Am Coll Cardiol*. 2006;48(9):1865–1870. https://doi.org/10.1016/j.jacc.2006.07.035
45. Watts K, Beye P, Siafarikas A, et al. Exercise training normalizes vascular dysfunction and improves central adiposity in obese adolescents. *J Am Coll Cardiol*. 2004;43(10):1823–1827. https://doi.org/10.1016/j.jacc.2004.01.032

46. McBride PE, Einerson JA, Grant H, et al. Putting the diabetes prevention program into practice: a program for weight loss and cardiovascular risk reduction for patients with metabolic syndrome or type 2 diabetes mellitus. *J Nutr Health Aging*. 2008;12(10):745–750. https://doi.org/10.1007/BF03028624
47. Alberti KGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications, part 1: diagnosis and classification of diabetes mellitus, provisional report of a WHO consultation. *Diabetic Med*. 1998;15(7):539–553. https://doi.org/10.1002/(SICI)1096–9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S
48. Alberti KGMM, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120(16):1640–1645. https://doi.org/10.1161/CIRCULATIONAHA.109.192644
49. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation*. 2005;112(17):2735–2752. https://doi.org/10.1161/CIRCULATIONAHA.105.169404
50. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285(19):2486–2497. https//doi.org/10.1001/jama.285.19.2486
51. Reisinger C, Nkeh-Chungag BN, Fredriksen PM, Goswami N. The prevalence of pediatric metabolic syndrome—a critical look on the discrepancies between definitions and its clinical importance. *Int J Obes*. 2021;45(1):12–24. https://doi.org/10.1038/s41366-020-00713-1
52. Steinberger J, Daniels SR, Eckel RH, et al. Progress and challenges in metabolic syndrome in children and adolescents: a scientific statement

from the American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular Nursing; and Council on Nutrition, Physical Activity, and Metabolism. *Circulation*. 2009;119(4):628–647. https://doi.org/10.1161/CIRCULATIONAHA.108.191394

53. Dai S, Fulton JE, Harrist RB, et al. Blood lipids in children: age-related patterns and association with body-fat indices—Project HeartBeat. *Am J Prevent Med*. 2009;37(suppl 1):S56–S64. https://doi.org/10.1016/j.amepre.2009.04.012
54. Moran A, Jacobs DR, Jr, Steinberger J, et al. Changes in insulin resistance and cardiovascular risk during adolescence: establishment of differential risk in males and females. *Circulation*. 2008;117(18):2361–2368. https://doi.org/10.1161/CIRCULATIONAHA.107.704569
55. Labarthe DR, Dai S, Fulton JE, Harrist RB, Shah SM, Eissa MA. Systolic and fourth- and fifth-phase diastolic blood pressure from ages 8 to 18 years: Project HeartBeat. *Am J Prevent Med*. 2009;37(suppl 1):S86–S96. https://doi.org/10.1016/j.amepre.2009.04.014
56. Srinivasan SR, Myers L, Berenson GS. Rate of change in adiposity and its relationship to concomitant changes in cardiovascular risk variables among biracial (black-white) children and young adults: the Bogalusa heart study. *Metabol Clin Experiment*. 2001;50(3):299–305. https://doi.org/10.1053/meta.2001.21019
57. Kelsey MM, Zeitler PS. Insulin resistance of puberty. *Curr Diab Rep*. 2016;16(7):64. https://doi.org/10.1007/s11892-016-0751-5
58. Ford, Earl S., MD, MPH, Li, Chaoyang, MD, PhD. Defining the metabolic syndrome in children and adolescents: will the real definition please stand up? *J Pediatrics*. 2008;152(2):160–164.e13. https://doi.org/10.1016/j.jpeds.2007.07.056
59. Jolliffe CJ, Janssen I. Development of age-specific adolescent metabolic syndrome criteria that are linked to the Adult Treatment Panel III and International Diabetes Federation criteria. *J Am Coll Cardiol*. 2007;49(8):891–898. https://doi.org/10.1016/j.jacc.2006.08.065

60. Moreno LA, Joyanes M, Mesana MI, et al. Harmonization of anthropometric measurements for a multicenter nutrition survey in Spanish adolescents. *Nutrition*. 2003;19(6):481–486. https://doi.org/10.1016/S0899-9007(03)00040–6
61. Moreno L, Pineda I, Rodriguez G, et al. Waist circumference for the screening of the metabolic syndrome in children. *Acta Pædiatr*. 2002;91(12):1307–1312. https://doi.org/10.1111/j.1651-2227.2002.tb02825.x
62. Seidell JC, Pérusse L, Després JP, Bouchard C. Waist and hip circumferences have independent and opposite effects on cardiovascular disease risk factors: the Quebec Family Study. *Am J Clin Nutr*. 2001;74(3):315–321. https://doi.org/10.1093/ajcn/74.3.315
63. Moran A, Jacobs DR, Steinberger J, et al. Association between the insulin resistance of puberty and the insulin-like growth factor-I/growth hormone axis. *J Clin Endocrinol Metabol*. 2002;87(10):4817–4820. http://doi.org/10.1210/jc.2002-020517
64. Hannon TS, Janosky J, Arslanian SA. Longitudinal study of physiologic insulin resistance and metabolic changes of puberty. *Pediatric Res*. 2006;60(6):759–763. https://doi.org/10.1203/01.pdr.0000246097.73031.27
65. Bremer AA, Auinger P, Byrd RS. Relationship between insulin resistance–associated metabolic parameters and anthropometric measurements with sugar-sweetened beverage intake and physical activity levels in US adolescents: findings from the 1999–2004 National Health and Nutrition Examination Survey. *Arch Pediatr Adolesc Medi*. 2009;163(4):328–335. https://doi.org/10.1001/archpediatrics.2009.21
66. Kosova EC, Auinger P, Bremer, AA. The relationships between sugar-sweetened beverage intake and cardiometabolic markers in young children. *J Acad Nutr Dietet*. 2013;113(2):219–227. https://doi.org/10.1016/j.jand.2012.10.020
67. Ambrosini GL, Oddy WH, Huang RC, et al. Prospective associations between sugar-sweetened beverage intakes and cardiometabolic risk factors in adolescents. *Am J Clin Nutr*. 2013;98(2):327–334. https://doi.org/10.3945/ajcn.112.051383

68. Bremer AA, Byrd RS, Auinger P. Differences in male and female adolescents from various racial groups in the relationship between insulin resistance-associated parameters with sugar-sweetened beverage intake and physical activity levels. *Clin Pediatr*. 2010;49(12):1134–1142. https://doi.org/10.1177/0009922810379043
69. Dubois L, Farmer A, Girard M, Peterson K. Regular sugar-sweetened beverage consumption between meals increases risk of overweight among preschool-aged children. *J Ame Dietet Assoc*. 2007;107(6):924–934. https://doi.org/10.1016/j.jada.2007.03.004
70. Harrington S. The role of sugar-sweetened beverage consumption in adolescent obesity: a review of the literature. *J School Nurs*. 2008;24(1):3–12. https://doi.org/10.1177/10598405080240010201
71. Fletcher S, Wright C, Jones A, et al. Tracking of toddler fruit and vegetable preferences to intake and adiposity later in childhood. *Matern Child Nutr*. 2017;13(2):e12290. https://doi.org/10.1111/mcn.12290
72. Maffeis C, Pietrobelli A, Grezzani A, et al. Waist circumference and cardiovascular risk factors in prepubertal children. *Obesity*. 2001;9(3):179–187. https://doi.org/10.1038/oby.2001.19
73. Freedman DS, Serdula MK, Srinivasan SR, Berenson GS. Relation of circumferences and skinfold thicknesses to lipid and insulin concentrations in children and adolescents: the Bogalusa Heart Study. *Amo J Clin Nutr*. 1999;69(2):308–317. https://doi.org/10.1093/ajcn/69.2.308
74. Freedman DS, Dietz WH, Srinivasan SR, Berenson GS. The relation of overweight to cardiovascular risk factors among children and adolescents: the Bogalusa Heart Study. *Pediatrics*. 1999;103(6):1175–1182. https://doi.org/10.1542/peds.103.6.1175
75. Savva SC, Tornaritis M, Savva ME, et al. Waist circumference and waist-to-height ratio and better predictors of cardiovascular disease risk factors in children than body mass index. *Int J Obes*. 2000;24(11):1453–1458. https://doi.org/10.1038/sj.ijo.0801401
76. Marshall SJ, Gorely T, Biddle SJH. A descriptive epidemiology of screen-based media use in youth: a review and critique. *J Adolesc*. 2006;29(3):333–349. https://doi.org/10.1016/j.adolescence.2005.08.016

77. Singh GK, Kogan MD, Van Dyck, PC Siahpush M. Racial/ethnic, socioeconomic, and behavioral determinants of childhood and adolescent obesity in the United States: analyzing independent and joint associations. *Ann Epidemiol*. 2008;18(9):682–695. https://doi.org/10.1016/j.annepidem.2008.05.001
78. Kotz K, Story M. Food advertisements during children's Saturday morning television programming: are they consistent with dietary recommendations? *J Am Dietet Assoc*. 1994;94(11):1296–1300. https://doi.org/10.1016/0002-8223(94)92463–5
79. Halford JCG, Gillespie J, Brown V, et al. Effect of television advertisements for foods on food consumption in children. *Appetite*. 2004;42(2):221–225. https://doi.org/10.1016/j.appet.2003.11.006
80. Halford JC, Boyland EJ, Hughes GM, et al. Beyond-brand effect of television food advertisements on food choice in children: the effects of weight status. *Public Health Nutr*. 2008;11(9):897–904. https://doi.org/10.1017/S1368980007001231
81. Schmitz KH, Jacobs DRJ, Hong CP, et al. Association of physical activity with insulin sensitivity in children. *Int J Obes*. 2002;26(10):1310–1316. https://doi.org/10.1038/sj.ijo.0802137
82. Holloszy JO, Schultz J, Kusnierkiewicz J, et al. Effects of exercise on glucose tolerance and insulin resistance—brief review and some preliminary results. *Acta Med Scandinav*. 1986;711(S711):55–65. https://doi.org/10.1111/j.0954-6820.1986.tb08932.x
83. Eriksson K-, Lindgärde F. Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise: the 6-year Malmö feasibility study. *Diabetologia*. 1991;34(12):891–898. https://doi.org/10.1007/BF00400196
84. Farpour-Lambert NJ, Aggoun Y, Marchand LM, et al. Physical activity reduces systemic blood pressure and improves early markers of atherosclerosis in pre-pubertal obese children. *J Am Coll Cardiol*. 2009;54(25):2396–2406. https://doi.org/10.1016/j.jacc.2009.08.030
85. Balducci S, Zanuso S, Nicolucci A, et al. Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. *Nutri Metabol Cardiovasc Dis*. 2009;20(8):608–617. https://doi.org/10.1016/j.numecd.2009.04.015

86. Rubin DA, Hackney AC. Inflammatory cytokines and metabolic risk factors during growth and maturation: influence of physical activity. In: Jurimae J, Hills AP, Jurimae T, eds. *Cytokines, Growth Mediators and Physical Activity in Children During Puberty*. Karger; 2010: 43–55.
87. Bosy-Westphal A, Onur S, Geisler C, et al. Common familial influences on clustering of metabolic syndrome traits with central obesity and insulin resistance: the Kiel Obesity Prevention Study. *Int Jo Obes*. 2007;31(5):784–790. https://doi.org/10.1038/sj.ijo.0803481
88. Tang W, Hong Y, Province MA, et al. Familial clustering for features of the metabolic syndrome: the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study. *Diabetes Care*. 2006;29(3):631–636. https://doi.org/10.2337/diacare.29.03.06.dc05-0679
89. Balletshofer BM, Rittig K, Enderle MD, et al. Endothelial dysfunction is detectable in young normotensive first-degree relatives of subjects with type 2 diabetes in association with insulin resistance. *Circulation*. 2000;101(15):1780–1784. https://doi.org/10.1161/01.CIR.101.15.1780
90. Ranadive SA, Vaisse C. Lessons from extreme human obesity: monogenic disorders. *Endocrinol Metabol Clin N Am*. 2008;37(3). https://doi.org/10.1016/j.ecl.2008.07.003
91. Stefan M, Nicholls RD. What have rare genetic syndromes taught us about the pathophysiology of the common forms of obesity? *Curr Diabetes Rep*. 2004;4(2):143–150. https://doi.org/10.1007/s11892-004-0070-0
92. Mitchell BD, Kammerer CM, Mahaney MC, et al. Genetic analysis of the IRS: pleiotropic effects of genes influencing insulin levels on lipoprotein and obesity measures. *Arteriosclerosis, Thrombos Vascul Biol*. 1996;16(2):281–288. https://doi.org/10.1161/01.ATV.16.2.281
93. Hong Y, Pedersen NL, Brismar K, De Faire U. Genetic and environmental architecture of the features of the insulin-resistance syndrome. *Am J Hum Genet*. 1997;60(1):143–152. https://pubmed.ncbi.nlm.nih.gov/8981957/
94. Rainwater DL, Mitchell BD, Mahaney MC, Haffner SM. Genetic relationship between measures of HDL phenotypes and insulin

concentrations. *Arteriosclerosis Thrombos Vascul Biol*. 1997;17(12):3414–3419. https://doi.org/10.1161/01.ATV.17.12.3414
95. Xiang AH, Azen SP, Raffel LJ, et al. Evidence for joint genetic control of insulin sensitivity and systolic blood pressure in Hispanic families with a hypertensive proband. *Circulation*. 2001;103(1):78–83. https://doi.org/10.1161/01.CIR.103.1.78
96. Dallo FJ, Weller SC. Effectiveness of diabetes mellitus screening recommendations. *Proceed Nat Acad Sci—PNAS*. 2003;100(18):10574–10579. https://doi.org/10.1073/pnas.1733839100
97. Bianco-Miotto T, Craig JM, Gasser YP, et al. Epigenetics and DOHaD: from basics to birth and beyond. *J Develop Orig Health Dis*. 2017;8(5):513–519. https://doi.org/10.1017/S2040174417000733
98. Kaufman J, Montalvo-Ortiz JL, Holbrook H, et al. Adverse childhood experiences, epigenetic measures, and obesity in youth. *J Pediatr*. 2018;202:150–156.e3. https://doi.org/10.1016/j.jpeds.2018.06.051
99. Duggan C, Watkins JB, Koletzko B, Walker WA. *Nutrition in Pediatrics: Basic Science, Clinical Applications.* 5th ed. People's Medical Publishing House; 2016.
100. Lazea C, Sur L, Florea M. ROHHAD (rapid-onset obesity with hypoventilation, hypothalamic dysfunction, autonomic dysregulation) Syndrome—what every pediatrician should know about the etiopathogenesis, diagnosis and treatment: a review. *Int J Gen Med*. 2021;14:319–326. https://doi.org/10.2147/IJGM.S293377
101. Lanza HI, Pittman P, Batshoun J. Obesity and cigarette smoking: extending the link to e-cigarette/vaping use. *Am J Hlth Behav*. 2017;41(3):338–347. https://doi.org/10.5993/AJHB.41.3.13
102. Miech R, Johnston L, O'Malley PM, et al. Trends in adolescent vaping, 2017–2019. *New Engl J Med*. 2019;381(15):1490–1491. https://doi.org/10.1056/NEJMc1910739
103. Stevens DR, Malek AM, Laggis C, Hunt KJ. In utero exposure to tobacco smoke, subsequent cardiometabolic risks, and metabolic syndrome among U.S. adolescents. *Ann Epidemiol*. 2018;28(9):619–624.e1. https://doi.org/10.1016/j.annepidem.2018.06.010
104. Walker SE, Gurka MJ, Oliver MN, et al. Racial/ethnic discrepancies in the metabolic syndrome begin in childhood and persist after

adjustment for environmental factors. *Nutr Metabol Cardiovasc Dis*. 2010;22(2):141–148. https://doi.org/10.1016/j.numecd.2010.05.006
105. Morrison JA, Friedman LA, Harlan WR, et al. Development of the metabolic syndrome in black and white adolescent girls: a longitudinal assessment. *Pediatrics*. 2005;116(5):1178–1182. https://doi.org/10.1542/peds.2004-2358
106. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114(2):555–576. https://doi.org/10.1542/peds.114.2.S2.555
107. Colley D, Cines B, Current N, et al. Assessing body fatness in obese adolescents: Alternative methods to dual-energy X-ray absorptiometry. *Digest*. 2015;50(3):1–7.
108. Dolan LM, Bean J, D'Alessio D, et al. Frequency of abnormal carbohydrate metabolism and diabetes in a population-based screening of adolescents. *J Pediatr*. 2005;146(6):751–758. https://doi.org/10.1016/j.jpeds.2005.01.045
109. Weiss R, Dufour S, Taksali SE, et al. Prediabetes in obese youth: a syndrome of impaired glucose tolerance, severe insulin resistance, and altered myocellular and abdominal fat partitioning. *Lancet (British edition)*. 2003;362(9388):951–957. https://doi.org/10.1016/S0140-6736(03)14364–4
110. Roden M, Price TB, Perseghin G, et al. Mechanism of free fatty acid-induced insulin resistance in humans. *J Clin Investigat*. 1996;97(12):2859–2865. https://doi.org/10.1172/JCI118742
111. Santomauro AT, Boden G, Silva ME, et al. Overnight lowering of free fatty acids with acipimox improves insulin resistance and glucose tolerance in obese diabetic and nondiabetic subjects. *Diabetes*. 1999;48(9):1836–1841. https://doi.org/10.2337/diabetes.48.9.1836
112. Shulman GI. Cellular mechanisms of insulin resistance. *J Clin Investigat*. 2000;106(2):171–176. https://doi.org/10.1172/JCI10583
113. Bergman RN, Kim SP, Catalano KJ, et al. Why visceral fat is bad: mechanisms of the metabolic syndrome. *Obesity*. 2006;14(suppl 2):16S-19S. https://doi.org/10.1038/oby.2006.277

114. Kadowaki T, Yamauchi T, Kubota N, et al. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *J Clin Investigat*. 2006;116(7):1784–1792. https://doi.org/10.1172/JCI29126
115. Amiel SA, Sherwin RS, Simonson DC, et al. Impaired insulin action in puberty—a contributing factor to poor glycemic control in adolescents with diabetes. *New Engl J Med*. 1986;315(4):215–219. https://doi.org/10.1056/NEJM198607243150402
116. Moran A, Jacobs DR, Steinberger J, et al. Insulin resistance during puberty: results from clamp studies in 357 children. *Diabetes*. 1999;48(10):2039–2044. https://doi.org/10.2337/diabetes.48.10.2039
117. Taittonen L, Uhari M, Nuutinen M, et al. Insulin and blood pressure among healthy children: Cardiovascular risk in young Finns. *Am J Hypertension*. 1996;9(3):193–199. https://doi.org/10.1016/0895-7061(95)00345–2
118. Odeleye OE, De Courten M, Pettitt DJ, Ravussin E. Fasting hyperinsulinemia is a predictor of increased body weight gain and obesity in Pima Indian children. *Diabetes*. 1997;46(8):1341–1345. https://doi.org/10.2337/diab.46.8.1341
119. Bao W, Srinivasan SR, Berenson GS. Persistent elevation of plasma insulin levels is associated with increased cardiovascular risk in children and young adults: the Bogalusa heart study. *Circulation*. 1996;93(1):54–59. https://doi.org/10.1161/01.CIR.93.1.54
120. Weiss R. Impaired glucose tolerance and risk factors for progression to type 2 diabetes in youth. *Pediatr Diabetes*. 2007;8(s9):70–75. https://doi.org/10.1111/j.1399-5448.2007.00336.x
121. Weiss R, Taksali SE, Tamborlane WV, Burgert TS, Savoye M, Caprio S. Predictors of changes in glucose tolerance status in obese youth. *Diabetes Care*. 2005;28(4):902–909. https://doi.org/10.2337/diacare.28.4.902
122. Greenberg AS, McDaniel ML. Identifying the links between obesity, insulin resistance and β-cell function: potential role of adipocyte-derived cytokines in the pathogenesis of type 2 diabetes. *Eur J Clin Investig*. 2002;32(s3):24–34. https://doi.org/10.1046/j.1365-2362.32.s3.4.x

123. Gustafson B, Hammarstedt A, Andersson CX, Smith U. Inflamed adipose tissue: a culprit underlying the metabolic syndrome and atherosclerosis. *Arteriosclerosis Thrombos Vasc Biol*. 2007;27(11):2276–2283. https://doi.org/10.1161/ATVBAHA.107.147835
124. Marette A. Mediators of cytokine-induced insulin resistance in obesity and other inflammatory settings. *Curr Opin Clin Nutr Metabol Care*. 2002;5(4):377–383. https://doi.org/10.1097/00075197-200207000-00005
125. Wärnberg J, Marcos A. Low-grade inflammation and the metabolic syndrome in children and adolescents. *Curr Opin Lipidol*. 2008;19(1):11–15. https://doi.org/10.1097/MOL.0b013e3282f4096b
126. Nemet D, Wang P, Funahashi T, et al. Adipocytokines, body composition, and fitness in children. *Pediatric Res*. 2003;53(1):148–152. https://doi.org/10.1203/00006450-200301000-00025
127. Sutherland JP, McKinley B, Eckel RH. The metabolic syndrome and inflammation. *Metabol Syndrome Related Dis*. 2004;2(2):82–104. https://doi.org/10.1089/met.2004.2.82
128. Cook DG, Mendall MA, Whincup PH, et al. C-reactive protein concentration in children: relationship to adiposity and other cardiovascular risk factors. *Atherosclerosis*. 2000;149(1):139–150. https://doi.org/10.1016/S0021-9150(99)00312–3
129. Ridker PM. C-reactive protein and the prediction of cardiovascular events among those at intermediate risk: moving an inflammatory hypothesis toward consensus. *J Am Coll Cardiol*. 2007;49(21):2129–2141. https://doi.org/10.1016/j.jacc.2007.02.052
130. Hatanaka K, Li X, Masuda K, et al. Immunohistochemical localization of C-reactive protein-binding sites in human atherosclerotic aortic lesions by a modified streptavidin-biotin-staining method. *Pathol Int*. 1995;45(9):635–641. https://doi.org/10.1111/j.1440-1827.1995.tb03515.x
131. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. *Circulation*. 2003;107(3):391–397. https://doi.org/10.1161/01.CIR.0000055014.62083.05

132. Mendall MA, Patel P, Ballam L, et al. C reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. *BMJ*. 1996;312(7038):1061–1065. https://doi.org/10.1136/bmj.312.7038.1061
133. Visser M, Bouter LM, McQuillan GM, et al. Elevated C-reactive protein levels in overweight and obese adults. *JAMA*. 1999;282(22):2131–2135. https://doi.org/10.1001/jama.282.22.2131
134. Moran A, Steffen LM, Jacobs DR, et al. Relation of C-reactive protein to insulin resistance and cardiovascular risk factors in youth. *Diabetes Care*. 2005;28(7):1763–1768. https://doi.org/10.2337/diacare.28.7.1763
135. Abd TT, Eapen DJ, Bajpai A, et al. The role of C-reactive protein as a risk predictor of coronary atherosclerosis: implications from the JUPITER trial. *Curr Atheroscler Rep*. 2011;13(2):154–161. https://doi.org/10.1007/s11883-011-0164-5
136. Lee S, Kwak H. Role of adiponectin in metabolic and cardiovascular disease. *J Exercise Rehab*. 2014;10(2):54–59. https://doi.org/10.12965/jer.140100
137. Nascimento H, Costa E, Rocha S, et al. Adiponectin and markers of metabolic syndrome in obese children and adolescents: impact of 8-mo regular physical exercise program. *Pediatric Res*. 2014;76(2):159–165. https://doi.org/10.1038/pr.2014.73
138. Lim S, Quon MJ, Koh KK. Modulation of adiponectin as a potential therapeutic strategy. *Atherosclerosis*. 2014;233(2):721–728. https://doi.org/10.1016/j.atherosclerosis.2014.01.051
139. Ferrannini E, Buzzigoli G, Bonadonna R, et al. Insulin resistance in essential hypertension. *New Engl J Med*. 1987;317(6):350–357. https://doi.org/10.1056/NEJM198708063170605
140. Balletshofer BM, Rittig K, Enderle MD, et al. Endothelial dysfunction is detectable in young normotensive first-degree relatives of subjects with type 2 diabetes in association with insulin resistance. *Circulation*. 2000;101(15):1780–1784. https://doi.org/10.1161/01.CIR.101.15.1780
141. Haynes WG, Morgan DA, Walsh SA, et al. Receptor-mediated regional sympathetic nerve activation by leptin. *J Clin Investigat*. 1997;100(2):270–278. https://doi.org/10.1172/JCI119532

142. DeFronzo RA, Cooke CR, Andres R, et al. The effect of insulin on renal handling of sodium, potassium, calcium, and phosphate in man. *J Clin Investigat*. 1975;55(4):845–855. https://doi.org/10.1172/JCI107996
143. Egan BM. Insulin resistance and the sympathetic nervous system. *Curr Hypertens Rep*. 2003;5(3):247–254. https://doi.org/10.1007/s11906-003-0028-7
144. Tripathy D, Mohanty P, Dhindsa S, et al. Elevation of free fatty acids induces inflammation and impairs vascular reactivity in healthy subjects. *Diabetes*. 2003;52(12):2882–2887. https://doi.org/10.2337/diabetes.52.12.2882
145. Wang M. The role of glucocorticoid action in the pathophysiology of the metabolic syndrome. *Nutrit Metabol*. 2005;2(1):3. https://doi.org/10.1186/1743-7075-2-3
146. Limberg JK, Harrell JW, Johansson RE, et al. Microvascular function in younger adults with obesity and metabolic syndrome: role of oxidative stress. *Am Jo Physiol—Heart Circul Physiol*. 2013;305(8):1230–1237. https://doi.org/10.1152/ajpheart.00291.2013
147. Virdis A, Neves MF, Duranti E, et al. Microvascular endothelial dysfunction in obesity and hypertension. *Curr Pharmaceut Design*. 2013;19(13):2382–2389. https://doi.org/10.2174/1381612811319130006
148. Correia MLG, Rahmouni K. Role of leptin in the cardiovascular and endocrine complications of metabolic syndrome. *Diab Obes Metabol*. 2006;8(6):603–610. https://doi.org/10.1111/j.1463-1326.2005.00562.x
149. Sinaiko A, Steinberger J, Moran A, et al. Relation of insulin resistance to blood pressure in childhood. *J Hypertens*. 2002;20(3):509–517. https://doi.org/10.1097/00004872-200203000-00027
150. Mukhtar Q, Cleverley G, Voorhees RE, McGrath JW. Prevalence of acanthosis nigricans and its association with hyperinsulinemia in New Mexico adolescents. *J Adolesc Health*. 2001;28(5):372–376. https://doi.org/10.1016/S1054-139X(00)00217–2
151. Sinha S, Schwartz RA. Juvenile acanthosis nigricans. *J Am Acad Dermatol*. 2007;57(3):502–508. https://doi.org/10.1016/j.jaad.2006.08.016

152. Ice CL, Murphy E, Minor VE, Neal WA. Metabolic syndrome in fifth grade children with acanthosis nigricans: results from the CARDIAC project. *World J Pediatr*. 2009;5(1):23–30. https://doi.org/10.1007/s12519-009-0004-7
153. Guran T, Turan S, Akcay T, Bereket A. Significance of acanthosis nigricans in childhood obesity. *J Paediatr Child Health*. 2008;44(6):338–341. https://doi.org/10.1111/j.1440-1754.2007.01272.x
154. Maffeis C, Banzato C, Talamini G. Waist-to-height ratio, a useful index to identify high metabolic risk in overweight children. *J Pediatrics*. 2008;152(2):207–213.e2. https://doi.org/10.1016/j.jpeds.2007.09.021
155. Adiels M, Olofsson S, Taskinen M, Boren J. Overproduction of very low-density lipoproteins is the hallmark of the dyslipidemia in the metabolic syndrome. *Arteriosclerosis Thrombos Vasc Biol*. 2008;28(7):1225–1236. https://doi.org/10.1161/ATVBAHA.107.160192
156. Kwiterovich PO. Clinical relevance of the biochemical, metabolic, and genetic factors that influence low-density lipoprotein heterogeneity. *Am J Cardiol*. 2002;90(8):30–47. https://doi.org/10.1016/S0002-9149(02)02749–2
157. Cominacini L, Zocca I, Garbin U, et al. High-density lipoprotein composition in obesity: interrelationships with plasma insulin levels and body weight. *Int J Obesity*. 1988;12(4):343–352.
158. Pascot A, Lemieux I, Prud'homme D, et al. Reduced HDL particle size as an additional feature of the atherogenic dyslipidemia of abdominal obesity. *J Lipid Res*. 2001;42(12):2007–2014. https://doi.org/10.1016/S0022-2275(20)31529–7
159. Goff DC, D'Agostino RB, Haffner SM, Otvos JD. Insulin resistance and adiposity influence lipoprotein size and subclass concentrations—results from the insulin resistance atherosclerosis study. *Metabol Clin Exp*. 2005;54(2):264–270. https://doi.org/10.1016/j.metabol.2004.09.002
160. Becker DM, Yook RM, Moy TF, et al. Markedly high prevalence of coronary risk factors in apparently healthy African-American and white siblings of persons with premature coronary heart disease. *Am J*

Cardiol. 1998;82(9):1046–1051. https://doi.org/10.1016/S0002-9149(98)00553–0
161. Schwimmer JB, Deutsch R, Kahen T, et al. Prevalence of fatty liver in children and adolescents. *Pediatrics*. 2006;118(4):1388–1393. https://doi.org/10.1542/peds.2006-1212
162. Manco M, Marcellini M, DeVito R, et al. Metabolic syndrome and liver histology in paediatric non-alcoholic steatohepatitis. *Int J Obesity*. 2008;32(2):381–387. https://doi.org/10.1038/sj.ijo.0803711
163. Schwimmer JB, Pardee PE, Lavine JE, et al. Cardiovascular risk factors and the metabolic syndrome in pediatric nonalcoholic fatty liver disease. *Circulation*. 2008;118(3):277–283. https://doi.org/10.1161/CIRCULATIONAHA.107.739920
164. Barshop NJ, Sirlin CB, Schwimmer JB, Lavine JE. Review article: epidemiology, pathogenesis and potential treatments of paediatric nonalcoholic fatty liver disease. *Alimentary Pharmacol Therapeut*. 2008;28(1):13–24. https://doi.org/10.1111/j.1365-2036.2008.03703.x
165. Setji TL, Brown AJ. Polycystic ovary syndrome: update on diagnosis and treatment. *Am J Med*. 2014;127(10):912–919. https://doi.org/10.1016/j.amjmed.2014.04.017
166. Cussons AJ, Watts GF, Burke V, et al. Cardiometabolic risk in polycystic ovary syndrome: a comparison of different approaches to defining the metabolic syndrome. *Human Reproduct*. 2008;23(10):2352–2358. https://doi.org/10.1093/humrep/den263
167. Coviello AD, Legro RS, Dunaif A. Adolescent girls with polycystic ovary syndrome have an increased risk of the metabolic syndrome associated with increasing androgen levels independent of obesity and insulin resistance. *J Clin Endocrinol Metabol*. 2006;91(2):492–497. https://doi.org/10.1210/jc.2005-1666
168. Glueck CJ, Morrison JA, Daniels S, et al. Sex hormone-binding globulin, oligomenorrhea, polycystic ovary syndrome, and childhood insulin at age 14 years predict metabolic syndrome and class III obesity at age 24 years. *J Pediatrics*. 2011;159(2):308–313.e2. https://doi.org/10.1016/j.jpeds.2011.01.018
169. Rossi B, Sukalich S, Droz J, et al. Prevalence of metabolic syndrome and related characteristics in obese adolescents with and without

polycystic ovary syndrome. *J Clin Endocrinol Metabol*. 2008;93(12):4780–4786. https://doi.org/10.1210/jc.2008-1198

170. Stuckey BGA, Opie N, Cussons AJ, et al. Clustering of metabolic and cardiovascular risk factors in the polycystic ovary syndrome: a principal component analysis. *Metab Clin Exp*. 2014;63(8):1071–1077. https://doi.org/10.1016/j.metabol.2014.05.004
171. Bachrach K, Danis DO, Cohen MB, Levi JR. The relationship between obstructive sleep apnea and pediatric obesity: a nationwide analysis. *Ann Otol Rhinol Laryngol*. 2022;131(5):520–526. https://doi.org/10.1177/00034894211028489
172. Hannon TS, Rofey DL, Ryan CM, et al. Relationships among obstructive sleep apnea, anthropometric measures, and neurocognitive functioning in adolescents with severe obesity. *J Pediatrics*. 2012;160(5):732–735. https://doi.org/10.1016/j.jpeds.2011.10.029
173. Harriger JA, Thompson JK. Psychological consequences of obesity: weight bias and body image in overweight and obese youth. *Int Rev Psychiatr)*. 2012;24(3):247–253. https://doi.org/10.3109/09540261.2012.678817
174. Bacchini D, Licenziati MR, Garrasi A, et al. Bullying and victimization in overweight and obese outpatient children and adolescents: an Italian multicentric study. *PloS One*. 2015;10(11):e0142715. https://doi.org/10.1371/journal.pone.0142715
175. Mason SM, Flint AJ, Field AE, et al. Abuse victimization in childhood or adolescence and risk of food addiction in adult women. *Obesity*. 2013;21(12):E775–E781. https://doi.org/10.1002/oby.20500
176. Mahmood S, Li Y, Hynes M. Adverse childhood experiences and obesity: a one-to-one correlation? *Clin Child Psychol Psychiatr*. 2023;28(2):785–794. https://doi.org/10.1177/13591045221119001
177. Centers for Disease Control and Prevention. Youth risk behavior surveillance system—2011 national overview. Accessed October 23, 2022. http://www.cdc.gov/healthyyouth/yrbs/pdf/us_overview_yrbs.pdf
178. Healthy eating index. Food and Nutrition Service, U.S. Department of Agriculture. Accessed October 23, 2022. https://fns.usda.gov/cnpp/hei-scores-americans

179. Merlo CL, Jones SE, Michael SL, et al. Dietary and physical activity behaviors among high school students—youth risk behavior survey, United States, 2019. *Morbid Mortal Weekly Rep. Suppl*. 2020;69(1):64–76. https://doi.org/10.15585/mmwr.su6901a8
180. American Dietetic Association. Position of the American Dietetic Association: individual-, family-, school-, and community-based interventions for pediatric overweight. *J Am Dietet Assoc*. 2006;106(6):925–945. https://doi.org/10.1016/j.jada.2006.03.001
181. Evidence analysis library. Academy of Nutrition and Dietetics. Accessed June 12, 2022. http://andevidencelibrary.com
182. Pereira AR, Oliveira A. Dietary interventions to prevent childhood obesity: a literature review. *Nutrients*. 2021;13(10):3447. https://doi.org/10.3390/nu13103447
183. Moore LL, Singer MR, Bradlee ML, et al. Intake of fruits, vegetables, and dairy products in early childhood and subsequent blood pressure change. *Epidemiology*. 2005;16(1):4–11. https://doi.org/10.1097/01.ede.0000147106.32027.3e
184. Couch SC, Saelens BE, Levin L, et al. The efficacy of a clinic-based behavioral nutrition intervention emphasizing a DASH-type diet for adolescents with elevated blood pressure. *J Pediatr*. 2008;152(4):494–501. https://doi.org/10.1016/j.jpeds.2007.09.022
185. Di Figlia-Peck S, Feinstein R, Fisher M. Treatment of children and adolescents who are overweight or obese. *Curr Probl Pediatr Adolesc*. 2020;50(9):100871. https://doi.org/10.1016/j.cppeds.2020.100871
186. Vajro P, Mandato C, Franzese A, et al. Vitamin E treatment in pediatric obesity-related liver disease: a randomized study. *J Pediatr Gastroenterol Nutr*. 2004;38(1):48–55. https://doi.org/10.1097/00005176-200401000-00012
187. Daniels SR, Greer FR, and Committee on Nutrition. Lipid screening and cardiovascular health in childhood. *Pediatrics*. 2008;122(1):198–208. https://doi.org/10.1542/peds.2008-1349
188. Inge TH, Jenkins TM, Xanthakos SA, et al. Long-term outcomes of bariatric surgery in adolescents with severe obesity (FABS-5+): a prospective follow-up analysis. *Lancet. Diabetes Endocrinol*. 2017;5(3):165–173. https://doi.org/10.1016/S2213-8587(16)30315–1

189. Olbers T, Beamish AJ, Gronowitz E, et al. Laparoscopic Roux-en-Y gastric bypass in adolescents with severe obesity (AMOS): a prospective, 5-year, Swedish nationwide study. *Lancet. Diabetes Endocrinol*. 2017;5(3):174–183. https://doi.org/10.1016/S2213-8587(16)30424–7
190. Messiah SE, Lopez-Mitnik G, Winegar D, et al. Changes in weight and co-morbidities among adolescents undergoing bariatric surgery: 1-year results from the bariatric outcomes longitudinal database. *Surg Obesity Related Dis*. 2013;9(4):503–513. https://doi.org/10.1016/j.soard.2012.03.007
191. Wing RR, Lang W, Wadden TA, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care*. 2011;34(7):1481–1486. https://doi.org/10.2337/dc10-2415
192. Dansinger ML, Gleason JA, Griffith JL, et al. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA*. 2005;293(1):43–53. https://doi.org/10.1001/jama.293.1.43
193. Wadden TA, Webb VL, Moran CH, Bailer BA. Lifestyle modification for obesity: new developments in diet, physical activity, and behavior therapy. *Circulation*. 2012;125(9):1157–1170. https://doi.org/10.1161/CIRCULATIONAHA.111.039453
194. Wing RR, Jeffery RW, Burton LR, et al. Food provision vs structured meal plans in the behavioral treatment of obesity. *Inte J Obesity*. 1996;20(1):56–62.
195. Appel LJ, Champagne CM, Harsha DW, et al. Effects of comprehensive lifestyle modification on blood pressure control: main results of the PREMIER clinical trial. *JAMA*. 2003;289(16):2083–2093. https://doi.org/10.1001/jama.289.16.2083
196. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. *New Engl J Med*. 2001;344(1):3–10. https://doi.org/10.1056/NEJM200101043440101
197. Hollis JF, Gullion CM, Stevens VJ, et al. Weight loss during the intensive intervention phase of the weight-loss maintenance trial. *Am*

J Prevent Med. 2008;35(2):118–126. https://doi.org/10.1016/j.amepre.2008.04.013
198. Appel LJ, Clark JM, Yeh H, et al. Comparative effectiveness of weight-loss interventions in clinical practice. *New Engl J Med*. 2011;365(21):1959–1968. https://doi.org/10.1056/NEJMoa1108660
199. Rodriguez J. *The Diet Selector.* Running Press; 2007.
200. Research findings. National Weight Control Registry. Accessed June 22, 2022. http://www.nwcr.ws/Research/published%20research.htm
201. Evans SA, Parsons AD, Overton JM. Homeostatic responses to caloric restriction: influence of background metabolic rate. *J Applied Physiol*. 2005;99(4):1336–1342. https://doi.org/10.1152/japplphysiol.01380.2004
202. Mason AE, Jhaveri K, Cohn M, Brewer JA. Testing a mobile mindful eating intervention targeting craving-related eating: feasibility and proof of concept. *J Behav Med*. 2018;41(2):160–173. https://doi.org/10.1007/s10865-017-9884-5
203. Epstein LH, Paluch RA, Beecher MD, Roemmich JN. Increasing healthy eating vs. reducing high energy-dense foods to treat pediatric obesity. *Obesity*. 2008;16(2):318–326. https://doi.org/10.1038/oby.2007.61
204. Atkins RC. *Atkins New Diet Revolution.* M. Evans & Co; 2002.
205. Agatson A. *The South Beach Diet.* Random House; 2003.
206. Sharman MJ, Gómez AL, Kraemer WJ, Volek JS. Very low-carbohydrate and low-fat diets affect fasting lipids and postprandial lipemia differently in overweight men. *J Nutr*. 2004;134(4):880–885. https://doi.org/10.1093/jn/134.4.880
207. Brehm BJ, Seeley RJ, Daniels SR, D'Alessio DA. A randomized trial comparing a very low carbohydrate diet and a calorie-restricted low fat diet on body weight and cardiovascular risk factors in healthy women. *J Clin Endocrinol Metabol*. 2003;88(4):1617–1623. https://doi.org/10.1210/jc.2002-021480
208. Shai I, Schwarzfuchs D, Henkin Y, et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *New Engl J Med*. 2008;359(3):229–241. https://doi.org/10.1056/NEJMoa0708681
209. Guasch-Ferré M, Willett WC. The Mediterranean diet and health: a comprehensive overview. *J Intern Med*. 2021;290(3):549–566.

https://doi.org/10.1111/joim.13333
210. Position of the American Dietetic Association: individual-, family-, school-, and community-based interventions for pediatric overweight. *J Am Dietet Assoc*. 2006;106(6):925–945. https://doi.org/10.1016/j.jada.2006.03.001
211. Ge L, Sadeghirad B, Ball GDC, et al. Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight and cardiovascular risk factor reduction in adults: systematic review and network meta-analysis of randomised trials. *BMJ (Online)*. 2020;370:m3095. https://doi.org/10.1136/bmj.m3095
212. Ornish D. *Eat More Weigh Less.* Harper Collins; 1993.
213. Cordain L. *The Paleo Diet.* John Wiley & Sons, Inc; 2011.
214. Jönsson T, Granfeldt Y, Ahrén B, et al. Beneficial effects of a paleolithic diet on cardiovascular risk factors in type 2 diabetes: a randomized cross-over pilot study. *Cardiovasc Diabetol*. 2009;8(1):35. https://doi.org/10.1186/1475-2840-8-35
215. Lindeberg S, Jönsson T, Granfeldt Y, et al. Palaeolithic diet improves glucose tolerance more than a mediterranean-like diet in individuals with ischaemic heart disease. *Diabetologia*. 2007;50(9):1795–1807. https://doi.org/10.1007/s00125-007-0716-y
216. Jönsson T, Granfeldt Y, Erlanson-Albertsson C, Ahrén B, Lindeberg S. A paleolithic diet is more satiating per calorie than a Mediterranean-like diet in individuals with ischemic heart disease. *Nutr Metabol*. 2010;7(1):85. https://doi.org/10.1186/1743-7075-7-85
217. Osterdahl M, Kocturk T, Koochek A, Wandell PE. Effects of a short-term intervention with a paleolithic diet in healthy volunteers. *Eur J Clin Nutr*. 2008;62(5):682–685. https://doi.org/10.1038/sj.ejcn.1602790
218. Jamka M, Kulczyński B, Juruć A, et al. The effect of the paleolithic diet vs. healthy diets on glucose and insulin homeostasis: a systematic review and meta-analysis of randomized controlled trials. *J Clin Med*. 2020;9(2):296. https://doi.org/10.3390/jcm9020296
219. Rolls B, Barnett RA. *The Volumetrics Eating Plan.* Harper Collins; 2005.
220. Welton S, Minty R, O'Driscoll T, et al. Intermittent fasting and weight loss: systematic review. *Can Fam Physician*. 2020;66(2):117–125.

https://www.cfp.ca/content/66/2/117.full
221. Home page. WeightWatchers. Accessed November 27, 2023. https://www.weightwatchers.com/us/
222. Cook CM, McCormick CN, Knowles M, Kaden VN. A commercially available portion-controlled diet program is more effective for weight loss than a self-directed diet: results from a randomized clinical trial. *Front Nutr*. 2017;4:55. https://doi.org/10.3389/fnut.2017.00055
223. Chin SO, Keum C, Woo J, et al. Successful weight reduction and maintenance by using a smartphone application in those with overweight and obesity. *Sci Rep*. 2016;6(1):34563. https://doi.org/10.1038/srep34563
224. Cusack L, De Buck E, Compernolle V, Vandekerckhove P. Blood type diets lack supporting evidence: a systematic review. *Am J Clin Nutr*. 2013;98(1):99–104. https://doi.org/10.3945/ajcn.113.058693
225. Jacob CM, Hardy-Johnson PL, Inskip HM, et al. A systematic review and meta-analysis of school-based interventions with health education to reduce body mass index in adolescents aged 10 to 19 years. *Int J Behav Nutr Physic Activ*. 2021;18(1):1. https://doi.org/10.1186/s12966-020-01065-9
226. Wang Y, Cai L, Wu Y, et al. What childhood obesity prevention programmes work? A systematic review and meta-analysis. *Obesity Rev*. 2015;16(7):547–565. https://doi.org/10.1111/obr.12277
227. Vasques C, Magalhães P, Cortinhas A, et al. Effects of intervention programs on child and adolescent BMI: a meta-analysis study. *J Physical Activ Health*. 2014;11(2):426–444. https://doi.org/10.1123/jpah.2012-0035
228. Vorland CJ, Bohan Brown MM, Cardel MI, Brown AW. Traffic light diets for childhood obesity: disambiguation of terms and critical review of application, food categorization, and strength of evidence. *Curr Devel Nutr*. 2022;6(3):nzac006. https://doi.org/10.1093/cdn/nzac006
229. Epstein LH, Valoski A, Wing RR, McCurley J. Ten-year follow-up of behavioral, family-based treatment for obese children. *JAMA*. 1990;264(19):2519–2523. https://doi.org/10.1001/jama.1990.03450190051027

230. Epstein LH, Valoski A, Wing RR, McCurley J. Ten-year outcomes of behavioral family-based treatment for childhood obesity. *Health Psychol*. 1994;13(5):373–383. https://doi.org/10.1037/0278-6133.13.5.373
231. MyPlate. U.S. Department of Agriculture. Accessed June 22, 2022. http://www.MyPlate.gov
232. Phillips JA. Dietary guidelines for Americans, 2020–2025. *AAOHN J*. 2021;69(8):395. https://doi.org/10.1177/21650799211026980
233. Chrisman M, Diaz Rios LK. Evaluating MyPlate after 8 years: a perspective. *J Nutr Educ Behav*. 2019;51(7):899–903. https://doi.org/10.1016/j.jneb.2019.02.006
234. Gelberg L, Rico MW, Herman DR, et al. Comparative effectiveness trial comparing MyPlate to calorie counting for mostly low-income Latino primary care patients of a federally qualified community health center: study design, baseline characteristics. *BMC Public Health*. 2019;19(1):990. https://doi.org/10.1186/s12889-019-7294-z
235. NIH National Cancer Institute. Obesity evidence-based programs listing. Accessed December 18, 2022. https://ebccp.cancercontrol.cancer.gov/topicPrograms.do?topicId=1592287&choice=default
236. Information and description. KidShape. Accessed December 18, 2022. http://www.kidshape.net/
237. McLean N, Griffin S, Toney K, Hardeman W. Family involvement in weight control, weight maintenance and weight-loss interventions: a systematic review of randomised trials. *Int J Obesity*. 2003;27(9):987–1005. https://doi.org/10.1038/sj.ijo.0802383

Test Your Knowledge Answers

1. The correct answer is **C**. The evidence-based analysis by the Academy of Nutrition and Dietetics of literature on pediatric overweight intervention programs reported positive effects from one specific kind of intervention: multicomponent, family-based programs for children between the ages of 5 and 12 years. The components included were

behavioral counseling, promotion of physical activity, parent training and modeling, dietary counseling, and nutrition education.

2. The correct answer is **A**. Interventions should be based on the family's readiness to change and include the following recommendations: consumption of ≥5 servings of fruits and vegetables per day; minimization or elimination of sugar-sweetened beverages; limits of ≤2 hours of screen time per day, no television in the room where the child sleeps, and no television if the child is <2 years of age; and ≥ 1 hour of physical activity per day.
3. The correct answer is **B**. The Traffic Light Diet was designed to promote weight loss, provide adequate kilocalories and nutrients for growth and development, and be easy to follow. Behavior change was designed as a general guide for diet and exercise in adults; however, it has been used as a dietary component in childhood weight management programs.
4. The correct answer is **D**. These diets have not been studied for use with children and adolescents because of the potential growth risks resulting from the elimination of key food groups, higher caloric restrictions, adverse behavioral patterns of eating, and/or lack of scientific evidence for the basis of the diet's recommendations. The key requirement for the dietary treatment of children and adolescents with overweight is to initiate and maintain lifelong healthy eating habits that focus on unhealthy weight in the short term and foster improved health outcomes in the long term.

The author of this chapter wishes to thank Catherine Christie, PhD, RDN, LDN, FAND; Claudia Sealey-Potts, PhD, RDN FAND; Corinne Labyak, PhD, RDN; and Judith C. Rodriguez, PhD, RDN, FAND, for their contributions to the previous editions of this text.

15

Lipid Disorders

Elizabeth L. Wright, MS, RDN, CSP, LDN, FAND, CLC; Danielle H. Campbell, MS, RDN, LDN; James Gherardi, BS, DTR

Learning Objectives

1. Understand cardiovascular disease risk and the etiologies of lipid disorders.
2. Describe how to screen for lipid disorders and interpret laboratory results.
3. Discuss the role of dietary factors and physical activity in treating lipid disorders.

Introduction

Cardiovascular disease (CVD) is the leading cause of death both globally and in the United States, and it is more prevalent for those living in low- and middle-income countries.[1–3] Although death occurs in adulthood, risk factors leading to CVD begin in early childhood and adolescence.[4] Risk factors include family history, age, gender, nutrition and diet, physical inactivity, tobacco exposure, high blood pressure, abnormal blood lipid levels, overweight and obesity, diabetes mellitus, predisposing conditions, metabolic syndrome, inflammatory markers, perinatal factors, and certain medications. This chapter focuses on how nutrition affects blood lipid levels in children. Nutrition intervention during childhood plays a critical

role in CVD prevention and is an important part of dyslipidemia treatment to reduce the risk of CVD.

Background

Blood lipid levels can be measured and monitored easily throughout the lifespan. Abnormal blood lipid levels can lead to atherosclerosis, which is plaque build-up in the heart vessels or arteries. Nearly 7% (or 1 in 5) of children in the United States ages 6 to 19 years have abnormal lipid levels. The specific abnormal serum lipid levels include a high concentration of total cholesterol (TC), high low-density lipoprotein (LDL) cholesterol, high non-high-density lipoprotein (non-HDL), low high-density lipoprotein (HDL) cholesterol, and high triglycerides (TGs). Dyslipidemias can be defined as abnormalities, including both deficiency and overproduction, in lipid and lipoprotein metabolism. Primary lipid disorders are caused by genetic or environmental factors. Dyslipidemia can also be due to secondary causes.[4]

Primary Lipid Disorders

The most common types of primary lipid disorders found in children and adolescents are familial hypercholesterolemia (FH), familial combined hyperlipidemia (FCH), and polygenic hypercholesterolemia.[4]

Familial Hypercholesterolemia

FH is typically caused by mutations in genes that affect LDL receptors, causing defective LDL clearance. There are two types of the disorder, heterozygous FH (HeFH) and homozygous FH (HoFH).[5] Individuals with HeFH have inherited a mutated gene from one parent and have LDL cholesterol levels >160 mg/dL with either normal or low HDL cholesterol levels and TC levels exceeding 230 mg/dL.[4] This form is more common, affecting approximately 1 in 250 people in the united States. [5] Symptoms are not present in childhood, but an acceleration of atherosclerosis and

premature CVD is present, which then causes a coronary event in 50% of men and 25% of women with HeFH by the age of 50 years.[4]

Individuals with HoFH have inherited 2 mutated genes and have LDL cholesterol levels >500 mg/dL with low HDL cholesterol levels, which lead to TC levels >600 mg/dL.[4,5] This form is rare, affecting approximately 1 in 300,000 people.[5] In HoFH, physical manifestations begin in infancy and childhood with the presence of xanthomata, tendonous xanthomata, and corneal arcus, with CVD developing by the first decade. Some individuals with HoFH may respond to traditional lipid-lowering medications, but newer medications including PCSK9 and ANGTPL3 inhibitors are being used in adolescents ages 12 years and older with good results.[6] Other therapies include LDL apheresis and liver transplantation.

Familial Combined Hyperlipidemia

FCH is an inherited disorder caused by a mutation on chromosome 19 passed down by either one or both parents. FCH is characterized by elevated TC levels with elevated LDL levels, low HDL levels, and possibly the presence of elevated TG levels as well.[7] Genes that are affected include LDLR, APOB, and PCSK9.[8] Presently, FCH has an estimated prevalence of 1 in 50 to 1 in 100 people in the general population worldwide.[9]

Polygenic Hypercholesterolemia

Polygenic hypercholesterolemia is caused by a combination of genetic susceptibility and environmental factors such as diet, weight, and physical inactivity. LDL cholesterol levels are elevated but generally milder than in FH. If obesity is present, some children may have high TG levels and low HDL cholesterol levels. Children with polygenic hypercholesterolemia often respond well to nutrition and lifestyle behavior modifications.[7]

Secondary Causes

Secondary causes of dyslipidemia include endocrine, metabolic, renal, hepatic, and storage diseases; inflammatory and infectious conditions

within the body; and certain medications.[4] Specific conditions in the pediatric population include but are not limited to the following:

- diabetes
- chronic kidney disease
- nephrotic syndrome
- obstructive liver disease
- Alagille syndrome
- systemic lupus erythematosus
- post solid organ transplantation
- anorexia nervosa
- obesity
- cancer

Certain medications include progestins, anabolic steroids, glucocorticoids, psychotherapeutic drugs, and retinoic acid acne treatment. Treatment of secondary causes usually normalizes lipid levels unless compounding factors are present.

Screening and Laboratory Interpretation

Exhibits 15-1 and 15-2 indicate who should be screened for lipid disorders and the screening procedure. The interpretation of the resultant fasting lipid profile is delineated in Table 15-1.

EXHIBIT 15-1. Screening Guidelines[a]

Who Should be Screened?

1. Universal screening should occur once between ages 9 and 11 years and once between ages 17 and 21 years.[b]
2. Any patient ≥ 2–8 or 12–16 years of age with any of the following CVD risk factors:
   - A parent, grandparent, aunt, or uncle with CVD before age ≤ 55 years (male) or ≤ 65 years (female). CVD includes myocardial infarction, sudden cardiac death, coronary bypass surgery, balloon angioplasty, angina pectoralis, coronary atherosclerosis, peripheral vascular disease, or stroke
   - A parent with a total cholesterol ≥ 240 mg/dL
   - A family history that is not available (adopted child)

- Other cardiovascular risk factors: obesity (BMI ≥ 95th percentile), smoking, diagnosed hypertension, type 1 or type 2 diabetes, chronic renal disease, nephrotic syndrome, end-stage renal disease, renal transplant (post-transplant), chronic inflammatory disease, Kawasaki disease with current or regressed coronary aneurysms, HIV infection, orthotopic heart transplant (post-transplant)
- Treatment with retinoid acid, anticonvulsants, or oral contraceptives

---

Abbreviations: BMI, body mass index; CVD, cardiovascular disease.

[a] Information compiled from the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents of the National Heart, Lung, and Blood Institute.[4]

[b] No universal screening needed between ages 12 and 16 years because total cholesterol and low-density lipoprotein levels decrease significantly by 10%–20% during puberty, then elevate again to prepuberty levels.[4]

EXHIBIT 15-2. Laboratory Testing[a]

How to screen?

- For universal screening, obtain non-FLP that includes the following:
  - TC
  - HDL
  - Non-HDL cholesterol (calculate using TC minus HDL)[b]
- If non-HDL >145 mg/dL or HDL <40 mg/dL, then obtain FLP twice, average, and include the following:
  - Triglycerides
  - Low-density lipoprotein cholesterol
- If cardiovascular disease risk factors are present, obtain FLP twice, then average. FLPs may be obtained 2 weeks to 3 months apart.

Abbreviations: FLP, fasting lipid profile; HDL, high-density lipoprotein; TC, total cholesterol.

[a] Information compiled from the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents of the National Heart, Lung, and Blood Institute.[4]

[b] Non-HDL has been found to be a more predictive indicator of atherosclerosis.[4]

TABLE 15-1. Interpretation of Lipid Profile[a]

Profile	Interpretation
TC <170 mg/dL LDL <110 mg/dL Non-HDL <120 mg/dl TGs (age 0–9 y) <75 mg/dL, (age 10–19 y) <90 mg/dL HDL ≥ 45 mg/dL	• Acceptable lipid profile • Recheck lipid profile if any of the CVD risk factors develop with patient or patient's family
TC ≥ 200 mg/dL LDL ≥ 130 mg/dL Non-HDL ≥ 145 mg/dL TGs (age 0–9 y) ≥ 100 mg/dL, (age 10–19 y) ≥ 130 mg/dL HDL<45 mg/dL	• Confirm with FLP twice, then average • Consider referral to lipid specialist, especially if LDL ≥ 250 mg/dL or TGs ≥ 500 mg/dL • Initiate appropriate nutrition management • Recheck levels in 3–6 mo • Consider pharmacological intervention for high-risk patients • Consider further assessment – Evaluate for secondary causes – Evaluate for familial disorders – Screen family members

Abbreviations: CVD, cardiovascular disease; FLP, fasting lipid profile; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TGs, triglycerides.

[a] Information compiled from the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents of the National Heart, Lung, and Blood Institute.[4]

Nutrition Management

The emphasis on a healthy diet and lifestyle is key in the prevention of CVD and treatment of abnormal blood lipid levels. To prevent CVD in all children ≥ 2 years of age, recommendations include a daily diet with total fat <30% of total calories, saturated fat <10% of total calories, and avoidance of trans fat, with monounsaturated and polyunsaturated fats limited to 20% of total calories, and dietary cholesterol <300 mg/dmg.[4] CVD prevention also includes increasing the consumption of fruits, vegetables, fish, whole grains, and reduced-fat dairy products, while reducing the intake of fruit juice, sugar-sweetened beverages and foods, and salt.[10] For children ≥ 2 years of age at risk for CVD, the daily diet should be

further restricted to saturated fat <7% of total calories and dietary cholesterol to <200 mg/d. For children between 12 months and 2 years of age who have overweight, obesity, or a family history of obesity, dyslipidemia, or CVD, unflavored reduced-fat cow's milk is considered safe and appropriate, but its use should be discussed with the child's primary care provider.[4] Additional dietary management for high-risk patients should always be tailored to the individual lipid profile and involve counseling with a lipid specialist and registered dietitian or other skilled clinician to ensure effective nutrition intervention while maintaining appropriate growth and development.

Dietary Cholesterol

Dietary cholesterol is found in animal-based foods and can be reduced by limiting foods such as butter, egg yolk, high-fat meat, beef, poultry with skin, and whole-milk dairy products. Although limiting dietary cholesterol has less of a serum-lipid-lowering effect and has a more variable response among individuals than limiting saturated and trans fats, it is still important because cholesterol and saturated fat are found together in most foods. In general, LDL may be decreased by 3% to 5% if dietary cholesterol is restricted to <200 mg/d. In addition, an increase of 100 mg/d of dietary cholesterol increases total serum cholesterol by 2 to 3 mg/dL.[11]

Dietary Fats: Saturated Fats

Limiting the intake of saturated fats can help to lower LDL levels.[4] Saturated fat is found more in animal-based foods than plant-based foods, and it is solid at room temperature. A major source of saturated fat is meat, mainly fatty beef, pork, poultry with skin, and lamb. However, dairy products (cream, butter, cheese, ice cream, and other dairy products made with whole milk) are commonly overlooked as a source of saturated fat in children's diets. Plant-based sources of saturated fat are mainly found in tropical oils (coconut, palm, and palm kernel), which are often used in commercially baked goods.[12]

To reduce saturated fat intake, replace whole-milk dairy products with low-fat or nonfat ("skim") dairy products, and recommend leaner cuts of meat. Low-fat; reduced-fat; and baked cookies, crackers, and other baked

goods should be consumed instead of full-fat versions. Limit the use of additional saturated fat in the cooking process.[13] Low-fat cooking methods and techniques such as broiling, grilling, steaming, sauteing, poaching, or baking are preferable to frying.[14] For children with high cholesterol, saturated fats should be limited to <7% of total calories,[4] which can be achieved by choosing foods/ products with <2 g of saturated fat per serving.

Dietary Fats: Trans Fats

Trans fats, or hydrogenated fats, are produced when hydrogen is added to liquid vegetable oil to make it solid at room temperature. In the process of hydrogenation, bonds in the *cis* position are switched to the *trans* position, thus giving them the name trans fats. Trans fats give foods a desirable taste and texture. Individuals who consume excessive trans fats typically have increased LDL and decreased HDL cholesterol levels.

Trans fats are found mostly in stick margarine, high-fat baked goods, shortening, commercial frying oils, and fried snack foods. Examples of these foods are doughnuts, pastries, biscuits, crackers, cookies, potato and tortilla chips, French fries, and other bakery and snack foods. Trans fats should be avoided in the diets of children ≥ 2 years old.[4] Nutrition labels can list 0 g of fat per serving if the product contains <0.5 g of trans fat per serving. Therefore, to ensure a food is completely free of trans fat, it is important to check the ingredients for hydrogenated and/or partially hydrogenated oils.[15]

Dietary Fats: Monounsaturated and Polyunsaturated Fats

Children with dyslipidemia are encouraged to replace saturated and trans fats with the healthier monounsaturated and polyunsaturated fats (20%–23% of total calories), which help decrease LDL cholesterol levels.[4] Monounsaturated fats are fat molecules that have one unsaturated carbon bond in the molecule. They are liquid at room temperature but can turn to solid when chilled. Monounsaturated fats are found in avocados; peanuts, and many other nuts and seeds; and in vegetable oils such as olive, canola, peanut, safflower, and sesame.[16] Polyunsaturated fats are fat molecules with more than one unsaturated carbon bond. They are also liquid at room temperature and can turn to solid when chilled just like monounsaturated

fats. Polyunsaturated fats are found in walnuts and sunflower seeds, fatty fish (salmon, tuna, mackerel, herring, trout), and vegetable oils such as soybean, corn, and sunflower.[17]

Simple Carbohydrates

Simple sugars and carbohydrates, found in foods such as sweetened beverages, desserts, snacks, and white breads and other refined starches, raise TGs more than saturated and trans fats. Patients with hypertriglyceridemia primarily need to limit their intake of simple carbohydrates and replace them with complex carbohydrates.[4,18] Strong evidence supports an association between added sugar consumption and CVD risk in children through increased energy intake, increased adiposity, and dyslipidemia.[19]

Children and adolescents should limit added sugar consumption to < 25 g/d (~6 teaspoons) and limit sugar sweetened beverages to no more than 8 oz per week. In addition, added sugars should be avoided in the diets of children <2 years old. The intake of 100% fruit juice is recommended to be no more than 4 to 6 oz/d depending on the age of the child and should not be introduced into an infant's diet before 12 months of age.[20] For children with overweight or obesity who have high TGs, limiting dietary fat (especially saturated and trans fats) and increasing physical activity should also be recommended in addition to limiting simple carbohydrates because obesity will have a direct effect on triglyceride levels.[4] Instructing patients to limit their intake of sugar-sweetened beverages and choosing food products with no more than 8 g of added sugar per serving can help decrease the overall amount of sugar in their diet.

Fiber

Fiber combined with a low-fat diet may help to improve cholesterol levels further.[7] The types of fiber include soluble and insoluble. Soluble fiber (found in beans, oats, oat bran, and flaxseeds) helps decrease LDL cholesterol levels and has some effect on increasing HDL cholesterol levels.[21] Soluble fiber increases excretion of bile salts by hindering reabsorption into the small intestine. Unabsorbed bile salts are then excreted from the body, thus recreating low levels of bile acids in the liver. The body

will then control this deficit of bile acids in the liver by increasing the production of bile salts from circulating cholesterol.[22] An increase in soluble fiber of 5 to 10 g/d may reduce LDL by 3% to 5%.[7] One study found that children who consumed psyllium fiber along with a diet low in dietary fats and cholesterol lowered LDL cholesterol by an additional 5% to 10%.[23]

Specific guidelines for the suggested amount of fiber intake for children with dyslipidemia currently do not exist and remain controversial. However, dietary reference intakes (DRIs) provide general guidelines for estimating adequate fiber intake of both soluble and insoluble fiber (14 g of fiber per 1000 estimated calories needed per day), which is typically much higher than most children and adolescents consume.[4,24] Another commonly used method for obtaining the recommended range of daily fiber intake in grams is adding 5 to 10 years to the child's age.[25,26]

One way to meet dietary fiber requirements is to increase the intake of whole fruit and vegetables by consuming them at each meal and snack time, aiming for at least 5 servings per day. Another way is to consume whole grain/high-fiber foods in place of refined grain products,[27] which can be achieved by choosing foods/products with at least 3 g of fiber per serving.

Plant Sterols and Stanols

Plant sterols and stanols are essential components of cell membranes in plants, and they are structurally similar to cholesterol. Plant stanols are saturated sterols and have no double bonds. They inhibit the absorption of dietary cholesterol and decrease the reabsorption of cholesterol from bile. Plant sterols are found naturally in foods but not in large quantities. They have been incorporated into products such as margarine and butter spreads, oatmeal, and some snacks, and they are also available as chews and capsules.

Several studies have shown improved LDL cholesterol levels in adults consuming plant sterols, but fewer studies have been done in children and adolescents.[28,29] A randomized controlled study in children using 2 g of plant sterol in margarine per day decreased LDL cholesterol levels by 8%.[30] More recently, a small prospective study fortified a yogurt-based drink with 2 g of plant sterols, and children consumed the drink daily for 6 to 12

months.[31] LDL cholesterol and small dense LDL cholesterol levels decreased significantly, but the levels remained higher than in the control group. The expert panel recommends 2 g/d of plant sterols and stanols for children and adolescents >2 years of age.[4]

Plant sterols may theoretically have the potential to decrease levels of fat-soluble vitamins such as vitamin A (β-carotene) or vitamin E (α-tocopherol).[30] One study showed lower levels of β-carotene with normal vitamin A levels after adults consumed 2 to 3 g of plant stanol esters daily.[32] However, fortification of vitamin A in phytosterol-enriched milk resulted in significantly improved levels of LDL cholesterol levels with no change in concentration of β-carotene.[33] Vitamin deficiencies can typically be prevented by increasing intake of food sources containing both vitamin A and vitamin E. A multivitamin may be considered if additional risk factors for vitamin deficiency are present.[30]

Omega-3 Fatty Acids

The omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are found in fish oils and ocean fish (herring, mackerel, salmon, sardines) and lower TG levels by inhibiting VLDL and apolipoprotein B synthesis. While fish intake alone is cardioprotective, it does not affect TC, LDL, or HDL cholesterol levels and has only lowers TG levels. The expert panel still recommends increasing fish consumption for CVD prevention; no specific guidelines exist for pediatrics, but the recommendation for adults is 2 to 3 servings per week.[34] In addition to fish oils and fish, DHA and EPA may also be synthesized from α-linolenic acid, which is found in flaxseeds and flaxseed oil, canola oil, soy oil, and walnuts.

The intake of food sources of omega-3 fatty acids may not meet the amount needed to decrease TG levels significantly; therefore, DHA and EPA supplementation may be needed. The supplementation with over-the-counter fish oil in the range of 1 to 4 g/d of DHA plus EPA may be recommended for children with TG levels of 200 to 499 mg/dL.[4] It should be noted that over-the-counter fish oil supplements are often dosed with the total grams of fish oil, but one should pay attention to total grams of

combined DHA and EPA and not total grams of fish oil in dosing supplements for the treatment of high TGs.

Soy Protein

The effect of soy on lowering cholesterol remains controversial. Whereas some studies show soy isoflavones can decrease LDL cholesterol levels and TG levels and increase HDL cholesterol levels, other studies show little or no effect.[35,36] Although a daily intake of 25 g of soy in adults may decrease TC and LDL cholesterol levels from 1.5% to 4.5%, this may be related more to the use of soy as a substitute for foods high in saturated fat. No recommendations have been made for children. Even though the cholesterol-lowering benefits of soy remain controversial, soy can provide polyunsaturated fatty acids, fiber, vitamins, and minerals that are beneficial for cardiovascular and overall health.[37]

Enteral Nutrition Management

There have been no studies to date that have specifically focused on pediatric patients with dyslipidemia receiving specialized enteral nutrition (EN) supplementation. However, the same principles for oral intake can be applied for enterally fed patients who are more than 2 years old. Therefore, formulas that are lower in fat, such as those with less than 30% of calories as fat, and that contain fiber can be chosen. Fiber supplementation can also be added to the formula to meet daily requirements of fiber if the formula does not contain fiber. For patients with elevated TG levels, recommendations are to monitor overall carbohydrate intake. If needed, a formula with lower carbohydrate content can be used. Formulas with added omega-3 fatty acids may also be considered for patients with high TG levels. Most formulas designed for oral intake may have added sugars with increased carbohydrate content and palatability. Therefore, choosing a formula that is unflavored may be more beneficial.[38,39]

Parenteral Nutrition Management

There have been no studies to date that have specifically focused on pediatric patients with dyslipidemia receiving specialized parenteral nutrition (PN). Elevated TG levels (>400 gm/dL) may occur in >30% of patients receiving PN. These elevated levels can occur due to underlying medical conditions including prematurity, infection, inflammation, carnitine deficiency, hypothyroidism, renal and liver failure, insulin resistance, poor glycemic control, medications, and prolonged PN use. Elevated TG levels can also occur with an excessive intake of carbohydrates or fat. If left untreated, elevated TG levels may cause complications such as pancreatitis, lipid pneumonitis, an impaired immune system, and neurologic changes such as kernicterus. The treatment for patients on PN with elevated TG levels includes withholding the intravenous lipid emulsion (ILE) or adding carnitine or heparin to the PN solution. Changing to an alternative ILE for some patients, such as one that is fish-oil based or contains fish oil, has been shown to lower TG levels significantly.[40]

Fats and Carbohydrates

An excessive amount of fat or carbohydrates can cause elevated TG levels in the patient receiving PN. High lipid infusion rates (>0.15 g/kg/h) may exceed the rate of metabolism and can lead to an accumulation of lipids in the liver cells, causing an increase in serum TG levels and impairing liver function. In this situation, ILE is held for 4 to 6 hours to allow for the clearance of fat from the blood. TG levels are checked again at the end of the hold. If TG levels are still elevated, the ILE would need to be decreased to provide at least 1% of total calories as linoleic acid with optimum levels of 3 to 4% of total calories (or 0.25 gm/kg) to avoid essential fatty acid deficiency.[41]

Oil Source of ILE

Soybean-oil-based ILE is the main product available for use in the United States. This type of oil is high in phytosterols, mainly sitosterol, campesterol, and stigmasterol, which are absorbed in small amounts in the small intestine and are slowly metabolized by the liver. Long-term use of soybean-oil-based ILE may lead to a progressive increase and accumulation

of phytosterols in cell membranes and plasma lipoproteins, which has been associated with the development of cholestasis in children on PN.[42] Along with prolonged PN, an accumulation of parenteral phytosterols may contribute to the development of intestinal-failure-associated liver disease in neonates.[43] Soybean-oil-based ILE can predispose patients to high TG levels because of the slow clearance of long-chain fatty acids. The amount of phospholipid content varies with different concentrations of ILE, its volume, and the rate of administration. The use of 10% is discouraged in children because of the high phospholipid content per gram of fat. Therefore, the use of 20% ILE is encouraged.

The use of multi-oil ILE can be beneficial in decreasing TG levels, especially those containing fish oil. These ILEs contain more EPA and DHA, metabolites of omega-3 fatty acids. Omega-3 fatty acids have hypolipidemic activity, which reduces TG concentration by reducing VLDL levels. However, elevated TG levels have been reported in all sources of ILE. Other oil sources include the combination of soybean, medium-chain triglyceride (MCT), olive, and fish.

Carnitine and Heparin

Carnitine is responsible for transporting long-chain fatty acids into the mitochondria for fatty acid oxidation to produce energy. Therefore, carnitine can aid in reducing TG levels. However, carnitine is not present in PN solutions and may need to be added if deficiency is present, indicated by free carnitine blood levels <8.0 mmol/L. Neonates born prior to 32 to 34 weeks of gestation have been found to be carnitine-deficient because carnitine accretion happens in the last trimester of gestation.[40] Supplementation as high as 5 to 10 mg/kg/d has been used in patients with elevated TG levels and those on PN longer than 7 days. If carnitine deficiency is present, then up to 50 mg/kg/d may be needed.[41]

Heparin stimulates lipoprotein lipase activity by degrading TGs into fatty acid and glycerol. This activity is depressed in preterm infants. Infants receiving 1 U/mL heparin had lower TG levels than those receiving 0.5 U/mL or no heparin in the PN solution.[44]

Physical Activity

Physical activity is beneficial for children and adolescents with dyslipidemia because of its effects on raising HDL cholesterol levels and decreasing TG and TC levels. Improvement of LDL cholesterol levels and insulin resistance have also been documented.[4] In addition, physical activity plays a critical role in maintaining an appropriate weight, which also affects blood lipid levels. Physical activity should be encouraged in all patients with dyslipidemia unless another medical condition contraindicates this. According to current physical activity guidelines, children should have at least 60 minutes of moderate-to-vigorous physical activity daily,[45] and vigorous-intensity physical activity as well as muscle- and bone-strengthening activities at least 3 days a week. Table 15-2 provides a summary of dietary interventions and physical activity recommendations for specific lipid abnormalities.

TABLE 15-2. Summary of Nutrition and Physical Activity Recommendations for Specific Lipid Abnormalities[a]

Lipid Abnormality	Fiber	Simple Carbohydrates	Dietary Cholesterol	Trans Fats	Saturated Fats	Omega-3 Fats	Physical Activity
High LDL	Increase	DGA	<200 mg	Avoid	<7% of total calories	DGA	Increase
High TGs	DGA	Decrease	<200 mg	Avoid	<7% of total calories	Increase	Increase
Low HDL	DGA	DGA	<200 mg	Avoid	<7% of total calories	DGA	Increase

Abbreviations: DGA, Dietary Guidelines for Americans, 2020–2025; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TGs, triglycerides.

[a] Data from the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents of the National Heart, Lung, and Blood Institute; [4] U.S. Department of Agriculture and U.S. Department of Health and Human Services;[10,45] and Bamba.[18]

Pharmacologic Intervention

Statins

Medications are considered for high-risk patients and those who do not receive an adequate response following 3 to 6 months of lifestyle changes. The decision to initiate lipid-lowering medication depends on the age of the child, severity of dyslipidemia, and the presence of other atherosclerotic cardiovascular disease risk factors. Statins are the first-line agents for children ages 8 years and older who meet criteria for pharmacotherapy.[4,46] Statins have been shown to be safe and effective in lowering cholesterol in several short- and long-term clinical trials.[47–51] Side effects are rare and include myopathy, new-onset type 2 diabetes mellitus, and hepatic enzyme elevation.

Cholesterol-Absorption Inhibitors, Bile Acid Sequestrants, and Niacin

Second-line lipid-altering agents can be considered when statin treatment is not successful in achieving the LDL-C goal or when statins are not tolerated. Second-line agents include cholesterol-absorption inhibitors (eg, ezetimibe), bile acid sequestrants (eg, cholestyramine), and niacin. Cholesterol-absorption inhibitors (eg, ezetimibe) prevent intestinal absorption of cholesterol and plant sterols and are the most used second-line agents in children.[6] Pediatric data are limited, but in a randomized controlled trial of ezetimibe versus placebo in 138 children with mostly heterozygous FH, treatment with ezetimibe resulted in greater reductions in LDL-C (28% vs 1%) and total cholesterol (21% vs 0.2%).[52]

Bile acid sequestrants form another class of cholesterol-lowering medications, but they are not routinely recommended for pediatric patients because of limited effectiveness and poor compliance, mainly due to gastrointestinal side effects such as gas, bloating, constipation, and cramps.[4]

Niacin may help decrease both LDL cholesterol and TG levels and raise HDL cholesterol levels. It may be used in conjunction with statin therapy in children with elevated TG levels ≥ 200 to 499 mg/dL and elevated non-HDL cholesterol levels ≥ 145 mg/dL if the LDL cholesterol target level has been achieved. However, pediatric evidence is limited, and compliance is

difficult because of frequently occurring adverse reactions (rash, flushing, headaches), and therefore niacin is rarely used.[53,54]

Fibrates and Prescription Omega-3 Fatty Acids

Fibrates and prescription omega-3 fatty acids are used to treat elevated TG levels. Fibric acid derivatives raise HDL-C and lower triglyceride levels and are used for treating severe hypertriglyceridemia in children. They are typically reserved for TG levels >1000 mg/dL but may also be considered for levels 400 to 1000 mg/dL.

Prescription omega-3 fatty acids are also used to treat hypertriglyceridemia in adults. In clinical trials, prescription omega-3 fatty acids of 4 g/d (providing >3 g DHA+EPA) in adults with high TGs (200–499 mg/dL) decreased TG levels by 20% to 30% and in adults with very high TGs (> 500 mg/dL) decreased TG levels by greater than 30%.[55] Prescription omega-3 fatty acids are not currently approved by the U.S. Food and Drug Administration for use in children, and the few studies of omega-3 fatty acid use in children with high TGs have not shown a significant TG-lowering effect.[56–58] However, these trials used lower doses, smaller samples sizes, and included subjects with only mildly elevated TG levels. Future research should examine the TG-lowering effects of omega-3 fatty acids in children using higher doses, larger sample sizes, and subjects with more elevated TG levels.

Test Your Knowledge Questions

1. What is the acceptable level for LDL cholesterol in a fasting lipid profile in children and adolescents?
   A. <120 mg/dL
   B. <110 mg/dL
   C. <150 mg/dL
2. What percentage of saturated fats is recommended by the National Heart, Lung, and Blood Institute and American Academy of Pediatrics in children with high cholesterol?
   A. ≤20% of total calories per day
   B. <10% of total calories per day

C. ≤30% of total calories per day
D. ≤7% of total calories per day

3. In which lipid profile would omega-3 fatty acid supplementation be beneficial for a pediatric patient?
   A. LDL 200 mg/dL, TGs 80 mg/dL, HDL 50 mg/dL
   B. LDL 110 mg/dL, TGs 550 mg/dL, HDL 25 mg/dL
   C. LDL 120 mg/dL, TGs 150 mg/dL, HDL 25 mg/dL
   D. LDL 180 mg/dL, TGs 100 mg/dL, HDL 30 mg/dL

References

1. World Health Organization. WHO reveals leading causes of death and disability worldwide: 2000–2009. Updated December 9, 2020. Accessed November 7, 2022. https://www.who.int/news/item/09-12-2020-who-reveals-leading-causes-of-death-and-disability-worldwide-2000-2019
2. Global health and protection-cardiovascular diseases. Centers for Disease Control and Prevention. Updated December 17, 2021. Accessed November 7, 2022. http://www.cdc.gov/globalhealth/healthprotection/ncd/cardiovascular-diseases.html
3. Leading causes of death. Centers for Disease Control and Prevention. Accessed November 7, 2022. http://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm
4. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics*. 2011;5(128):S213–S256. https://doi.org/10.1542/peds.2009-2107c
5. Mytilinaiou M, Kyrou I, Khan M, et al. Familial hypercholesterolemia: new horizons for diagnosis and effective management. *Front Pharmacol*. 2018;9(707):1–29. https://doi.org/10.3389/fphar.2018.00707

6. Schefelker JM, Peterson AL. Screening and management of dyslipidemia in children and adolescents. *J Clin Med*. 2022;11:6479–6491. https://doi.org/10.3390/jcm11216479
7. Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285(19):2486–2497. https://doi.org/10.1001/jama.285.19.2486
8. Roland J. Familial combined hyperlipidemia and other inherited lipid disorders. Updated August 17, 2022. Accessed December 6, 2022. http://healthline.com/health/cholesterol/familial-hyperlipidemia#symptoms
9. Davidson MH, Pulipati VP. Dyslipidemia. Updated September 2022. Accessed December 2, 2022. http://www.merckmanuals.com/professional/endocrine-and-metabolic-disorders/lipid-disorders/dyslipidemia#v989709
10. Dietary Guidelines for Americans 2020–2025. U.S. Department of Agriculture, U.S. Department of Health and Human Services. Accessed November 22, 2023. https://www.dietaryguidelines.gov
11. Howell WH, McNamara DJ, Tosca MA, et al. Plasma lipid and lipoprotein responses to dietary fat and cholesterol: a meta-analysis. *Am J Clin Nutr*. 1997;65:1747–1764. https://doi.org/10.1093/ajcn/65.6.1747
12. Saturated fat. American Heart Association. Updated November 1, 2021. Accessed December 8, 2022. http://www.heart.org/en/healthy-living/healthy-eating/eat-smart/fats/saturated-fats
13. Smart substitutions to eat healthy. American Heart Association. Updated December 31, 2014. Accessed December 8, 2022. http://www.heart.org/en/healthy-living/healthy-eating/cooking-skills/cooking/smart-substitutions-to-eat-healthy
14. Don’t fry! Give healthy cooking methods a try! American Heart Association. Updated February 9, 2017. Accessed December 8, 2022. http://www.heart.org/en/healthy-living/healthy-eating/cooking-skills/cooking/techniques/healthy-cooking-methods

15. Trans fats. American Heart Association. Updated March 23, 2017. Accessed December 14, 2022. https://www.heart.org/en/healthy-living/healthy-eating/eat-smart/fats/trans-fat
16. Monounsaturated fats. American Heart Association. Updated June 1, 2015. Accessed December 14, 2022. https://www.heart.org/en/healthy-living/healthy-eating/eat-smart/fats/monounsaturated-fats
17. Polyunsaturated fats. American Heart Association. Updated June 1, 2015. Accessed December 14, 2022. http://www.heart.org/en/healthy-living/healthy-eating/eat-smart/fats/polyunsaturated-fats
18. Bamba V. Update on screening, etiology, and treatment of dyslipidemia in children. *J Clin Endocrinol Metabol*. 2014;99(9):3093–3102. https://doi.org/10.1210/jc.2013-3860
19. Vos MB, Kaar JL, Welsh JA, et al. Added sugars and cardiovascular disease risk in children: a scientific statement from the American Heart Association. *Circulation*. 2017;135:e1017–e1034. https://doi.org/10.1161/cir.0000000000000439
20. Heyman MB, Abrams SA. Fruit juice in infants, children, and adolescents: current recommendations. *Pediatrics*. 2017;139(6):1–8. https://doi.org/10.1542/peds.2017-0967
21. Dietary fiber: essential for a healthy diet. Mayo Clinic. Updated November 4, 2022. Accessed December 19, 2022. http://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/fiber/art-20043983
22. Fiber benefits: heart health. FiberFacts.org. Updated June 15, 2016. Accessed December 19, 2022. https://www.fiberfacts.org/fiber-benefits-heart-health/
23. Kwiterovich PO. Recognition and management of dyslipidemia in children and adolescents. *J Clin Endocrinol Metabol*. 2008;93(11):4200–4209. https://doi.org/10.1210/jc.2008-1270
24. Food and Nutrition Board Institute of Medicine. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients)*. National Academies Press; 2005. https://doi.org/10.17226/10490
25. Williams C, Bollella M, Wynder E. A new recommendation for dietary fiber in childhood. *Pediatrics*. 1995;96(5):985. https://doi.org/10.1542/peds.96.5.985

26. Marcason W. What is the “age+5” rule for fiber? *J Am Diet Assoc*. 2005;105(2):301–302. https://doi.org/10.1016/j.jada.2004.12.025
27. MyPlate: Grains. What foods are in the grains group? U.S. Department of Agriculture. Accessed December 21, 2022. https://www.myplate.gov/eat-healthy/grains
28. McKenney JM, Jenks BH, Shneyvas E, et al. A softgel dietary supplement containing esterified plant sterols and stanols improves the blood lipid profile of adults with primary hypercholesterolemia: a randomized, double-blind, placebo-controlled replication study. *J Acad Nutr Dietet*. 2014;114(2):244–249. https://doi.org/10.1016/j.jand.2013.09.023
29. Eussen ST, de Jong N, Rompelberg CJ, et al. Dose-dependent cholesterol-lowering effects of phytosterols/phytostanol-enriched margarine in statin users and statin non-users under free-living conditions. *Pub Health Nutr*. 2011;14(10):1823–1832. https://doi.org/10.1017/s1368980011000164
30. Tammi A, Ronnemaa T, Miettinen TA, et al. Effects of gender, apolipoprotein E phenotype and cholesterol-lowering by plant stanol esters in children: the STRIP study—Special Turku Coronary Risk Factor Intervention Project. *Acta Paediatr*. 2002;91(11):1155–1162. https://doi.org/10.1080/080352502320777379
31. Garoufi A, Vorre S, Soldatou A, et al. Plant sterols-enriched diet decreases small, dense LDL-cholesterol levels in children with hypercholesterolemia: a prospective study. *Italian J Pediatr*. 2014;40(42). https://doi.org/10.1186/1824-7288-40-42
32. Gylling H, Hallikainen M, Nissinen MJ, Miettinen TA. The effect of a very high daily plant stanol ester intake on serum lipids, carotenoids, and fat-soluble vitamins. *Clin Nutr*. 2010;29(1):112–118. https://doi.org/10.1016/j.clnu.2009.08.005
33. Petroglanni M, Kanellakis S, Moschonis G, Manios Y. Fortification of vitamin A in a phytosterol enriched milk maintains plasma beta-carotene levels. *J Food Science Technol*. 2014;51(1):196–199. https://doi.org/10.1007/s13197-013-1103-y
34. Dalidowitz C. Disorders of lipid metabolism. In: Leonberg B, ed. *Pediatric Nutrition Care Manual*. American Academy of Nutrition and Dietetics; 2014.

35. Fletcher B, Berra K, Ades P, et al. Managing abnormal blood lipids: a collaborative approach. *Circulation*. 2005;112(20):3184–3209. https://doi.org/10.1161/circulationaha.105.169180
36. Erdman JW. AHA Science Advisory. Soy protein and cardiovascular disease: a statement for healthcare professionals from the Nutrition Committee of the AHA. *Circulation*. 2000;106:2555–2559. https://doi.org/10.1161/01.cir.102.20.2555
37. Dalidowitz C. Nutrition management of dyslipoproteinemia. In: Nevin-Folino N, ed. *Pediatric Manual of Clinical Dietetics*. 2nd ed. American Dietetic Association; 2003:319–340.
38. Nestle Nutrition Medical Hub Product Support. Nestle Health Science. Accessed December 22, 2022. https://www.nestlemedicalhub.com/product-support
39. Product Guides. Abbott Nutrition. Accessed December 22, 2022. http://abbottnutrition.com/product-guides
40. Cober MP, Gura KM, Mirtallo JM, et al. ASPEN lipid injectable emulsion safety recommendations part 2: neonate and pediatric considerations. *Nutr Clin Pract*. 2021;36(6):1106–1125. https://doi.org/10.1002/ncp.10778
41. Lapillonne A, Fidler Mis N, Goulet O, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: lipids. *Clin Nutr*. 2018;37:2324–2336. https://doi.org/10.1016/j.clnu.2018.06.946
42. Nghiem-Rao TH, Tunc I, Mavis AM, et al. Kinetics of phytosterol metabolism in neonates receiving parenteral nutrition. *Pediatr Res*. 2015;78(2):181–189. https://doi.org/10.1038/pr.2015.78
43. Kurvinen A, Nissinene MJ, Andersson S, et al. Parenteral plant sterols and intestinal failure-associated liver disease in neonates. *J Pediatr Gastroenterol Nutr*. 2012;54(6):803–811. https://doi.org/10.1097/mpg.0b013e3182474118
44. Lim MS, Choi CW, Kim B, Yang HR. Clinical factors affecting lipid metabolism and optimal dose of heparin in preterm infants on parenteral nutrition. *Ped Gastro Hep Nutr*. 2013;16(2):116–122. https://doi.org/10.5223/pghn.2013.16.2.116
45. U. S. Department of Health and Human Services. *Physical Activity Guidelines for Americans.* 2nd ed. Updated August 24, 2021. Accessed

January 6, 2023. https://health.gov/our-work/nutrition-physical-activity/physical-activity-guidelines/current-guidelines
46. de Ferranti SD, Steinberger J, Ameduri R, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association. *Circulation*. 2019;139(13):e603–e634. https://doi.org/10.1161/cir.0000000000000618
47. Avis HJ, Vissers MN, Stein EA, et al. A systematic review and meta-analysis of statin therapy in children with familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol*. 2007;27(8):1803–1810. https://doi.org/10.1161/atvbaha.107.145151
48. Lambert M, Lupien PJ, Gagne C, et al. Treatment of familial hypercholesterolemia in children and adolescents: effect of lovastatin. *Pediatrics*. 1996;97(5):619–628. https://doi.org/10.1542/peds.97.5.619
49. Luirink IK, Wiegman A, Kusters DM, et al. 20-year follow-up of statins in children with familial hypercholesterolemia. *N Engl J Med*. 2019;381(16):1547–1556. https://doi.org/10.1056/NEJMoa1816454
50. Wiegman A, Hutten BA, de Groot E, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA* 2004;292(3):331–337. https://doi.org/10.1001/jama.292.3.331
51. Eiland LS, Luttrell PK. Use of statins for dyslipidemia in the pediatric population. *J Pediatr Pharmacol Ther*. 2010;15:160–172. https://doi.org/10.5863/1551-6776-15.3.160
52. van der Graaf A, Cuffie-Jackson C, Vissers MN, et al. Efficacy and safety of coadministration of ezetimibe and simvastatin in adolescents with heterozygous familial hypercholesterolemia. *J Am Coll Cardiol*. 2008;52(17):1421–1429. https://doi.org/10.1016/j.jacc.2008.09.002
53. McCrindle BW, Urbina EM, Dennison BA, et al. Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. *Circulation*. 2007;115(14):1948–1967. https://doi.org/10.1161/circulationaha.107.181946
54. Pasquali SK, Li JS. Prevention of future cardiovascular disease in high-risk pediatric patients: a role for lipid lowering therapy? *Circ*

Cardiovasc Qual Outcomes. 2008;1:131–133. https://doi.org/10.1161/CIRCOUTCOMES.108.819235
55. Skulas-Ray AC, Wilson PWF, Harris WS, et al. Omega-3 fatty acids for the management of hypertriglyceridemia: a science advisory from the American Heart Association. *Circulation*. 2019;140:e673–e691. https://doi.org/10.1161/cir.0000000000000709
56. de Ferranti SD, Milliren CE, Denhoff ER, et al. Using high-dose omega-3 fatty acid supplements to lower triglyceride levels in 10- to 19-year-olds. *Clin Pediatr* (Phila). 2014;53(5):428–438. https://doi.org/10.1177/0009922814528032
57. Engler MM, Engler MB, Malloy MJ, Paul SM, Kulkarni KR, Mietus-Snyder ML. Effect of docosahexaenoic acid on lipoprotein subclasses in hyperlipidemia children (the EARLY study). *Am J Cardiol*. 2005;95(7):869–871. https://doi.org/10.1016/j.amjcard.2004.12.014
58. Gidding SS, Prospero C, Hossain J, et al. A double-blind randomized trial of fish oil to lower triglycerides and improve cardiometabolic risk in adolescents. *J Pediatr*. 2014;165(3):497–503. https://doi.org/10.1016/j.jpeds.2014.05.039

Test Your Knowledge Answers

1. The correct answer is **B**. The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set <110 mg/dL LDL cholesterol level as the acceptable level. Less than 120 mg/dL is an acceptable level for young adults ages 20 to 24 years. An LDL cholesterol level ≥ 130 mg/dL is considered high.
2. The correct answer is **D**. Children with elevated LDL cholesterol, non-HDL cholesterol, and TG levels should further restrict their diet from containing no more than 10% saturated fats of total calories to ≤ 7% saturated fats of total calories.
3. The correct answer is **B**. Children with elevated TG levels ≥ 200 to 499 mg/dL may be considered for omega-3 fatty acid supplementation along with increased fish intake, 25% to 30% calories from fat, ≤ 7% of total calories from saturated fat, <200 mg/d of cholesterol, avoidance of

trans fats, decreased sugar intake along with no sweetened drinks, and increased intake of complex carbohydrates.

The authors of this chapter wish to thank Shirley Huang, MD; Melanie Katrinak, RD, CSP, LDN; Megan Dougherty, RD, CSP, LDN, CNSC; and Kristi Drabouski, RD, CSP, LDN, CNSC for their contributions to previous editions of this text.

PART III

Disease States and Nutrition

16. Severe Neurological Impairment
Gina Rempel, MD, FRCPC, FASPEN

17. Eating Disorders
Mary Pat Turon-Findley, MEd, RD, CMHIMP, LD

18. Food Allergies
Mary Beth Feuling, MS, RD, CSP, CD
Leslie M. Gimenez, MD
Nicole M. Martin, RD, CSP, CD
Praveen S. Goday, MBBS

19. Diabetes Mellitus and Other Endocrine Disorders
Michelle Reed, MS, RD, CSP, LDN, CDCES

20. Inborn Errors of Metabolism
Sandy van Calcar, PhD, RD, LD

21. Cardiac Disease
Kavisha Shah, MD

22. Renal Disease
Christina L. Nelms, MS, RD, LMNT/LD
Marisa Juarez-Calderon, MPH, RD, CSP, LD

Bradley A. Warady, MD

23. Gastrointestinal Disease

Jill Dorsey, MD, MS
Donald George, MD
Elizabeth Bobo, MS, RD, LDN, CNSC, FAND

24. Hepatic Disease

Julie Bonn, MD
Samuel A. Kocoshis, MD

25. Intestinal Failure

Vikram Raghu, MD, MS
Kishore R. Iyer, MBBS, FRCS (Eng), FACS

26. Pulmonary Disorders

Laura Padula, MS, RD, LDN
Rachel Kofsky, MA, RD, CSP, LDN, CLC
Maria Mascarenhas, MBBS

27. Pediatric Oncology and Hematopoietic Stem Cell Transplant Patients

Hannah Williams, RD, LDN, CSP, CSO
Bethany Squillante, MS, RD, CSP, LDN
Darielle Wilhelm, RD, LDN, CNSC
Karen Smith, MS, RD, CSO, LD/LDN
Erika May Murphy, PharmD, BCPPS
Susan Rheingold, MD

28. Trauma and Burns

Arlet G. Kurkchubasche, MD

29. Surgery

Arlet G. Kurkchubasche, MD

16

Severe Neurological Impairment

Gina Rempel, MD, FRCPC, FASPEN

Learning Objectives

1. Identify factors that place children with severe neurological impairment (NI) at increased risk for nutrition problems.
2. Demonstrate an assessment strategy for growth and nutrition in children with severe NI.
3. Elucidate an approach to providing oral and enteral nutrition support to children with severe NI.

Introduction

The term *neurological impairment* (NI) is commonly used but inconsistently defined to describe a large heterogeneous group of children. Children with NI are those with

- damage to a developing brain as seen in children with cerebral palsy (CP)
- neurodegenerative conditions (eg, Rett Syndrome)
- brain injury/trauma
- spinal cord cell (eg, spinal muscular atrophy) damage

- spinal cord development abnormalities or myelodysplasia as seen in children with spina bifida

A recent consensus document states that severe NI "describes a group of disorders of the central nervous system (CNS) which arise in childhood, resulting in motor impairment, cognitive impairment and medical complexity, where much assistance is required with activities of daily living."[1] This chapter outlines nutrition deficiencies, a nutrition assessment approach, and various modalities of nutrition support in children with severe NI.

Children with severe NI with significant motor impairment who present with feeding problems at an early age are at the greatest risk of undernutrition.[2,3] These children are also at risk for poor linear growth, micronutrient deficiencies, and osteopenia.[4–6] However, overweight status is also not infrequent in these children largely because of inactivity and low metabolic rates.

Both undernutrition and overweight status of children with NI can result in poor general health, increased use of healthcare services, and decreased participation in activities at home and school.[7,8] On the other hand, appropriate nutrition support with resultant improvement in nutrition status has beneficial effects on linear growth, weight gain, quality of life, neurological and developmental progress, improved bone health, wound healing, and immune function.[9–13] In fact, good nutrition status in children with severe NI is a powerful prognosticator of their survival.[14–16]

For children with severe NI, management of both their nutrition and their eating and drinking difficulties is best accomplished by a multidisciplinary team of physicians, nurses, registered dietitians (RDs), feeding therapists (physical, occupational, and/or speech therapists) psychologists, and social workers to avoid the negative consequences of poor nutrition. The disease spectrum for children with severe NI varies widely, and nutrition assessment and interventions must be tailored to the individual child and their family.

Common Nutrition Problems in Children With Severe Neurological Impairment

Undernutrition, Growth Failure, and Overweight Status

The true prevalence of nutrition problems in children with NI is not known. Estimates have been made in individual categories of NI and specific conditions including CP, spina bifida, spinal cord injury, and Rett syndrome.[2,17–21] Parental and caregiver surveys show a high prevalence of feeding difficulties in children with NI.[22]

Undernutrition based on weight, weight-for-length, and triceps skinfold thickness has been documented with varying degrees of frequency in individuals with NI and becomes more pronounced as oral feeding difficulties, age, and NI severity increase.[6,23–26] Expected height-for-age and weight-for-age of children with severe NI are generally lower than those of the reference population.[5,11,16,17] Children with CP who have only minimal motor impairment have similar weights and heights to age-matched and sex-matched peers without NI.[25] NI may impact linear growth even when the child is receiving appropriate nutrition support. This may be related to the underlying condition causing the NI. In these circumstances, nutrition intervention may not resolve the growth failure.[27] Other non-nutritional factors such as endocrine dysfunction, immobility, and lack of weight bearing may impact growth and nutrition as well.[28]

Although children with NI may be shorter and weigh less than age-matched peers without NI, when assessing weight-for-height or triceps skinfold thickness, many are overweight.[6,18] Excessive weight gain may not be noticed as quickly in children with severe NI because of their small body size, unusual fat distribution, and low muscle mass (altered body composition). Thus, a child with NI who does not look “lean” may be overweight.

Pathophysiology of Growth-Related Issues

DIETARY INTAKE Inadequate intake is the most common cause of undernutrition or growth failure in children with severe NI.[2,29–31] Contributing factors include the inability to effectively communicate hunger, thirst, satiety, food preferences, or feeding styles. In addition, oral-motor function and positioning challenges can make feeding difficult and time-consuming, thus the amount of food given may be inadequate and the child may stop eating before consuming an adequate amount. Increasing the child's energy intake through enteral nutrition (EN) support will generally result in weight gain, suggesting that undernutrition is largely remedial.[32,33] Careful monitoring is needed to avoid overfeeding and excessive weight gain in children with severe NI who are transitioning to or adding EN support.[18,23,34]

ORAL-MOTOR DYSFUNCTION Early and persistent oral-motor challenges in children with NI are correlated with poor nutritional outcomes including lower body fat and decreased linear growth and weight gain.[5,32,33,35–37] Oral-motor dysfunction generally parallels overall motor impairment in children with severe NI.[38] Increased feeding difficulty correlates with successively decreased weight, body fat stores, and arm muscle mass. Sialorrhea may be a marker for oral-motor dysfunction, especially when posterior drooling occurs, which increases the child's aspiration risk.[39,40]

Common concerns in children with oral-motor dysfunction include the following:

- Poor suck resulting in difficulty breastfeeding or bottle feeding
- Food spillage from the mouth because of inadequate lip closure
- Problems with biting
- Poor tongue control causing the inability to lateralize solid food to the teeth for appropriate processing and difficulty chewing, preventing the advancement of food textures. Coughing or choking while eating may indicate aspiration during swallowing, which is related to poor control and processing of the food bolus, delays in triggering the swallow, and difficulty propelling it through the pharynx.[35,36,39]

Children with feeding, eating, and drinking difficulties can have prolonged mealtimes, which can be stressful for them and their parents.[41] These longer mealtimes may not compensate for feeding inefficiency because the energy expenditure can negate the impact of increased intake. Furthermore, prolonged mealtimes can negatively impact hunger and satiety. EN support can alleviate some of the nutrition issues resulting from eating and drinking difficulties; however, some parents experience uncertainty about EN because they value the shared sensory experience of mealtimes with their children. Having a clear understanding of parents' nutrition goals for their children, and if possible, working on improving oral intake (even when providing nutrition support) can alleviate a parent's fear of EN support.

NUTRIENT LOSS Children with NI with oral-motor problems who feed themselves may lose food before and after it reaches their mouths. The use of adaptive utensils may enhance movement performance and minimize food spillage.[39,42] Poor lip closure and poor oral-motor processing can result in food loss from the mouth. Some of this can be mitigated with augmentative techniques to enhance lip closure and stabilize the jaw to assist in processing.[39] Gastroesophageal reflux (GER) may result in loss of nutrients after ingestion.[5]

ENERGY EXPENDITURE Energy requirements for children with NI are influenced by many factors that are not routinely of concern in children without NI.[5] The underlying cause of the NI and consequently the severity and distribution of the motor impairment, the presence of movement disorders (dyskinesia, spasticity hypotonia), and a child's sedentary behavior, all influence the child's total energy expenditure (TEE).[5] This causes considerable variability in TEE among children even when they are matched for motor abilities.[9,18,29,43,44]

Children with NI generally have a lower fat-free mass than their peers without NI. This contributes to lower resting energy expenditure (REE) and energy requirements. The greatest predictor of energy needs in children with severe NI is their fat-free mass, followed by their ambulatory status.[45,46]

REE and TEE are significantly lower in children with NI who are marginally ambulant and non-ambulant compared to children without NI.[44,47] In general, energy expenditure decreases as the severity of motor impairment increases.[5] While the energy cost of movement may be higher in children with motor impairment because of muscle inefficiency, this is offset by decreased motor activity.[48] Energy requirements can be as low as 50%–70% of the dietary reference intake (DRI) for age and sex in non-ambulant children who have bilateral CP or myelodysplasia (spina bifida).[18,29,47,49,50] Children with CP or spina bifida who are ambulant have similar energy expenditures to their age-matched peers even though the energy cost of ambulation can be higher than in children without NI.[48] Children with dyskinesias may have similar or even increased energy requirements relative to children without NI because of increased involuntary movement at rest.[29]

Because of these individual factors and the significant heterogeneity of the population of children with severe NI, predicting energy requirements in these children is challenging. In their consensus document, Romano et al recommend basing calorie estimates for children with NI on the same dietary reference standards for children without NI, such as the dietary reference intakes (DRIs) or the World Health Organization (WHO) equations (see Table 16-1).[5,50–52] There are also proponents of the Schofield[53] and Harris-Benedict equations for calculating energy requirements.[29,47] All of these formulas overestimate the caloric requirements of children with NI (even when correction factors are added to the calculation) because of linear growth problems and decreased activity. Thus, some researchers have recommended using 75% of the suggested energy requirement for age when starting nutrition support to prevent overnutrition.[9,54,55] Using indirect calorimetry may overcome some of the challenges in estimating energy requirements using traditional formulas, but this method is not available in all settings.[47,56]

TABLE 16-1. World Health Organization Equations for Determining Energy Needs

Sex	Age (y)	Energy Needs,[a] kcal/d
Males	0–3	60.9 W − 54
	3–10	22.7 W + 495
	10–18	17.5 W + 651
	18–30	15.3 W + 679
Females	0–3	61 W − 51
	3–10	22.5 W + 499
	10–18	12.2 W + 746
	18–30	14.7 W + 496

Abbreviation: W, weight.

[a] World Health Organization Equations.[52]

If nutrition support clinicians choose to use any of the previously mentioned formulas (with or without correction factors to calculate energy requirements), the value obtained should only be considered a starting point in nutrition management. Frequent reassessment of a child's nutrition status is indicated to ensure that the energy requirements are not overestimated especially after starting nutrition support.[5]

Fluid Requirements

Children with NI are at increased risk of dehydration because they may not sense thirst or be able to communicate their need for water. In addition, they may be unable to swallow liquids safely and may lose liquids through salivation and GER. Thus, careful attention is crucial to ensure adequate hydration is provided. While there are no specific recommendations for fluid requirements for children with NI, calculations should begin with the recommendations for age-matched peers without NI and be adjusted depending on the child's specific needs.

Protein Requirements

Because evidence-based guidelines specific for children with NI do not exist, protein intake for children with NI should be provided based on the DRIs for age-matched and sex-matched peers without NI.[5]

Micronutrient Requirements

Children with NI are at risk of developing micronutrient deficiencies because providing adequate amounts of these nutrients in children with very low calorie needs or those with a limited dietary repertoire can be challenging.[56] Studies have documented low intake of several micronutrients (eg, iron; folate; vitamins C, D, E; zinc; selenium; and essential fatty acids) in cohorts of children with NI who are orally or enterally fed.[30,31,57–60]

Like fluids and protein, specific vitamin and mineral requirement guidelines for children with NI do not exist. Hence these should be provided based on the DRIs for age-matched and sex-matched peers without NI,[5] which can be found on the U.S. Department of Agriculture website (https://www.nal.usda.gov/human-nutrition-and-food-safety/dietary-guidance).[61] Multivitamin, mineral, and electrolyte supplementation may also be needed to meet nutrient needs. While there are no clear guidelines for monitoring laboratory parameters, annual laboratory testing should be considered for iron, bone health, and other micronutrients in children with NI.[5]

Osteopenia

Children with NI are at high risk for low bone mineral density (BMD), which is associated with osteoporosis and fragility/low-impact fractures, especially of the vertebral column, hip, and lower extremities. BMD is related to the severity of NI and its resultant decreased motor function and physical activity. In addition, nutrition status (especially regarding vitamin D and calcium intake), limited sun exposure, and anticonvulsant use all impact bone health and BMD. Furthermore, a child's genetics and hormonal factors such as later onset of puberty can affect BMD.[62,63,64]

Dual-energy x-ray absorptiometry (DXA) scan evaluation is the standard for evaluating BMD in children.[65] The recommended scanning sites in children include the total body (excluding the head) and posterior-anterior lumbar spine. Other sites (eg, proximal femur, lateral distal femur, forearm) can be used in children for whom the standard measurements are difficult to obtain because of positioning problems or other factors interfering with the ability to get an accurate image (eg, spinal rods or vagal nerve stimulators).[65,66]

A decreased BMD (z-score –2.0) does not equate with osteoporosis. Pediatric osteoporosis should only be diagnosed when a BMD z-score <−2.0 is present in association with vertebral fractures or with 2 long-bone fractures for children up to 10 years of age or 3 long-bone fractures before age 19 years.[67] Fernández et al report that on average, children with CP (at all levels of functional ability) have a BMD z-score of –2.1. This score decreases as the severity of motor impairment increases (z-score = –3.1 in children with CP Gross Motor Function Classification [GMFCS] 5).[64] Of children with low BMD z-score <−2.1, 25.9% were found to have vertebral fractures on radiography.[64] Caregivers and health professionals need to be cautious to avoid fractures in children at risk of low BMD. Both spasticity and weakness can contribute to falls and thus should be addressed, if possible, to decrease fracture risk.

Optimization of calcium intake should be considered in children at risk of low BMD; however, it is important to ensure that the calcium given is not just being excreted, as this can increase the risk of nephrolithiasis.[63] Calcium supplementation can be guided by measuring urine calcium excretion with a urine calcium/urine osmolality or urine calcium/urine creatinine level appreciating that a low creatinine level is seen in many children with NI because of their low lean body mass. Checking the parathormone, alkaline phosphatase level, and vitamin D status is helpful. Appropriate supplementation and the use of weight-bearing activities to enhance bone strength are indicated.[63]

Research on the use of bisphosphonates in children with NI is limited and the topic remains controversial.[68,69] The certainty of evidence for improved bone health in children with CP is low according to the Cochrane Review by Hurley et al.[70] On the other hand, Ozel[63] and Simm[71]conclude

that there is probable evidence for bisphosphonate use in children with osteoporosis; however, even if there is improvement in BMD, it is unclear whether or not low-impact fracture rates will be reduced. Prophylactic bisphosphonate therapy (ie, treating a low BMD z-score in the absence of a fracture) is difficult to justify in young people with CP except in cases of severe pain presumed to be of bone origin.

Growth and Anthropometric Measurements

Weight gain and growth along predicted trajectories reassure us that a child is healthy and thriving regardless of whether they have a disability. For children without NI, nutrition status can often be understood with weight and height measurements, and the resultant body mass index (BMI); however, things are not so simple in children with NI. First, measuring children with severe NI is more difficult because of their motor impairment and skeletal deformities. Second, equipment required for alternate anthropometric measurements may be difficult to access. Lastly, the standards used to interpret growth data in children without NI may not be appropriate for children with NI.[9]

Whenever possible, obtain weight and length or height measurements under the same conditions and with the same equipment each time. There is significant value in obtaining detailed and accurate anthropometrics for all children, as each measurement may have merit in identifying a child who is at risk for malnutrition.[25] Staff should be specially trained to perform anthropometric measurements in children with NI and record them in the child's clinical record.

Weight

Weight can be obtained using standardized techniques and equipment. Children should be weighed with little or no clothing. An infant scale should be used for small children who cannot stand, while a platform scale (table, chair, bed, or wheelchair) or mechanical lift scale can be used for older children. While direct weights are preferred, if an appropriate scale is not available a caregiver can be weighed with and without holding the child. The weight difference is the (indirect) weight of the child.

Length/Height

Length/height should also be obtained using standard techniques and equipment for children without skeletal deformities who can stand. Children under 2 years of age and those who are unable to stand should be measured on a recumbent length board. For children over 2 years of age who can stand without crouching, obtain a standing height without braces or shoes using a stadiometer.

Alternate Measurements of Stature

Children with NI may have scoliosis or hip, knee, and ankle contractures that can make accurate length/height measurement challenging. In this case, alternate height measurements can be used. Upper arm length, ulnar length, lower leg length, and knee height measured with sliding calipers are reliable alternatives.[72] These alternate measurements can be either plotted on corresponding charts or converted to height using corresponding formulas.[72,73] While it is appealing to consider arm span as an appropriate measurement for children with severe NI, this measurement is fraught with challenges too, as skeletal deformities and scoliosis can skew the measurement.[74] Table 16-2 provides details on measuring anthropometrics.

TABLE 16-2. Measuring Anthropometrics in Children With NI Who Are Unable to Stand

Measurement	Age	Equipment	Technique	Calculation
Knee height	All ages	KH calipers	With the child sitting, place the bottom blade of the caliper under the heel. With the knee and ankle joint at 90°, position the top blade of the caliper just behind the patella on the end of the femur.	• KH (cm) is the distance between the blades of the caliper • For children up to 12 y with NI: Estimated height = (2.69) × KH (cm) + 24.2[72] • For youth >12 y use age-specific formulas stratified by age & gender
Tibial length	2–12 y	Tape measure	The tibia is measured on the inside of the leg (medial side). With the child sitting or supine, find and mark the joint space between the tibia and the femur. Then mark the distal edge of the medial malleolus.	The TL is the distance between these points in centimeters: Estimated height = 3.26 × TL (cm) + 30.8
Upper arm length	All ages	Anthropometer	The child should be sitting up with their arm relaxed at their side. Measure from the lateral edge of the acromion to the head of the radius,	Estimated stature (cm) = (4.35 × upper arm length in cm) + 21.8[72]

Measurement	Age	Equipment	Technique	Calculation
			which is the forearm bone on the side of the thumb.	

Abbreviations: KH, knee height; NI, neurological impairment; TL, tibial length. In children with motor impairment related to NI, measure the less-affected side. Reproduced with permission from the American Society for Parenteral and Enteral Nutrition from Becker PJ, Rempel G. Nutrition screening and history. In: Larson-Nath C, ed. *ASPEN Pediatric and Neonatal Nutrition Support Handbook*. 3rd ed. American Society for Parenteral and Enteral Nutrition; 2024:20–21.

Body Mass Index or Weight-for-Length

Weight-for-length is used for children under the age of 2 years. In theory, for children with NI who are older than 2 years, BMI calculated from height and weight measurements should be used; however, BMI is difficult to interpret in children using extrapolated height measurements because measurement errors are magnified by the BMI calculation.

Upper-Arm Anthropometrics

A triceps skinfold (TSF) is an easy measure to obtain, it's reproducible, the calipers are affordable, and reference data is available online (refer to https://www.peditools.org).[75,76] It is an important nutrition indicator when assessing a child with NI who is unable to stand and therefore does not have an easily interpretable BMI. A TSF is a good screening tool for depleted fat stores.[77] A measurement of >10th percentile for age on standard TSF charts[76] is associated with lower healthcare system use and improved community participation while a measurement of <10th percentile for age may indicate a need for nutrition intervention.[7]

Like other anthropometric measurements, TSF cannot be interpreted in isolation in children with NI because they store fat centrally and thus the TSF might underestimate overweight status. Mid-upper arm circumference (MUAC) is also important in the assessment of nutrition status. Reference ranges for MUAC are available for children of all ages.[76,78] Serial TSF and MUAC measurements are useful to track changes in body composition in children with and without NI. However, it is important to remember that

children with NI generally have a low lean body mass and MUAC will usually be low because of this.[18]

Measuring both TSF and MUAC is important because the TSF screens for fat stores while the MUAC measures fat, muscle, and bone. The TSF may be high and the MUAC may be low and the child with NI may still appear to be "lean" even though their fat mass is high. This can be an important point to communicate to parents when explaining the clinical appearance of their child. While TSF and MUAC are proxy measurements for body composition, DXA is the standard for measuring body composition in children with severe NI.[5]

Growth Charts

For all children with and without NI, anthropometrics (height, length, weight, weight-for-length, or BMI) should be properly measured and plotted on sex-appropriate and age-appropriate growth charts like the WHO or Centers for Disease Control and Prevention (CDC) growth charts. The WHO Growth Standards demonstrate how children from various ethnic backgrounds will grow when raised in favorable environmental conditions with access to good nutrition. These charts should be used to plot all anthropometrics (including extrapolated lengths) for all children from birth to 2 years of age.[79] In the United States, all anthropometrics (including extrapolated heights) for children older than 2 years should be plotted on the CDC growth charts because they represent US national growth standards.[80] Many other countries (including Canada) use the WHO Growth Standards for children of all ages.[81]

Weight and length or height measurements can also be plotted on condition-specific growth charts, however, these charts should be used with caution because they are descriptive, often represent small cohorts of children, and some were developed using small historical samples that predate optimized nutrition care. Specialized growth charts should always be used in conjunction with CDC or WHO growth charts even if the children plot significantly differently than their age-matched peers without NI.

CP Growth Charts

The most current CP-specific growth charts (published in 2011)[24] are stratified by a child's age, sex, and functional status using the GMFCS.[82] Children classed as GMFCS 5, which represents significant motor impairment, are further stratified by tube-feeding status.

Knowing that children who are better nourished have fewer healthcare system visits and miss fewer days of social activity,[7] Brooks et al[24] re-examined their previously published[23] data and found that children in GMFCS levels 1–5 without EN support had lower morbidity (based on numbers of chronic co-occurring conditions) and mortality rates when their weight was above the 20th percentile on the corresponding CP growth chart. Children who were classified as GMFCS 5 who were tube-fed also experienced an increased risk of mortality when they plotted in the "zone of concern" (<20th percentile); however, for reasons not fully understood, this group of children experienced less morbidity when their weights were very low.

The use of the Brooks 2011 growth charts[24] remains controversial because they have not been clinically validated and they indicate the growth of a large cohort of children with CP but do not tell us how the children *should* grow.[5] While it is appropriate for children with weight measurements plotting in the zone of concern on the CP growth charts to be referred for further nutrition assessment, plotting above this level does not mean the child's nutrition has been optimized, it simply reflects how they plot compared to other children similarly affected. Despite their limitations, these growth charts are valuable tools for discussions with caregivers regarding nutrition rehabilitation and the possible need for a significant change in their child's nutrition care plan, such as adding EN support.

Interpretation of Nutrition and Growth

When using the CP charts, weights above the 20th percentile may be reassuring, but the individual plots should be used in conjunction with a child's other anthropometric measurements, especially the TSF. When using the WHO and CDC charts for children with NI, practitioners assessing growth trends should consider using z-scores instead of percentile measurements because children with severe NI may plot far from the curves

compared to children with typical growth patterns and thus, changes in weight gain or growth can be seen more clearly. Z-scores are also more precise because they are expressed in actual numbers. Z-scores for weight- and length-/height-for-age that are more than 2 SD from the mean indicate growth patterns requiring close monitoring and investigation. In children with NI, weight-for-age z-scores may be of more significance than their height-for-age z-scores, as the underlying conditions may impact their height measurements.[25]

Growth patterns are concerning when sharp inclines or declines in weight or growth occur, when there is a plateau in weight or height percentiles, or the z-scores exhibit a downward trend from a previously established trajectory. Investigation of changes in weight and height should occur before a child has crossed 2 percentiles on a growth curve. Serial measurements are required to determine whether the growth pattern is truly abnormal, if it represents constitutional short stature, or if there is a re-channeling of the genetic growth potential in children with NI.

Clinical judgment should be used when interpreting BMI for establishing weight status in children with NI because BMI measurements are problematic, as previously discussed. Alterations in body composition, decreased muscle mass, body fat distribution, and skeletal deformities that impact height measurements all affect the BMI and make interpretation challenging. BMI is one piece of information for determining what nutrition intervention is needed, but like any other single anthropometric measure, it cannot be the sole determinant of nutrition status.

Nutrition Assessment

Nutrition assessment is the systematic process of gathering and interpreting information related to a child's condition and nutrition status so that a detailed nutrition care plan can be developed.[83] For children with NI, this includes the following information:

- Comprehensive medical history from the medical chart (if available) and interview
  - Medical/surgical history

  - Information from other health professionals/teams involved in their care
  - Biochemical data
  - Medications
  - Meticulous nutrition history
  - Social and environmental history[84]
- Accurate anthropometric measurements
- Assessment of weight gain and growth patterns by comparing parameters to standard references
- Nutrition-focused physical examination (NFPE)
- Subjective Global Nutrition Assessment (SGNA), if indicated
- Selected diagnostic studies

Medical History

When developing a nutrition care plan, it is important to understand the specific type of NI including its manifestations, severity, and prognosis, as well as co-occurring conditions, because all these factors impact nutrition risk and potential nutrition interventions.[22]

Medications

Various medications may influence children's eating patterns and nutrition requirements. In turn, some medications may enhance the child's ability to take in nutrients. If children have food refusal, this can be related to gastrointestinal (GI) discomfort from constipation or GER. Proton-pump inhibitors are widely used in children with GER disease (GERD) but they do not impact the frequency of the reflux events, they only modify potential discomfort from stomach acid.[5] Thickening of the liquids offered orally or via enteral tubes can also ameliorate some GER symptoms, as do blenderized diets for children who are enterally fed (see "Blenderized Tube Feeding" section). Prokinetics are not routinely used in children with NI because of weak efficacy and high side-effect profile.[5] Constipation is often a significant issue for children with NI and frequently requires the regular use of osmotic laxatives.[5] Oil-based laxatives should be avoided in children with NI who are at increased risk of aspiration as oil aspiration results in lipoid pneumonia.[5]

Many anticonvulsants can affect appetite both positively and negatively and can also affect alertness level, which may in turn impact oral-motor skills. Some anticonvulsants can affect vitamin D metabolism, further increasing the risk for low BMD.[85]

Glycopyrrolate and other anticholinergic medications are commonly used to decrease oral secretions in children with sialorrhea. However, these medications have side effects and may dry the secretions so much that the child is unable to swallow them. Because the anticholinergics have systemic effects, they can also worsen constipation, cause urinary retention, and impact the central nervous system.[86]

Review of Systems

Reviewing all the body's systems helps identify potential problems contributing to eating and drinking difficulties and overall nutrition status. For children with NI, it is important to ask questions about every system in the body to potentially reveal other factors that could impact nutrition. While some conditions like alertness and seizures may be more difficult to manage, others like dental/oral health are remedial and can significantly impact a child's food intake, as well as their respiratory health and overall well-being.[87] Dental disease is increased in children with NI because of oral care difficulties, swallowing dysfunction, sialorrhea, malnutrition (especially related to calcium and vitamin D status), and GERD, which increases the risk of dental erosions.[88]

The cardiovascular system plays a special role in children with muscular dystrophies that impact cardiac function and thereby affect endurance and energy requirements. Food allergies are a unique consideration in children with spina bifida who are at high risk of latex allergy. Proteins that are present in latex cross-react with a wide variety of fruits, necessitating close review of food allergies including, but not limited to, avocado, banana, bell pepper, chestnut, fig, kiwi, peach, and tomato.[89,90]

Respiratory problems are the most common cause of morbidity and mortality in children with NI because of the increased aspiration risk and aspiration pneumonia. Weakness, poor cough, and skeletal deformities all contribute to chronic lung disease, which may impact swallowing safety. [91]

Careful questioning about risk factors for aspiration and feeding skills is an important part of a complete review of systems for children with NI. Impairment of oral-motor function limits bolus control and accentuates food loss from the mouth. Sensory factors such as oral hyposensitivity can affect bolus control, mouth packing, and poor timing of breaths and swallows.[22] Ineffective swallow trigger and incomplete clearing of the pharynx after swallowing increases the risk of aspiration. Effective cough recruitment may assist in mitigating some risks of aspiration. (See "Nutrition History" and "Feeding Observation" sections later in the chapter).

Gastrointestinal issues from visceral pain, GERD, and constipation all impact children's well-being and their food intake. Genitourinary issues such as difficulty voiding or urinary retention can impact comfort and cause frequent infections, which impact growth and nutrition.[92]

Contractures, scoliosis, and joint dislocations can all influence a child's eating and drinking skills, not only because of pain, but positioning may be difficult because of the orthopedic challenges they experience. Poor feeding positioning may impact airway closure (aspiration risk), lip closure (food loss and difficulty triggering a swallow), and poor breath−swallow control.[39] Questions regarding bone health are also important when considering the musculoskeletal system as described previously (low-impact fractures, cervical fractures).[85]

Growth History

Previous measures of weight and stature are important for monitoring growth in children with NI. These measurements can be plotted on the WHO[79] or CDC[80] growth charts. While it may be enticing to use CP growth charts[24] for serial measurements, they are better when used episodically to compare to other children similarly affected or to check if the child plots within the zone of concern. CP growth charts do not indicate how children with CP should grow, rather they provide insight into how they grow and gain weight in comparison to similarly affected children.[5] (See "Growth and Anthropometric Measurements" section earlier in the chapter)

Nutrition History

There are several methods for obtaining a diet history. These include a 24-hour recall of food intake or an actual 3-day diet diary, both of which may reflect the adequacy of dietary energy and nutrient intake.[33] Both are associated with challenges. The former may not adequately reflect that usual intake can be skewed because the child may be given less food or consumes less food, or have food loss due to spillage, than was recorded in the food recall.[93] On the other hand, a 3-day diet diary may be subject to reporting fatigue and requires literacy.[94]

Environmental and Social History

Caring for children with NI is time-consuming and impacts their family in many ways including work, travel, and leisure activities. When planning nutrition interventions, it is important to engage all key stakeholders in a shared decision-making process[95] with the child, their caregivers, and their health professionals to ensure that the nutrition plans are compatible with family practices and beliefs. Additional considerations include financial and insurance issues along with the types of home healthcare services available.[39] Nutrition interventions should be thoughtfully integrated into the routine of the family.[22,96]

Psychosocial and Environmental Factors

Feeding and nutrition concerns related to mealtime behavior, mood and anxiety, as well as the child's degree of NI increases caregiver stress. Despite challenges at mealtime, many families of children with NI are very resilient and develop coping strategies for managing chronic feeding problems.[97] Health professionals assessing children with eating and drinking difficulties should be aware of parental stresses and address how to best support the families and help them address remedial mealtime challenges.

Feeding Observation

A mealtime or feeding observation can provide an opportunity to observe the child and caregiver while they are engaged in the activity of eating/feeding. Observation of a child's distress with feeding, positioning,

oral-motor skills, dental health, cranial nerve function, and facial structures can all be integrated into a feeding observation. The mealtime observation provides the opportunity to see how a child accepts, manipulates, and swallows foods of different viscosities, consistencies, and textures while observing elements of their oral skills including lip, tongue, cheek, and mastication control, as well as the augmentative measures needed to facilitate these motor actions. In addition, the coordination of respiration with the bolus collection and transport provides further insight into a child's feeding skills and swallowing safety. A feeding observation also provides insight into the caregiver's response to the child's feeding pattern.

Frequent coughing, wet vocal quality, or evidence of declining respiratory status at mealtimes are important indicators of aspiration risk in children. Mealtime observation should focus on feeding and swallowing safety by mitigating risks brought on by challenges in all aspects of oral intake. Understanding how children consume nutrients is the key to assessing their impediments to adequate oral nutrition.[35,39,98]

Complementary and Alternative Medicine

Complementary and alternative medicine (CAM) represents a wide range of interventions in addition to, or instead of, conventional medical treatment. CAM use is higher in children with chronic conditions such as CP.[99] Many parents do not inform healthcare professionals that they are using CAM for their children. An American Academy of Pediatrics (AAP) task force reviewed different therapy modalities and developed resources for families and practitioners,[100] as well as a set of recommendations to assist physicians in counseling families about CAM.[101] Families who are optimally informed can better contribute to a shared decision-making process (see Appendix 16-1) that best meets the needs and goals of their child.

Red Flags for Undernutrition

Clear guidelines for diagnosing undernutrition in children with NI are lacking. Hence, a combination of historical, clinical, and nutrition indicators from the nutrition assessment must be used to guide nutrition support teams in understanding undernutrition. Some of the "red flags" that present

concern about undernutrition in children with NI are outlined in Table 16-3.[5,9,25] Nutrition-focused physical examination (NFPE) and the Subjective Global Nutrition Assessment (SGNA) can provide more objective information regarding nutrition status.

TABLE 16-3. Red Flags for Undernutrition in Children With NI

Historical Considerations	Nutrition Indicators	Clinical Signs
• Children with severe functional limitations and feeding difficulties • Stressful and prolonged (>30 min) mealtimes	• Weight-for-age z score more than 2 SD below the mean • TSF: <10th percentile for age • Weight loss in between visits	• Decubitus skin ulcers • Clinical signs of aspiration

Abbreviations: NI, neurological impairment; TSF, triceps skinfold. Reproduced with permission from the American Society for Parenteral and Enteral Nutrition from Rempel G. Neurological impairment and developmental disabilities. In: Larson-Nath C, ed. *ASPEN Pediatric and Neonatal Nutrition Support Handbook*. 3rd ed. American Society for Parenteral and Enteral Nutrition; 2024:311.

Nutrition-Focused Physical Examination

The NFPE is an important part of the overall nutrition assessment of children with NI. It is the method used by nutrition professionals to detect the presence of malnutrition in children and the factors contributing to a child's nutrition status. Inspection and palpation techniques are used to identify both macronutrient and micronutrient deficiency and can provide additional clues to determine energy needs,[102] such as muscle tone, activity level, and the presence or absence of dyskinesias. Other factors such as head control, truncal tone, contractures, and scoliosis impact positioning during meals, which affects food intake. Examination of the skin, hair, mouth, and nails provides evidence of micronutrient deficiencies.

Subjective Global Nutrition Assessment

The SGNA can also guide nutrition professionals by providing a validated framework for nutrition assessment of children with NI.[103,104] Use of the SGNA has identified more children with NI who are malnourished than anthropometric data alone.[105]

Diagnostic Studies

NFPE and the SGNA clinical findings help guide laboratory evaluation of macronutrients and micronutrients. While there is some debate about whether children on stable EN require regular laboratory evaluation, Romano et al suggest that children with NI should have their blood counts, iron, zinc, and bone health status (vitamin D, calcium, and phosphate) assessed.[5] Because of the potential of limited dietary repertoire in children with NI, they suggest further evaluation of micronutrients including copper, carnitine, folic acid, and vitamin B_{12}.[58,59,106] In the absence of clear guidelines regarding the frequency of diagnostic studies, nutrition professionals will need to use their clinical judgment but an annual review is prudent.

No single laboratory indicator can be used to determine nutrition status. Prealbumin and albumin were traditionally used as nutrition markers, however, they are actually better inflammation markers.[107] Other diagnostic tests may enhance the understanding of a child's nutrition-related and feeding-related issues and help address their symptoms as well as evaluate the need for nutrition support. The following are tests often conducted in children with eating and drinking difficulties:

- Instrumental swallowing assessments such as a videofluoroscopic swallowing study (VFSS) or a fiberoptic endoscopic evaluation (FEES) of swallowing are extensions of the clinical information obtained in the feeding observation and are the only way to definitively diagnose swallowing dysfunction and aspiration.
  - *Videofluoroscopic swallowing study (VFSS)*: Also known as a "modified barium swallow" can assess all phases of swallowing and assist in the decisions about making the oral feeding experience safer. Food and liquids of different skill-level-appropriate consistencies,

viscosities, and textures are mixed with contrast and offered to the child while sitting in a chair that supports them well.[108] The VFSS is not the same as an upper GI series, which is also sometimes called a "barium swallow." While the VFSS focuses on the path of a food bolus from the mouth, through the pharynx and esophagus, an upper GI series looks more broadly at the upper GI tract anatomy.

  - *Fiberoptic endoscopic evaluation of swallowing (FEES):* An evaluation using a laryngoscope placed above the patient's larynx while swallowing different foodstuffs and liquids, including saliva. While the FEES can determine aspiration by direct visualization, part of the swallowing process cannot be seen as the food/liquid bolus envelopes the scope and blanks out the screen. When the bolus has cleared, the presence of food or liquid can be detected in the airway.[109]

- Salivagram (scintigraphy) is a nuclear medicine test showing the transit of saliva from the mouth to the stomach or, if not swallowed correctly, into the lungs. A small amount of tracer is placed on the child's tongue and the progress of the tracer is followed to see if any enters the lung.[110] Scintigraphy can also be used to assess for pulmonary aspiration after swallowing by putting a tracer in a child's feeding or assessing for gastric emptying in case of gastroparesis.[5]
- Endoscopy of the aerodigestive tract, the respiratory system, and the GI tract may be required to fully diagnose the complex interplay of conditions involving all three systems (anatomic and physiologic).
- Objective measures for diagnosis of GERD in children with NI such as esophageal pH-multichannel intraluminal impedance monitoring, which can identify both acid and nonacid reflux and/or endoscopy, are encouraged in children with NI. However, given the fragility of this population, investigations are sometimes deferred in favor of a trial of proton pump inhibitors (PPIs) with careful follow-up.[5,111]
- An upper GI series is an x-ray contrast study that does not quantitate reflux but can provide valuable information about the anatomy of the upper GI tract, gastroparesis, outflow obstruction of the stomach as seen in superior mesenteric artery (SMA) syndrome, or malrotation of the intestine. Children with NI are vulnerable to SMA syndrome because they often have scoliosis and undernutrition can result in the depletion of

retroperitoneal fat, which can trigger the symptoms.[5] An upper GI series may also be required before the placement of an enteral access device because of ongoing emesis/regurgitation[112] or in some cases if there is concern that the child may have unusual anatomy given their skeletal deformity.

Nutrition Support

Estimating Nutrition Requirements

For information regarding estimating nutrition requirements, see the "Energy Expenditure" and "Micronutrient Requirements" sections earlier in the chapter.

Modes of Nutrition Support

Oral feeding is the preferred method for children with NI along with appropriate supports and modifications to improve the safety and feeding experience and to enhance nutrition, hydration, and medication administration. However, some children may require EN support when they cannot meet their energy, fluid, or nutrient needs orally, their mealtimes are prolonged and stressful, or the risk of aspiration cannot be managed.[112,113]

For children who are orally fed, many options exist for increasing their calorie intake and the nutrition profile of the foods they eat. Modular commercial products are available to increase carbohydrate, protein, and fat in foods, as well as nutritionally balanced commercial products that are usually cow's milk–based or plant-based. Readily available food items such as vegetable oils, butter, margarine, dry milk powder, cream, cheese, and other high-fat dairy products and gravy can also be added to foods to increase caloric density and improve the nutritional profile.

An evaluation by a registered dietitian (RD) is essential for developing an appropriate plan and monitoring the child's weight gain and growth. Small children should be monitored several times per year while older children on established enteral ± oral regimes can be followed annually. The frequency of nutrition reassessment also depends on the child's health and underlying condition. All children should be evaluated during and after illness and when feeding issues arise.

Interventions to Promote Safe Oral Feeding

Proper positioning is essential for oral feeding safety. This requires the use of positioning and support devices. A physical and/or occupational therapist can help with positioning equipment such as a feeding chair, standing table, or (with proper alignment) a wheelchair to promote safe feeding. Adapted utensils, such as spoons, cups, scoop plates, and assistive self-feeding devices can enhance feeding success. The feeding, speech, or occupational therapist working with a child and family can assist with utensils, as well as augmentative techniques to enhance lip closure and promote bolus control/manipulation. Appropriate food consistency, texture, and viscosity to match the child's oral skills is essential. Correct food presentation and meal pacing are important skills for anyone participating in the child's mealtime routine. Feeding safety across all environments—including all the elements that create a safe mealtime plan—should be ensured with appropriate caregiver training and support.[39]

Dedicated behavioral therapy for the child and their family may be required, especially if the child has negative responses to oral intake that can be mitigated by intervention.[114] Behavioral intervention addresses the child's emotional/behavioral function, mealtime aggression, mood, and parenting stress. Intervention can positively impact mealtime duration, food consumption in terms of quantity and texture, and most importantly, the interactions between the parent and the child during a meal.[114,115]

For children with NI, the feeding team must reevaluate the child's oral feeding skills and nutrition status as part of routine monitoring to determine if oral feeding remains the best modality for achieving the child's nutrition goals. Feeding team members should remember that feeding skills can change over time for children with NI. For example, oral intake improves once seizures are better controlled, or the child has recovered from a respiratory illness. On the other hand, feeding skills can deteriorate over time due to illness or the child's underlying condition that is causing the NI.

Enteral Nutrition Support

EN support via an enteral access device should be considered for children with NI if they cannot take in enough orally for adequate weight gain, linear growth, and hydration.[3] Additional indications for enteral feeds include

inability to manage a child's aspiration risk and prolonged/stressful mealtimes caused by oral-motor and swallowing dysfunction or behavioral concerns.[3,5,9,27]

Enteral feeding should only be pursued after performing an appropriate workup to investigate the child's underlying medical and nutrition diagnosis.[113] Nutrition support professionals should seek active engagement of the parents in the development and implementation of the feeding care plan, especially when switching feeding modalities (oral to enteral nutrition support) to ensure the parent's wishes and goals are met.

Factors to consider in determining the type of enteral access to recommend include the current nutrition and clinical status of the child, how long EN support is likely to be required, and the type of feeding regimen that may best fit the needs of the child and family.

Enteral Access

Nasogastric (NG) or nasojejunal (NJ) nutrition support is used for "short-term" nutrition support although the duration of use is highly variable among different centers.[118] Long-term use of NG or NJ tubes is not usually recommended due to discomfort and risk of dislodgement during feeding, which can lead to aspiration. The most significant complication during NG use is tube misplacement on insertion. Care must be taken to ensure that NG tube verification practices are evidence-based to minimize the risk of this complication. NG safety techniques include accurate tube length measurement (nose-ear-midpoint of xiphoid-umbilicus for children), careful insertion and verification of the tube location by testing the pH of the gastric effluent, and/or performing a chest radiograph to confirm that the end of the tube lies in the stomach. Local complications, such as skin and mucosal irritation, nasal congestion, and sinusitis have been described with NG use.[116,117]

Berman et al[112] are strong proponents of "extended" use of NG tubes to ensure that the child truly requires a "long-term" enteral feeding option. Trialing NG feeding even in children who may require long-term enteral support may be of value in children with severe NI because they will probably be better nourished after a period of NG feeding when they are ready for gastrostomy tube (GT) placement. However, home NG feeding is

more complicated in older children because they are more resistant than infants to safe NG placement.

A GT is generally preferable for children with NI who need long-term nutrition support, although the cost is significantly higher than via NG and complication/rehospitalization rates are also increased compared to NG feeding. GT placement complications include

- skin irritation,
- granulation tissue formation,
- leakage, premature tube dislodgement before stoma maturity, and
- cellulitis.[113,116]

Several options are available for GT placement, including surgical or laparoscopic, percutaneous endoscopic, or via enteral access device by interventional radiology professionals. At present, a laparoscopic approach using a low-profile enteral access device with a balloon retention system is favored.[113,116] GT placement procedures are for the most part minimally invasive, with little post-procedure pain, and the GT can be used for feeding within a few hours of placement.[119] Children who receive nutrition support via GT early in the course of their neurological illness have better growth and nutrition outcomes. Children who receive late GT feeding may gain weight, but linear growth deficits often persist.[120,121]

Jejunal feeding is becoming the standard of care for children with poor tolerance of intragastric feeds, gastroparesis, or severe GER, as well as unmanageable feeding-related aspiration.[122] It can be done via nasojejunal or gastrojejunal tube (placed through an existing, mature gastrostoma), or surgical placement. However, aspiration risk is not eliminated with jejunal feeding, as children with NI can still aspirate saliva and gastric contents. Thus, aspiration events and reflux-related hospitalizations may not be decreased with jejunal feeding.[123]

Jejunal feeding has some drawbacks including the need for slow pump feeding (as the jejunum is not a “reservoir” like the stomach) and tube re-insertion in a hospital interventional radiology setting when dislodgement and plugging occur. The complication rate of jejunal feeding is increased in preterm infants and thus is generally discouraged.[124] Other complications of jejunal feeding include intestinal obstruction, jejunal perforation,

intussusception, and volvulus. Electrolyte disturbances, dumping syndrome, as well as vitamin and trace element deficiency can also occur with jejunal feeding. The bioavailability of medications given via jejunal tubes is unpredictable and should be avoided whenever possible.[122]

In the past, GER in children with NI was frequently managed with concurrent laparoscopic or open surgical fundoplication when a GT was placed, however, this practice is now discouraged.[125,126] With the advent of PPIs in the 1990s and the widespread use of post-pyloric feeding, fundoplication use has decreased and is generally reserved for children who have exhausted all avenues for improving their aspiration risk or feeding intolerance.[5,127] Clear guidelines for fundoplication use have not been established and there is great variability in its pediatric application.

Complications include post-fundoplication feeding difficulty, gas bloat, or dumping syndrome, sometimes with significant hypoglycemia. This requires monitoring once bolus feeding is initiated after fundoplication.[128] Retching is a frequent, distressing symptom after fundoplication that can be difficult to manage.[129] Sometimes it can be controlled by the rate of formula administration, or the use of a blenderized tube feeding can ameliorate the symptoms, but occasionally the retching is intractable.[129] The incidence of these complications and the recurrence of acid reflux/surgical failure following fundoplication vary in children with NI and are relatively poorly characterized. They are, however, important considerations when fundoplications are being entertained.[125,130]

Enteral Feeding Regimens

There are several ways to administer EN to a child with NI. Feeding can be given by "bolus" method using a syringe, by gravity bag, or by extending the feeding times using a volumetric pump. Bolus feedings mimic the physiological response to food intake and are more convenient and flexible. Children with GER or delayed gastric emptying may not tolerate bolus feeds and may require slower gravity feeding or pump feeding. For children receiving jejunal feeds, continuous formula infusions are needed, although feeding rates can be adjusted (if tolerated) so that the feeds do not run over 24 hours.[122]

The duration of the continuous feeding depends on the infusion volume and what delivery rate is tolerated. While widely practiced, nighttime feeds can interfere with sleep (both the child and the parent), cause changes in the circadian rhythm, and increase the child's risk of entanglement and aspiration should they experience reflux and not be able to reposition themselves or call for help.[131,132]

Formula Selection

When choosing a formula for EN support, consider the child's age, co-occurring medical conditions, estimated calorie/nutrient requirements, and GI tolerance. The initial selection is generally a standard age-appropriate casein-based or whey-based polymeric formula. Children with formula intolerance may require plant-based, extensively hydrolyzed protein or amino acid-based formulas, or blenderized diets. Pay special attention to the macronutrient and micronutrient content of the formula, especially in children with NI with low energy needs who will require fewer calories, but still require the macronutrients and micronutrients of their peers without NI. Supplemental vitamins, minerals, or electrolytes can help avoid or treat deficiencies. When using high-energy formulas (1.2, 1.5, or 2 kcal/ml), hydration status must be carefully monitored to ensure fluid requirements are met. Similarly, protein and micronutrient intake must be monitored to ensure body systems are not stressed from excessive intake. Formulas with added fiber may help with stooling. Formula choices can be compared using ASPEN online resources (see https://www.nutritioncare.org/Guidelines_and_Clinical_Resources/EN_Formula_Guide/EN_Pediatric_Formulas/).[133]

Blenderized Tube Feeding

Blenderized tube feeding (BTF) is merging as a popular alternative to conventional commercial formula for nutrition support. Blenderized diets were used for many years before the development of commercially prepared, sterile, standardized liquid enteral formulas. The 2 most common types of BTF are home-prepared BTF and commercially available BTF. Both types of BTF provide a variety of puréed whole foods from all food groups and are generally well tolerated. Prepared BTF can be relatively low

cost and have the advantage of being customizable to a child's tolerance and nutrient requirements. A growing number of peer-reviewed publications address safe and effective BTF use for medical purposes as well as family preference.[134]

Nutrition support professionals from a variety of disciplines recommend BTF for several medical indications. Using BTFs decreases retching post fundoplication[129] and lessens healthcare use by reducing emergency department visits and hospital admissions for general and respiratory causes for children with NI, even when compared to postpyloric feeding. In addition, BTFs improve gastrointestinal symptom scores for emesis, regurgitation, and stooling.[135,136] Some of the BTF health benefits may be related to viscosity (decreasing full column reflux), a better nutrient profile, as well as decreased inflammation and improved gut microbiome diversity from whole foods.[136,137]

Families are also opting for BTFs because of concerns about the dietary quality of conventional formulas. The use of BTFs provides increased parental and child satisfaction compared to conventional formulas, as families have a fundamental urge to share family mealtime experiences, which is possible with blenderized meals and provides families with a sense of normalcy and empowerment.[136,138]

In the past, many contraindications for BTF were cited; however, these can be overcome with careful considerations, appropriate food safety techniques, and education for families preparing BTFs. Hang time for the prepared BTF must be kept under 2 hours,[134] which is generally not a concern as syringe feeding is the most common administration method. Clogging of the enteral access device with BTF can occur with any device size. While there is no clear evidence regarding the device size that should be used, at least a 14-French enteral access device is suggested.[134,135]

There are no clear guidelines for the use of BTF for jejunal feeding but the use of BTFs needs to be viewed with caution for jejunal administration. This is related to both the restricted hang time given the need for pump feeding into the jejunum and the possibility of intolerance when whole foods are administered directly into the jejunum.[134]

Some of the biggest barriers to using BTF are parental capacity to prepare the feeds and lack of financial resources and infrastructure (ie,

refrigeration, access to clean/hot water and sanitization supplies, blenders, and equipment).[134,136,137] Home-prepared BTF requires a significant time commitment from the parents and the RD assisting the family because of the follow-up needed to ensure the child's nutritional needs are met.[137]

Regardless of the reason for BTF use, the support of an RD with experience in blenderized diets (preferably with access to a nutrition analysis program) is needed to provide diet plans ensuring adequate energy, fluid, and macronutrient and micronutrient intake,[139] as well as to help families overcome some of the BTF barriers mentioned previously.

Feeding Intolerance

Feeding intolerance may present as abdominal distension, discomfort, vomiting or regurgitation, constipation or diarrhea, or delayed gastric emptying. Factors confounding feeding tolerance include progression of the child's neurological condition, co-occurring illness, mechanical obstruction in the GI tract, or changes in the feeding modality and nutrition care plan. Interventions to ameliorate feeding intolerance include the following:

- Altering the feeding schedule (eg, smaller, more frequent boluses or continuous feeds instead of bolus feeds).
- Changing the formula concentration (either increasing the concentration to decrease the volume of feeds or decreasing the concentration if osmolarity is a concern).
- Trying an alternative formula, such as hydrolyzed or amino acid-based formula, thickened feeding, or initiating a blenderized diet.

Post-pyloric feeding can also be considered if there is ongoing emesis. If symptoms persist, it is important to contemplate the possible underlying conditions. Constipation must always be considered when there is feeding intolerance. Dietary changes to improve stooling and the use of stool-softening agents and osmotic laxatives are often necessary. Rectal inertia may require local treatment with suppositories or enemas. In children with severe constipation, antegrade enemas through a surgically created antegrade colonic enema stoma or cecostomy can also be considered.[5]

Ethical Considerations

Discussing the need for a GT is often very difficult for families. Sometimes, parents of children requiring EN feel a sense of inadequacy and loss when healthcare providers raise the issue of nutrition support via an enteral access device.[16] Health professionals and families should engage in a process of shared decision-making by involving all key stakeholders, gathering information about the family's values and goals regarding nutrition and feeding, and deciding together on a safe nutrition care plan. Despite the initial uncertainty that many parents face when considering a GT, they typically experience a high satisfaction rate and improvement in quality of life after their children have a GT. [140,141] Conversations with the family should include discussions of nutrition, quality of life, and meaningful family relationships, and parenteral wishes should always be considered when making medical recommendations.

Summary and Conclusion

Optimization of nutrition status in children with severe NI is critical to their health, well-being, and survival. A thorough multidisciplinary evaluation is central to nutrition assessment for children with NI and should include medical and feeding history, consideration of psychosocial factors, accurate growth and anthropometric measurements, nutrition-focused physical examination, and selected diagnostic studies. In addition, the evaluation should include a feeding observation aimed at improving oral intake and assessing aspiration risk. An individualized nutrition care plan can be created with the information gleaned from the assessment and evaluation. This plan is determined through input from the family and all members of the team through a shared decision-making process. It should aim to achieve the child's growth potential and maintain adequate nutrition status using multimodal feeding techniques (oral and enteral) if needed.

Oral nutrition should be maintained in children with adequate oral-motor skills and whose aspiration risk can be mitigated by appropriate positioning, augmentative techniques to facilitate lip close and jaw stability, appropriate utensils and food consistency, and texture and viscosity appropriate to the

child's needs. Caregiver training is critical across all settings to ensure consistency of oral feeding techniques.

EN support may need to be considered when oral intake is inadequate to meet nutritional needs, mealtimes are prolonged or stressful, or aspiration risk cannot be managed. The decision to embark on EN support requires assessment and monitoring. When feeding a child with NI enterally, nutrient requirements, formula type, administration method, feeding/GI tolerance, and psychosocial and ethical issues should all be considered. Discussing EN support can be difficult at times and must be approached with understanding and compassion using a shared decision-making model. Parents may resist starting enteral feeds for a variety of reasons, including lack of control, feelings of failure, or cultural reasons.

Continued evaluation of growth and intake is imperative for the health and well-being of children with NI. The frequency of visits depends on the age of the child and their level of health. Young children should be seen at least 3 to 4 times per year. Older, stable children can be seen 1 to 2 times per year. Laboratory monitoring of micronutrients and nutrition indicators is suggested annually. All children should also be evaluated at times of illness and when feeding issues arise. When possible, a multidisciplinary team (including physicians, nurses, RDs, psychologists, speech therapists, physical therapists, and occupational therapists), together with the parents, should participate in individualized nutrition assessments and nutrition care plans to successfully support children with NI.

Test Your Knowledge Questions

1. Which anthropometric measurements are most useful to determine the nutrition status of children with NI?
   A. Height and length
   B. Weight, head circumference, and arm circumference
   C. Head circumference, body mass index, and skinfold thickness
   D. Triceps skinfold, mid-upper arm circumference, weight, and height
2. What are the most common reasons for poor weight gain in children with NI?
   A. Inadequate dietary intake and constipation

B. Increased basal metabolic rate
C. Eating/drinking difficulties and inadequate dietary intake
D. Athetoid or repetitive motor movements and aspiration

3. What is the best way to determine the adequacy of diet for children with NI?
   A. Calculate energy needs based on the WHO equation for estimating needs
   B. Monitor the rate of weight gain or loss and follow the triceps skinfold
   C. Measure hemoglobin concentration and serum albumin levels
   D. Provide a protein hydrolysate or amino acid formula as the main source of nutrients

References

1. Allen J, Brenner M, Hauer J, Molloy E, McDonald D. Severe neurological impairment: a delphi consensus-based definition. *Eur J Paediatr Neurol*. 2020;29:81–86. https://doi.org/10.1016/j.ejpn.2020.09.001
2. Karagiozoglou-Lampoudi T, Daskalou E, Vargiami E, Zafeiriou D. Identification of feeding risk factors for impaired nutrition status in paediatric patients with cerebral palsy. *Acta Paediatr*. 2012;101(6):649–654. https://doi.org/10.1111/j.1651-2227.2012.02641.x
3. Stevenson RD, Conaway M, Chumlea WC, et al; of the North American Growth in Cerebral Palsy Study. Growth and health in children with moderate-to-severe cerebral palsy. *Pediatrics*. 2006;118:1010–1018. https://doi.org/10.1542/peds.2006-0298
4. Rosenbaum P, Rosenbloom L. *Cerebral Palsy From Diagnosis to Adult Life*. MacKeith Press; 2012.
5. Romano C, van Wynckel M, Hulst J, et al. European Society for Paediatric Gastroenterology, Hepatology and Nutrition guidelines for the evaluation and treatment of gastrointestinal and nutritional complications in children with neurological impairment. *J Pediatr*

Gastroenterol Nutr. 2017;65:242–264. https://doi.org/10.1097/mpg.0000000000001646
6. Sullivan PB. Nutrition and growth in children with cerebral palsy: setting the scene. *Eur J Clin Nutr*. 2013;67(suppl 2):S3–S4. https://doi.org/10.1038/ejcn.2013.222
7. Samson-Fang L, Fung E, Stallings VA, et al. Relationship of nutritional status to health and societal participation in children with cerebral palsy. *J Pediatr*. 2002;141:637–643. https://doi.org/10.1067/mpd.2002.129888
8. Kim HJ, Kang TU, Park KY, Kim J, Ahn HS, Yim SY. Which growth parameters can affect mortality in cerebral palsy? *PLoS One*. 2019;14:e0218320. https://doi.org/10.1371/journal.pone.0218320
9. Rempel G. The importance of good nutrition in children with cerebral palsy. *Phys Med Rehabil Clin N Am.* 2015;26:39–56. https://doi.org/10.1016/j.pmr.2014.09.001
10. Marpole R, Langdon K, Wilson A. Gastrostomy feeding in children with severe cerebral palsy in Western Australia. Acta *Paediatr*. 2022;111:680–681. https://doi.org/10.1111/apa.16214
11. Di Leo G, Pascolo P, Hamadeh K, et al. Gastrostomy placement and management in children: a single-center experience. *Nutrients*. 2019;11:1555. https://doi.org/10.3390/nu11071555
12. Ferluga ED, Sathe NA, Krishnaswami S, Mcpheeters ML. Surgical intervention for feeding and nutrition difficulties in cerebral palsy: a systematic review. *Dev Med Child Neurol*. 2014;56:31–43. https://doi.org/10.1111/dmcn.12170
13. Lin JL, Rigdon J, Van Haren K, Buu M, et al. Gastrostomy tubes placed in children with neurologic impairment: associated morbidity and mortality. *J Child Neurol*. 2021;36:727–734. https://doi.org/10.1177/08830738211000179
14. Strauss D, Brooks J, Rosenbloom L, Shavelle R. Life expectancy in cerebral palsy: an update. *Dev Med Child Neurol*. 2008;50:487–493. https://doi.org/10.1111/j.1469-8749.2008.03000.x
15. Brooks JC, Strauss DJ, Shavelle RM, et al. Recent trends in cerebral palsy survival. Part II: individual survival prognosis. *Dev Med Child Neurol*. 2014;56:1065–1071. https://doi.org/10.1111/dmcn.12519

16. Mahant S, Friedman JN, Connolly B, Goia C, Macarthur C. Tube feeding and quality of life in children with severe neurological impairment. *Arch Dis Child*. 2009;94:668–673. https://doi.org/10.1136/adc.2008.149542
17. Samson-Fang L, Bell KL. Assessment of growth and nutrition in children with cerebral palsy. *Eur J Clin Nutr*. 2013;67(suppl 2):S5–S8. https://doi.org/10.1038/ejcn.2013.223
18. Oftedal S, Davies PS, Boyd RN, et al. Body composition, diet, and physical activity: a longitudinal cohort study in preschoolers with cerebral palsy. *Am J Clin Nutr.* 2017;105:369–378. https://doi.org/10.3945/ajcn.116.137810
19. Leonard H, Ravikumara M, Baikie G, et al; Telethon Institute for Child Health Research. Assessment and management of nutrition and growth in Rett syndrome. *J Pediatr Gastroenterol Nutr.* 2013;57:451–460. https://doi.org/10.1097/mpg.0b013e31829e0b65
20. Stevenson RD, Hayes RP, Carter LV, Blackman JA. Clinical correlates of linear growth in children with cerebral palsy. *Dev Med Child Neurol*. 1994;3:135–142. https://doi.org/10.1111/j.1469-8749.1994.tb11822.x
21. Nelson MD, Widman LM, Abresch RT, et al. Metabolic syndrome in adolescents with spinal cord dysfunction. *J Spinal Cord Med*. 2007;30(suppl 1):S127–S139. https://doi.org/10.1080/10790268.2007.11754591
22. Goday P, Huh S, Silverman A, et al. Pediatric feeding disorder-consensus definition and conceptual framework. *JPGN.* 2019;68:124–129. https://doi.org/10.1097/mpg.0000000000002188
23. Day SM, Strauss DJ, Vachon PJ, Rosenbloom L, Shavelle RM, Wu YW. Growth patterns in a population of children and adolescents with cerebral palsy. *Dev Med Child Neurol*. 2007;49:167–171. https://doi.org/10.1111/j.1469-8749.2007.00167.x
24. Brooks J, Day S, Shavelle R, Strauss D. Low weight, morbidity, and mortality in children with cerebral palsy: new clinical growth charts. *Pediatrics*. 2011;128:e299–e307. https://doi.org/10.1542/peds.2010-2801
25. Huysentruyt K, Geeraert F, Allemon H, et al. Nutritional red flags in children with cerebral palsy. *Clin Nutr*. 2020;39:548–553.

https://doi/10.1016/j.clnu.2019.02.040
26. Ruiz-Brunner M, Cuestas E, Heinen F, Schroeder AS. Growth in infants, children and adolescents with unilateral and bilateral cerebral palsy. *Sci Rep.* 2022;12:1879. https://doi.org/10.1038/s41598-022-05267-y
27. Kuperminc MN, Stevenson RD. Growth and nutrition disorders in children with cerebral palsy. *Dev Disabil Res Rev*. 2008;14:137–146. https://doi.org/10.1002/ddrr.14
28. Calis EA, Veugelers R, Rieken R, Tibboel D, Evenhuis HM, Penning C. Energy intake does not correlate with nutritional state in children with severe generalized cerebral palsy and intellectual disability. *Clin Nutr.* 2010;29(5):617–621. https://doi.org/10.1016/j.clnu.2010.02.006
29. Walker JL, Bell KL, Boyd RN, Davies PS. Energy requirements in preschool-age children with cerebral palsy. *Am J Clin Nutr*. 2012;96:1309–1315. https://doi.org/10.3945/ajcn.112.043430
30. Tinkov AA, Skalnaya MG, Skalny AV. Serum trace element and amino acid profile in children with cerebral palsy. *J Trace Elem Med Biol*. 2021 Mar;64:126685. https://doi.org/10.1016/j.jtemb.2020.126685
31. Penagini F, Mameli C, Fabiano V, Brunetti D, Dilillo D, Zuccotti GV. Dietary intakes and nutritional issues in neurologically impaired children. *Nutrients*. 2015;7:9400–9415. https://doi.org/10.3390/nu7115469
32. Sullivan PB, Lambert B, Rose M, Ford-Adams M, Johnson A, Griffiths P. Prevalence and severity of feeding and nutritional problems in children with neurological impairment: Oxford Feeding Study. *Dev Med Child Neurol*. 2000;42:674–680. https://doi.org/10.1017/s0012162200001249
33. Sullivan PB, Juszczak E, Lambert BR, Rose M, Ford-Adams ME, Johnson A. Impact of feeding problems on nutritional intake and growth: Oxford Feeding Study II. *Dev Med Child Neurol*. 2002;44:461–467. https://doi.org/10.1017/s0012162201002365
34. Sullivan PB, Alder N, Allison ME, et al. Gastrostomy feedings in cerebral palsy: too much of a good thing? *Dev Med Child Neurol*. 2006;48:877–882. https://doi.org/10.1017/s0012162206001927

35. Arvedson JC. Feeding children with cerebral palsy and swallowing difficulties. *Eur J Clin Nutr*. 2013;67(suppl 2):S9–S12. https://doi.org/10.1038/ejcn.2013.224
36. Fung EB, Samson-Fang L, Stallings VA, et al. Feeding dysfunction is associated with poor growth and health status in children with cerebral palsy. *J Am Diet Assoc*. 2002;102:361–373. https://doi.org/10.1016/s0002-8223(02)90084-2
37. Herrera-Anaya E, Angarita-Fonseca A, Herrera-Galindo VM, Martínez-Marín RD, Rodríguez-Bayona CN. Association between gross motor function and nutritional status in children with cerebral palsy: a cross-sectional study from Colombia. *Dev Med Child Neurol*. 2016;58: 936–41. https://doi.org/10.1111/dmcn.13108
38. Benfer KA, Weir KA, Bell KL, Ware RS, Davies PS, Boyd RN. Oropharyngeal dysphagia and gross motor skills in children with cerebral palsy. *Pediatrics*. 2013;131:e1553–e1562. https://doi.org/10.1542/peds.2012-3093
39. Gellert-Jones ME. Assessment and treatment of feeding in children and youth with cerebral palsy. In: Miller F, Bachrach S, Lennon N, O'Neil M, eds. *Cerebral Palsy*. Springer; 2020:1–26. https://doi.org/10.1007/978-3-319-50592-3_176-1
40. Tanaka N, Nohara K, Ueda A, et al. Effect of aspiration on the lungs in children: a comparison using chest computed tomography findings. *BMC Pediatr*. 2019;19:162. https://doi.org/10.1186/s12887-019-1531-6
41. Benfer KA, Weir KA, Ware RS, et al. Parent-reported indicators for detecting feeding and swallowing difficulties and undernutrition in preschool-aged children with cerebral palsy. *Dev Med Child Neurol*. 2017;59:1181–1187. https://doi.org/10.1111/dmcn.13498
42. van Roon D, Steenbergen B. The use of ergonomic spoons by people with cerebral palsy: effects on food spilling and movement kinematics. *Dev Med Child Neurol*. 2006;48:888–891. https://doi.org/10.1111/j.1469-8749.2006.01940a.x
43. Rieken R, van Goudoever JB, Schierbeek H, et al. Measuring body composition and energy expenditure in children with severe neurologic impairment and intellectual disability. *Am J Clin Nutr*. 2011;943:759–766. https://doi.org/10.3945/ajcn.110.003798

44. Becker PJ, Nieman Carney L, Corkins MR, et al. Consensus statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: Indicators Recommended for the Identification and Documentation of Pediatric Malnutrition (Undernutrition). *J Acad Nutr Diet.* 2014;114(12):1988–2000. https://doi.org/10.1016/j.jand.2014.08.026
45. Walker JL, Bell KL, Stevenson RD, Weir KA, Boyd RN, Davies PS. Relationships between dietary intake and body composition according to gross motor functional ability in preschool-aged children with cerebral palsy. *Ann Nutr Metab*. 2012;61:349–357. https://doi.org/10.1159/000342557
46. Snik DAC, de Roos NM. Criterion validity of assessment methods to estimate body composition in children with cerebral palsy: a systematic review. *Ann Phys Rehabil Med.* 2021;64(3):101271. https://doi.org/10.1016/j.rehab.2019.05.003
47. Penagini F, Borsani B, Bosetti A, et al. Resting energy expenditure in children with cerebral palsy: Accuracy of available prediction formulae and development of a population-specific formula. *Clin Nutr ESPEN*. 2018;25:44–49. https://doi.org/10.1016/j.clnesp.2018.04.006
48. Becker P, Nieman Carney L, Corkins MR, et al. Consensus Statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: Indicators Recommended for the Identification and Documentation of Pediatric Malnutrition (undernutrition). *Nutr Clin Pract*. 2015;30:147–161. https://doi.org/10.1177/0884533614557642
49. Polfuss M, Sawin KJ, Papanek PE, et al. Total energy expenditure and body composition of children with developmental disabilities. *Disabil Health J*. 2018;11:442–446. https://doi.org/10.1016/j.dhjo.2017.12.009
50. Calis EA, Veugelers R, Rieken R, et al. Energy intake does not correlate with nutritional state in children with severe generalized cerebral palsy and intellectual disability. *Clin Nutr*. 2010;29:617–621. https://doi.org/10.1016/j.clnu.2010.02.006
51. Joint WHO/FAO/UNU Expert Consultation. Protein and amino acid requirements in human nutrition. *World Health Organ Tech Per Service*. 2007;935:1–265.

52. Food and Agriculture Organization of the United Nations, United Nations University, World Health Organization. Human energy requirements: Report of a Joint FAO/WHO/UNU Expert Consultation: Rome, 17–24 October 2001. Food and Agricultural Organization of the United Nations; 2004.
53. Schofield EN. Predicting basal metabolic rate, new standards and review of previous work. *Hum Nutr Clin Nutr.* 1985;39(suppl 1):5–41.
54. Andrew M, Parr J Sullivan P. Feeding difficulties in children with cerebral palsy. *Arch Dis Child Edu Pract Ed*. 2012;97:222–229. https://doi.org/10.1136/archdischild-2011-300914
55. Vernon-Roberts A, Wells J, Grant H, et al. Gastrostomy feeding in cerebral palsy: enough and no more. *Dev Med Child Neurol*. 2010;52:1099–1105. https://doi.org/10.1111/j.1469-8749.2010.03789.x
56. Scarpato E, Staiano A, Molteni M, Terrone G, Mazzocchi A, Agostoni C. Nutritional assessment and intervention in children with cerebral palsy: a practical approach. *Int J Food Sci Nutr*. 2017;68(6):763–770. https://doi.org/10.1080/09637486.2017.1289502
57. Piccoli R, Gelio S, Fratucello A, Valletta E. Risk of low micronutrient intake in neurologically disabled children artificially fed. *J Pediatr Gastroenterol Nutr*. 2002;35(4):583–584. https://doi.org/10.1097/00005176-200210000-00025
58. Jones M, Campbell KA, Duggan C, et al. Multiple micronutrient deficiencies in a child fed an elemental formula. *J Pediatr Gastroenterol Nutr*. 2001;33:602–605. https://doi.org/10.1097/00005176-200111000-00016
59. Hals J, Bjerve KS, Nilsen H, Svalastog AG, Ek J. Essential fatty acids in the nutrition of severely neurologically disabled children. *Br J Nutr*. 2000;83:219–225. https://doi.org/10.1017/s0007114500000283
60. Kothari P, Tate A, Adewumi A, Kinlin LM, Ritwik P. The risk for scurvy in children with neurodevelopmental disorders. *Spec Care Dentist*. 2020;40(3):251–259. https://doi.org/10.1111/scd.12459
61. U.S. Department of Agriculture. USDA Dietary Reference Intakes. Accessed March 10, 2024. https://www.nal.usda.gov/human-nutrition-and-food-safety/dietary-guidance

62. Uddenfeldt Wort U, Nordmark E, Wagner P, Düppe H, Westbom L. Fractures in children with cerebral palsy: a total population study. *Dev Med Child Neurol*. 2013;55(9):821–826. https://doi.org/10.1111/dmcn.12178
63. Ozel S, Switzer L, Macintosh A, Fehlings D. Informing evidence-based clinical practice guidelines for children with cerebral palsy at risk of osteoporosis: an update. *Dev Med Child Neurol*. 2016;58(9):918–923. https://doi.org/10.1111/dmcn.13196
64. Martínez de Zabarte Fernández JM, Ros Arnal I, Peña Segura JL, García Romero R, Rodríguez Martínez G. Bone health impairment in patients with cerebral palsy. *Arch Osteoporos*. 2020;15(1):91. https://doi.org/10.1007/s11657-020-00753-0
65. Crabtree NJ, Arabi A, Bachrach LK, et al; International Society for Clinical Densitometry. Dual-energy X-ray absorptiometry interpretation and reporting in children and adolescents: the revised 2013 ISCD Pediatric Official Positions. *J Clin Densitom*. 2014;17(2):225–42. https://doi.org/10.1016/j.jocd.2014.01.003
66. Finbraten AK, Syversen U, Skranes J, Andersen GL, Stevenson RD, Vik T. Bone mineral density and vitamin D status in ambulatory and non-ambulatory children with cerebral palsy *Osteoporos Int.* 2015;26:141–150. https://www.doi.org/10.1007/s00198-014-2840-0
67. Gordon CM, Leonard MB, Zemel BS; International Society for Clinical Densitometry. 2013 Pediatric Position Development Conference: executive summary and reflections. *J Clin Densitom*. 2014;17(2):219–224. https://doi.org/10.1016/j.jocd.2014.01.007
68. Arman S. How safe and effective is the use of bisphosphonates in the treatment of osteoporosis in children with cerebral palsy? A Cochrane Review summary with commentary. *Dev Med Child Neurol*. 2022;64:286–288. https://doi.org/10.1111/dmcn.15148
69. Whitney DG. 5-year fracture risk among children with cerebral palsy. *Pediatr Res.* 2023;93(4):996–1002. https://doi.org/10.1038/s41390-022-02207-4
70. Hurley T, Zareen Z, Stewart P, McDonnell C, McDonald D, Molloy E. Bisphosphonate use in children with cerebral palsy. *Cochrane Database Syst Rev*. 2021;7:CD012756. https://doi.org/10.1002/14651858.CD012756.pub2

71. Simm PJ, Biggin A, Zacharin MR; APEG Bone Mineral Working Group. Consensus guidelines on the use of bisphosphonate therapy in children and adolescents. *J Paediatr Child Health*. 2018;54:223–233. https://doi.org/10.1111/jpc.13768
72. Stevenson RD. Use of segmental measures to estimate stature in children with cerebral palsy. *Arch Pediatr Adolesc Med*. 1995;149(6):658–662. https://doi.org/10.1001/archpedi.1995.02170190068012
73. Forman M, Zhu Y, Hernandez L, et al. Arm span and ulnar length are reliable and accurate estimates of recumbent length and height in a multiethnic population of infants and children under 6 years of age. *J Nutr*. 2014;144:1480–1487. https://doi.org/10.3945/jn.114.194340
74. Tsuji M, Ayabe T, Tanaka R, et al. Comparative study on three different methods for arm-span measurement: the Japan environment and Children's study pilot. *Environ Health Prev Med*. 2017;22(1):28. https://doi.org/10.1186/s12199-017-0632-9
75. Addo OY, Himes JH. Reference curves for triceps and subscapular skinfold thicknesses in U.S. children and adolescents. *Am J Clin Nutr*. 2010;91(3):635–642. https://doi.org/10.3945/ajcn.2009.28385
76. Chou JH, Roumiantsev S, Singh R. PediTools electronic growth chart calculators: applications in clinical care, research, and quality improvement. *J Med Internet Res*. 2020;22(1):e16204. https://www.jmir.org/2020/1/e16204/pdf
77. Samson-Fang L, Stevenson R. Identification of malnutrition in children with cerebral palsy: poor performance of weight-for-height centiles. *Dev Med Child Neurol*. 2000;42:162–168. https://doi.org/10.1017/s0012162200000293
78. Abdel-Rahman SM, Bi C, Thaete K. Construction of lambda, mu, sigma values for determining mid-upper arm circumference z-scores in U.S. children aged 2 months through 18 years. *Nutr Clin Pract*. 2017;32(1):68–76. https://doi.org/10.1177/0884533616676597
79. World Health Organization. WHO Growth Standards. Accessed November 20, 2022. https://www.who.int/tools/child-growth-standards/standards
80. Centers for Disease Control and Prevention. CDC Growth Standards. Accessed November 20, 2022.

https://www.cdc.gov/growthcharts/clinical_charts.htm
81. Dietitians of Canada and Canadian Paediatric Society. A Health Professional's Guide for Using the WHO Growth Charts for Canada. 2014. Accessed November 20, 2022. https://www.dietitians.ca/DietitiansOfCanada/media/Documents/WHO%20Growth%20Charts/2014-A-Health-Professionals-Guide-to-Using-the-Charts.pdf
82. Palisano R, Rosenbaum P, Bartlett D, Livingston M. Gross Motor Function Classification System Expanded and Revised (GMFCS-E&R). McMaster University: CanChild Centre for Childhood Disability Research; 2007.
83. Swan WI, Vivanti A, Hakel-Smith NA, et al. Nutrition care process and model update: toward realizing people-centered care and outcomes management. *J Acad Nutr Diet*. 2017;117(12):2003–2014. https://doi.org/10.1016/j.jand.2017.07.015
84. American Academy of Pediatrics Committee on Nutrition. Assessment of nutritional status. In: Kleinman RE, Greer FR, eds. *Pediatric Nutrition*. 8th ed. American Academy of Pediatrics; 2019:723–774.
85. Jesus A, Stevenson R. Optimizing nutrition and bone health in children with cerebral palsy. *Phys Med Rehabil Clin N Am*. 2020;31:25–37. https://doi.org/10.1016/j.pmr.2019.08.001
86. Reid S, Westbury C, Guzys A, Reddihough D. Anticholinergic medications for reducing drooling in children with developmental disability. *Dev Med Child Neurol*. 2020;62:346–353. https://doi.org/10.1111/dmcn.14350
87. Costa A, Martin A, Arreola V, et al. Assessment of swallowing disorders, nutritional and hydration status, and oral hygiene in students with severe neurological disabilities including cerebral palsy. *Nutrients*. 2021;13:2413. https://doi.org/10.3390/nu13072413
88. Jan BM, Jan MM. Dental health of children with cerebral palsy. *Neurosciences (Riyadh).* 2016;21(4):314–318. https://doi.org/10.17712/nsj.2016.4.20150729
89. Meneses V, Parenti S, Burns H, Adams R. Latex allergy guidelines for people with spina bifida. *J Pediatr Rehabil Med.* 2020;13(4):601–609. https://doi.org/10.3233/PRM-200741

90. Asthma and Allergy Foundation of America. Latex allergy Reviewed July 2022. Accessed March 10, 2024. https://aafa.org/allergies/types-of-allergies/latex-allergy/
91. Marpole R, Blackmore AM, Gibson N, Cooper MS, Langdon K, Wilson AC. Evaluation and management of respiratory illness in children with cerebral palsy. *Front Pediatr*. 2020;8:333. https://doi.org/10.3389/fped.2020.00333
92. Belthur M, Singleton I, Burns J, Temkit M, Stizman T. Postoperative urinary retention after pediatric orthopedic surgery. *Children (Basel)*. 2022;9:1488. https://doi.org/10.3390/children9101488
93. Sharman SJ, Skouteris H, Powell MB, Watson B. Factors related to the accuracy of self-reported dietary intake of children aged 6 to 12 years elicited with interviews: a systematic review. *J Acad Nutr Diet*. 2016;116:76–114. https://doi.org/10.1016/j.jand.2015.08.024
94. Mauch C, Magarey A, Byrne R, Daniels L. Serve sizes and frequency of food consumption in Australian children aged 14 and 24 months. *Aust N Z J Public Health*. 2017;41:38–44. https://doi.org/10.1111/1753-6405.12622
95. Boland L, Graham I, Légaré F, et al. Barrier and facilitators for pediatric shared decision-making: a systematic review. *Implement Sci*. 2019;14:7. https://doi.org/10.1186/s13012-018-0851-5
96. Kon AA, Morrison W. Shared decision-making in pediatric practice: a broad view. *Pediatrics*. 2018;142(suppl 3):S129–S132. https://doi.org/10.1542/peds.2018-0516B
97. Silverman AH, Erato G, Goday P. The relationship between chronic paediatric feeding disorders and caregiver stress. *J Child Health Care*. 2021;25(1):69–80. https://doi.org/10.1177/1367493520905381
98. Tutor JD, Gosa MM. Dysphagia and aspiration in children. *Pediatr Pulmonol*. 2012 Apr;47(4):321–37. https://doi.org/10.1002/ppul.21576
99. Oskoui M, Mg P, Zaman M, et al. Complementary and alternative therapy use in children with cerebral palsy. *Can J Neurol Sci*. 2021;487:408–414. https://doi.org/10.1017/cjn.2020.188
100. Kemper KJ, Vohra S, Walls R; Task Force on Complementary and Alternative Medicine; Provisional Section on Complementary, Holistic, and Integrative Medicine. The use of complementary and

alternative medicine in pediatrics. *Pediatrics*. 2008;122:1374–1386. https://doi.org/10.1542/peds.2008-2173

101. Sandler AD, Brazdziunas D, Cooley WC, et al. Counseling families who choose complementary and alternative medicine for their child with chronic illness or disability. *Pediatrics*. 2001;107:598–601.
102. DeTallo C. *The Practitioner's Guide to Nutrition-Focused Physical Exam of Infants, Children, and Adolescents: An Illustrated Handbook*. American Society for Parenteral and Enteral Nutrition. 2019:6–7.
103. Secker DJ, Jeejeebhoy KN. How to perform Subjective Global Nutritional Assessment in children. *J Acad Nutr Diet*. 2012;112(3):424–431.e6. https://doi.org/10.1016/j.jada.2011.08.039
104. Carter L, Hulst JM, Afzal N, Jeejeebhoy K, Brunet-Wood K. Update to the pediatric Subjective Global Nutritional Assessment (SGNA). *Nutr Clin Pract.* 2022;37:1448–1457. https://doi.org/10.1002/ncp.10859
105. Bell K, Benfer K, Ware R, et al. The pediatric Subjective Global Nutrition Assessment classifies more children with cerebral palsy as malnourished compared with anthropometry. *J Aca Nutr Diet.* 2020;1201893–1901. https://doi.org/10.1016/j.jand.2020.04.012
106. Leonard M, Dain E, Pelc K, Dan B, De Laet C. Nutritional status of neurologically impaired children: impact on comorbidity. *Archives de Pédiatrie*. 2020;17:95–103. https://doi.org/10.1016/j.arcped.2019.11.003
107. Evans DC, Corkins MR, Malone A, et al; ASPEN Malnutrition Committee. The use of visceral proteins as nutrition markers: an ASPEN position paper. *Nutr Clin Pract.* 2021;36:22–28. Erratum in: *Nutr Clin Pract*. 2021;36:909. https://doi.org/10.1002/ncp.10588
108. Martin-Harris B, Canon C, Bonilha H, Murray J, Davidson K, Lefton-Greif M. Best practices in modified barium swallow studies. *Am J Speech Lang Patho*. 2020;29:1078–1093. https://doi.org/10.1044/2020_ajslp-19-00189
109. Miller CK, Willging J. Fiberoptic endoscopic evaluation of swallowing in infants and children: protocol, safety, and clinical efficacy: 25 years of experience. *Ann Otol Rhinol Laryngol.* 2020;129:469–481. https://doi.org/10.1177/0003489419893720

110. Shao F, Zhao X, Toyaa H, et al. Semi-quantitative assessment optimized the grading of pulmonary aspiration on salivagram in children. *Ann Nucl Med*. 2021;35:321–327. https://doi.org/10.1007/s12149-020-01564-6
111. Rosen R, Vandenplas Y, Singendonk M, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr.* 2018;66:516–554. https://doi.org/10.1097/mpg.0000000000001889
112. Berman L, Baird R, Sant'Anna A, et al. Gastrostomy tube use in pediatrics: a systematic review. *Pediatrics.* 2022;149:e2021055213. https://doi.org/10.1542/peds.2021-055213
113. Bechtold M, Brown P, Escuro A, et al. When is enteral nutrition indicated. *JPEN* 2022;46:1470–1496 doi:10l1002;jpen.2364
114. Knight R, Albright J, Huth-Bocks A, et al. Impact of behavioral feeding intervention on child emotional and behaviour function, parenting stress and parent-child attachment. *JPGN* 2019;69:363–387. https://doi.org/10.1097/mpg.0000000000002382
115. Bryant-Waugh R. Feeding and eating disorders in children. *Psychiatr Clin North Am*. 2019;42(1):157–167. https://doi.org/10.1016/j.psc.2018.10.005
116. Ricciuto A, Baird R, Sant'Anna A. A retrospective review of enteral nutrition support practices at a tertiary pediatric hospital: a comparison of prolonged nasogastric and gastrostomy tube feeding. *Clin Nutr.* 2015;134:652–658. https://doi.org/10.1016/j.clnu.2014.07.007
117. Irving S, Rempel G, Lyman B, Sevilla W, Northington L, Guenter P; American Society for Parenteral and Enteral Nutrition. Pediatric nasogastric tube placement and verification: best practice recommendations from the NOVEL project. *Nutr Clin Pract*. 2018;33:921–927. https://doi.org/10.1002/ncp.10189
118. Boullata JI, Carrera AL, Harvey L, et al.; ASPEN Safe Practices for Enteral Nutrition Therapy Task Force. ASPEN safe practices for

enteral nutrition therapy. *JPEN J Parenter Enteral Nutr*. 2017;41(1):15–103. https://doi.org/10.1177/0148607116673053
119. Jensen A, Renaud E, Drucker N, et al. Why wait: early enteral feeding after pediatric gastrostomy tube placement. *J Pediatr Surg*. 2018;53:656–660. https://doi.org/10.1016/j.jpedsurg.2017.06.015
120. Bell K, Samson-Fang L. Nutritional management of children with cerebral palsy. *Eur J Clin Nutr* 2013:67(suppl 2):S13–16. https://doi.org/10.1038/ejcn.2013.225
121. Sullivan P, Juszczak, Bachlet A, et al. Gastrostomy tube feeding in children with cerebral palsy: a prospective, longitudinal study. *Dev Med Child Neurol*. 2005;47:77–85. https://doi.org/10.1017/s0012162205000162
122. Broekaert I, Falconer J, Bronsky J, et al. The use of jejunal tube feeding in children: a position paper by the Gastroenterology and Nutrition Committees of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition 2019. *J Pediatr Gastroenterol Nutr.* 2019;69(2):239–258. https://doi.org/10.1097/mpg.0000000000002379
123. Rosen R, Hart K, Warlaumont M. Incidence of gastroesophageal reflux during transpyloric feeds. *J Pediatr Gastroenterol Nutr.* 2011;52(5):532–5. https://doi.org/10.1097/MPG.0b013e31820596f8
124. Watson J, McGuire W. Transpyloric versus gastric tube feeding for preterm infants. *Cochrane Database Syst Rev*. 2013;2013(2):CD003487. https://doi.org/10.1002/14651858.CD003487.pub3
125. Vernon-Roberts A, Sullivan P. Fundoplication versus postoperative medication for gastro-esophageal reflux in children with neurological impairment undergoing gastrostomy. *Cochrane Database Sys Rev.* 2013;2013(8):CD006151. https://doi.org/10.1002/14651858.CD006151.pub3
126. Dreznik Y, Baazov A, Dvir N, et al. Is fundoplication mandatory in children with neurological impairment undergoing gastrostomy? *J Paediatrics and Child Health.* 2022; 58:588–592. https://doi.org/10.1111/jpc.15767
127. Barnhart D. Gastroesophageal reflux disease in children. *Seminar in Pediatric Surgery* 2016;25:212–218.

https://doi.org/10.1053/j.sempedsurg.2016.05.009
128. Yamoto M, Fukumoto, Takahashi, et al. Risk factors for dumping syndrome after fundoplication for gastroesophageal reflux in child. *Pediatr Surg Int*. 2021;37:183–189. https://doi.org/10.1007/s00383-020-04783-0
129. Cook RC, Blinman TA. Alleviation of retching and feeding intolerance after fundoplication. *Nutr Clin Pract*. 2014;29:386–396. https://doi.org/10.1177/0884533614525211
130. Lauriti G, Lisi G, Chiesa P, Zani A, Pierro A. Gastroesophageal reflux in children with neurological impairment: a systematic review and meta-analysis. *Pediatr Surg Int.* 2018;34:1139–1149. https://doi.org/10.1007/s00383-018-4335-0
131. Smith H, Betts J. Nutrient time and metabolic regulation. *J Physiol.* 2022;600:1299–1313. https://doi.org/10.1113/jp280756
132. Larimer C, Sumner V, Wander D. Medical line entanglement: the unspoken patient safety hazard of medical devices. *Nutr Clin Pract*. 2023;38:1296–1308. https://doi.org/10.1002/ncp.11000
133. American Society for Parenteral and Enteral Nutrition. EN Pediatric Formulas. Accessed February 26, 2024. https://www.nutritioncare.org/Guidelines_and_Clinical_Resources/EN_Formula_Guide/EN_Pediatric_Formulas/
134. Epp L, Blackmer A, Church A, et al. Blenderized tube feedings: practice recommendations from the American Society for Parenteral and Enteral Nutrition. *Nutr Clin Pract.* 2023;38:1190–1219. https://doi.org/10.1002/ncp.11055
135. Gallagher K, Flint A, Mouzaki M, et al. Blenderized enteral nutrition diet study: feasibility, clinical, and microbiome outcomes of providing blenderized feeds through a gastric tube in a medically complex pediatric population. *JPEN J Parenter Enteral Nutr*. 2018;42:1046–1060. https://doi.org/10.1002/jpen.1049
136. Hron B, Fishman E, Lurie M et al. Health outcomes and quality of life indices of children receiving blenderized feeds via enteral tube. *J Peds*. 2019;211:139–145. https://doi.org/10.1016/j.jpeds.2019.04.023
137. Chandrasekar N, Dehlsen K, Leach S, Krishnan U. Blenderised tube feeds vs commercial formula: which is better for gastrostomy-fed

children? *Nutrients*. 2022:14:1349. https://doi.org/10.3390/nu14153139
138. Soscia J, Adams S, Cohen E, et al. The parental experience and perceptions of blenderized tube feeding for children with medical complexity. *Paediatr Child Health.* 2021;26:462–469. https://doi.org/10.1093/p/ch/pxab034
139. Epp L, Lammert L, Vallumsetla N, Hurt R, Mundi N. Use of blenderized tube feeding in adult and pediatric home enteral nutrition patients. *Nutr Clin Pract*. 2017;32:201–205. https://doi.org/10.1177/0884533616662992
140. Ogundele M, Bassi Z. A survey of carers' satisfaction with gastrostomy tube feeding from a tertiary children's hospital. *Arch Dis Child*. 2013;98(suppl 1):A53.
141. Van Riper C. Position of the American Dietetic Association: providing nutrition services for people with developmental disabilities and special health care needs. *J Am Diet Assoc*. 2010;110:296–307. https://doi.org/10.1016/j.jada.2009.12.003

Test Your Knowledge Answers

1. The correct answer is **D**. Length and height are difficult to obtain and are not always a good representation of nutrition status. Head circumference should be measured and monitored, but its use as a nutrition indicator is challenged in children with NI because head size is impacted by the children's underlying condition.
2. The correct answer is **C**. Inadequate dietary intake is the most important contribution to poor weight gain in children with severe NI.
3. The correct answer is **B**. Calculating energy requirements may be important, but monitoring the response to a nutrition intervention is integral to determining the correct energy and nutrition requirements for children with NI without providing too many calories.

APPENDIX 16-1. Case Study

HH is a 14.5-year-old male with bilateral CP (GMFCS 5) who is orally fed and is being referred to the CP clinic for assessment of his nutrition status and his aspiration risk, and to ascertain if enteral nutrition support is required.

HH has seizures and is underweight for age having only gained 2 pounds in the past year according to his mother. A review of systems reveals constipation with bowel movements rarely occurring more than once per week. His fluid intake is borderline, and he has only 3 wet diapers per day of concentrated urine. He has considerable liquid loss with anterior drooling. He has spasticity that is not being treated in a concerted way. He sleeps poorly and needs frequent repositioning at night, during which his parents observe some gagging and occasional regurgitation.

While he has challenges with eating and drinking, he has not had any lower respiratory tract infections and enjoys his feeding times with his parents. School staff are more concerned than his parents about oral intake.

His medications include lamotrigine, which keeps his seizures under good control, and diazepam, which is given intermittently to help him relax.

At the first visit, he is being fed orally and has never received EN support or oral calorie-boosting techniques. The family reports that he eats 3 meals of puréed food and 1 to 2 snacks per day. Milk is mixed into the puréed food to achieve the correct consistency for swallowing ease.

Table A16-1 provides the growth parameters at the initial visit plotted using PediTools (https://www.peditools.org) and CDC parameters.[76]

During the feeding assessment, HH coughs when drinking thin liquids and sometimes when swallowing purées. He frequently pauses before swallowing and his father massages his neck to help trigger a swallow. When being fed, HH sits in his stroller or on his father's lap.

The feeding-focused assessment by the feeding team, facilitated by the team of occupational and physical therapists, reveals the need for better during feedings. The speech therapist recommends augmentative techniques for lip closure to ease swallowing and using mildly thick liquids to alleviate some of the coughing during meals. The team also recommends a cut-away cup to aid in giving liquids.

Laboratory parameters reveal iron deficiency and low vitamin D status without elevation of parathormone or alkaline phosphatase.

The feeding team develops a nutrition care plan together with the family with clear nutrition goals and feeding goals elucidated. The family expresses their goal of continuing oral intake despite the challenges.

- The feeding team discusses their concerns regarding HH's nutrition status given his plots on conventional and CP growth charts, his low triceps skinfold, and his poor weight gain history.
  - They recommended calorie boosting for his oral intake using 1 kcal/ml commercial polymeric formula instead of milk and adding oil or butter to the blended food to boost calories.
  - A multivitamin, vitamin D, and iron supplementation is added.
    - Short-term goal: Optimize oral intake and gain weight (7–10 g/d, which is age-appropriate with a bit extra for catch-up)
    - Long-term goal: Plot above the zone of concern on the CP growth chart, have a z-score for weight at –2, and increase the TSF to the 10th percentile for age.
  - Positioning, augmentative oral feeding techniques, and use of appropriate utensils were demonstrated.
  - A swallow study was recommended but the family declined, thus thickening recommendations were based on clinical assessment, which included thickening with food (eg, yogurt, pudding, purées) for boosting nutritional intake or using commercial thickeners to mitigate aspiration risk.
  - Managing constipation with fluid and osmotic laxatives was suggested.
- The feeding team provided HH's parents with information regarding EN support and asked them to consider it if weight gain could not be achieved. They informed the parents that enteral access is a tool that can help destress mealtime and optimize nutrition without removing pleasurable oral intake or negatively impacting HH's lifestyle.

Four weeks later at another clinic visit, the parents acknowledged that mealtimes were stressful, and that intake was not improving. They had many questions about nutrition support, particularly focused on whether HH could continue to have pleasurable feeds after GT placement and

whether he would be able to continue his time in the therapy pool, which he particularly enjoyed. When they were reassured of both, they consented to a GT placement.

The RD on the feeding team calculated HH's approximate energy requirements following GT placement. Based on the WHO calculation,[52] HH requires 19.1 × 17.5 + 651 = 985 kcal/d.

Appreciating that this is likely an overestimate of his energy requirements especially when oral intake was continuing, his RD started him on a polymeric 1-kcal/ml formula for about 700 kcals/d given in 3 feedings in the mid-morning and mid-afternoon and 1 feeding 2 hours before bed so that he could have an empty stomach at night. Night feeding was not given because of HH's poor sleep pattern, his risk of reflux, and his inability to call for help if he experienced a feeding-related problem at night. Target fluid intake of 1375 mL/d (Harris-Benedict) was given as water by GT (total fluids = oral fluids + enteral product + water = 1375 mL/d).

Four months after the initial evaluation, HH returned for re-evaluation. He is eating a bit orally (300 calories) and enjoying it. The family has adapted some of the previous suggestions and calorie boosting for oral intake is still occurring. He is taking 700 calories by GT. His parents acknowledge their appreciation of the GT (as does the school), and that meals are much less stressful. The GT stoma has healed nicely although there were some local challenges with the site that the feeding team nurse addressed.

Table A16-2 provides growth parameters 4 months after the initial evaluation.

His nutrition team is very happy with his improvement in TSF and weight gain, even though plots on the growth charts (both CP and CDC) are still on similar trajectories to his previous plots. His z-scores show significant improvement in weight and BMI, and his TSF is better. His weight gain is exceeding expectations for his age, such that the nutrition support likely needs to be tweaked to ensure he does not gain too rapidly.

His caloric requirements were carefully assessed, revealing that the yogurt used to thicken the liquids added substantial calories. The feeding

team suggested stopping boosting calories in his oral intake and to check his weight in 4 weeks.

Shortly after this clinic visit, HH was hospitalized for severe pneumonia accompanied by significant weight loss and poor oral intake. He could not be positioned appropriately for oral intake and his appetite disappeared. Without the oral intake, the calorie intake in his nutrition support was not enough to meet his caloric needs. His family wanted to continue the nutrition support but did not want to increase the volume of formula given, hence a 1.2 kcal/ml standard polymeric formula was started to ensure weight gain.

Twelve months after his illness, oral intake continues to be minimal despite intervention by his multidisciplinary team. His weight gain is well established and on target for his age, and he is close to meeting his long-term nutrition goals of plotting above the 20th percentile on the CP growth chart.

This case highlights the importance of a multidisciplinary approach to help families overcome obstacles in meeting the goals and values for optimizing nutrition in children with NI. It emphasizes the need for close monitoring of nutrition parameters and for strategies that support a families' choice for continued oral intake while mitigating the risks of aspiration.

TABLE A16-1. Growth Parameters at Initial Visit

Parameter	Measurement	CDC Growth Chart	z-Score	CP Growth Chart GMFCS 5 for Boys with Oral Intake Only
Weight (kg)	19.1	0 percentile	−7.81	10th percentile (zone of concern)
Height (cm) extrapolated from knee height	137	0 percentile	−3.45	—
BMI (kg/m^2)	10.18	0 percentile	−10.58	—
TSF (mm)	4	3rd percentile	−1.88	—
MUAC (cm)	20 cm	1st percentile	−2.51	—
Weight gain velocity	3 g/d past year	∼50% of expected weight gain/d for age	—	—

Abbreviations: BMI, body mass index; CDC, Centers for Disease Control and Prevention; CP, cerebral palsy; GMFCS, Gross Motor Function Classification; MUAC, mid upper arm circumference; TSF, triceps skinfold.

TABLE A16-2. Growth Parameters at Follow-Up Visit

Parameter	Measurement	CDC Growth Chart	z-Score	CP Growth Chart GMFCS 5 for Boy Receiving EN Support
Weight (kg)	22	0 percentile	−6.89	10th percentile (still plotting in zone of concern)
Height (cm) extrapolated from knee height	138.5	0 percentile	−3.49	—
BMI (kg/m^2)	11.5	0 percentile	−7.59	—
TSF	5	11th percentile	−1.25	—
MUAC	22	3rd percentile	−1.86	—
Weight gain velocity	32 g/d	3 times expected for age		—

Abbreviations: BMI, body mass index; CDC, Centers for Disease Control and Prevention; CP, cerebral palsy; EN, enteral nutrition; GMFCS, Gross Motor Function Classification; MUAC, mid upper arm circumference; TSF, triceps skinfold.

Kathleen J. Motil, MD, PhD; Ala K. Shaikhkhalil, MD; and Robin Meyers, MPH, RD, LDN contributed to the previous editions of this text.

17

Eating Disorders

Mary Pat Turon-Findley, MEd, RD, CMHIMP, LD

Learning Objectives

1. Discuss the basic macronutrient and micronutrient needs in patients with an eating disorder.
2. Determine assessment tools for managing the treatment of patients with an eating disorder or disordered eating.
3. Summarize the rationale for providing patients with eating disorders oral nutrition versus enteral or parenteral nutrition.
4. Identify patients at risk for refeeding syndrome and identify key monitoring parameters for prevention and treatment.

Introduction

Eating disorders are classified as mental disorders in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*).[5] The highest premature fatality rates from the DSM-5 list are associated with suicide, followed by anorexia nervosa.[1] Eating disorders are often underdiagnosed despite their prevalence among children, adolescents, and young adults.[1,2] This may be due in part to the nondisclosure and concealment of symptoms, which can impose extended delays in detection

and diagnosis. Eating disorders not only detrimentally impact growth in young individuals but also disrupt the maintenance of health status in adults.[2,4]

In the United States, 10 to 20 million females are reported to have a current diagnosis classified as an eating disorder such as anorexia nervosa or bulimia nervosa. Of those, approximately 5 million are under the age of 18 years.[1] Eating disorders are not specific to the female sex or to any culture or gender identity. Approximately 30% of individuals diagnosed with anorexia nervosa are male. Diagnosis of males with eating disorders typically occurs later than females as males are less likely to seek treatment due to stigma.[1]

Eating disorders are present in all cultures and socioeconomic classes. Perez et al found an increasing variety of disordered eating among all ages, primarily starting with binge eating disorder (BED), which fluctuated to restriction and increased guilt among Hispanic populations.[3] Additionally, significantly more body dissatisfaction has been reported among Asian populations than among Caucasian groups.[1] In African American populations, a growing number of people have had cultural attitude changes associated with altered body image issues, leading to an increase in the number of eating disorder cases. Similarly, the increase of Western influence on Hispanic and Asian populations has resulted in an increase in eating disorder cases.[1,4]

This chapter reviews the classification, diagnosis, assessment, and etiology of eating disorders; describes nutrition therapy strategies, interdisciplinary teamwork, and monitoring interventions for eating disorders; defines and describes the pathogenesis of refeeding syndrome; and discusses prevention and treatment of refeeding syndrome.

Classification and Diagnosis of Eating Disorders

Anorexia nervosa, bulimia nervosa, binge-eating disorder, and eating disorder not otherwise specified are eating disorders that share commonalities of extreme emotion and behaviors around food, thinking

errors, environment, and body image. The American Psychiatric Association recommends using a multiaxial system in assessing and diagnosing mental disorders according to the following *DSM* subcategories (see Table 17-1)[5]:

- Anorexia nervosa
- Bulimia nervosa
- Avoidant/restrictive food intake disorder
- Rumination disorder
- Binge-eating disorder
- Other specified feeding or eating disorder
- Unspecified feeding or eating disorder
- Pica

TABLE 17-1. Eating Disorder/Feeding Disorder Summary From the *Diagnostic and Statistical Manual of Mental Disorders*[a]

Eating Disorder Type	Characteristics
Anorexia nervosa	• Restriction of energy intake or requirements leading to significantly low body weight for age, sex, development trajectory, or physical health • Intense fear of weight gain and disturbances in one's body perceptions and false self-evaluations • Types: restricting (occurring during last 3 mo) and binge-eating/purging (occurring during last 3 mo) • Ranges of mild, moderate, severe, and extreme are dependent on BMI values
Bulimia nervosa	• Recurrent episodes of binge eating over a discrete period and a sense of lacking control over eating during the episode, which is done to prevent weight gain with the use of compensatory behaviors such as self-induced vomiting, misuse of laxatives or diuretics or other medications, fasting, or excessive exercise. • Behaviors occur at least weekly for 3 mo, and a dysmorphic body image is present. Ranges of mild, moderate, severe, and extreme based on episodes of compensatory behaviors per week.
Avoidant/restrictive food intake disorder	• An eating or feeding disturbance with significant weight loss or failure to achieve expected growth • May result from low interest in eating or food; avoidance secondary to sensory issues, or reality-altered thoughts about the consequences of eating • Sometimes seen with medications or other mental disorders
Rumination disorder	• Characterized by repeating regurgitation or chewing and spitting of foods for at least 1 mo • Symptoms may occur in the context of another mental disorder or in addition to other eating disorder categories
Binge-eating disorder	• Recurrent episodes of binge eating over a discrete period characterized by consuming larger amounts of food than what most people consume during that time and a sense of lacking control • Eating is more rapid than normal and in larger amounts and accompanied by feelings of being uncomfortably full, embarrassment, loneliness, and guilt or self-disgust

Eating Disorder Type	Characteristics
	• Ranges of mild, moderate, severe, and extreme dependent on binge-eating episodes per week
Other specified feeding or eating disorder	This category applies to presentations associated with distress or impairment in social, occupational, or other important areas of function over the following designations: • atypical anorexia nervosa • bulimia nervosa (low frequency or limited duration) • binge-eating disorder (low frequency or limited duration) • purging disorder • night eating syndrome
Unspecified feeding or eating disorder	Patient may present as having an eating disorder due to various signs of clinical distress or impairment of important functional areas in which the patient does not meet the full criteria.

Abbreviation: BMI, body mass index.

[a]Data from the American Psychiatric Association.[5]

These subcategories are diagnosed and classified on Axis 1 of the multiaxial system.[5] Of note, amenorrhea (ie, the absence of at least 3 consecutive menstrual cycles) is one of the diagnostic criteria listed in *DSM-5* for anorexia nervosa with some medical exclusions (eg, high-performance athletes). However, this may not be useful in the assessment of adolescent children with eating disorders because healthy adolescent females may normally have episodes of amenorrhea during the first 1 to 2 years after the onset of menarche, as may those who are athletes.[6,7] In addition, a variety of disordered eating presentations exist (see Table 17-2).

TABLE 17-2. Additional Disordered-Eating Presentations

Disordered-Eating Type	Characteristics
Diabulimia	• Characterized by presentation in type 1, insulin-dependent diabetic, manipulation of or lack of insulin injections as well as possible purging and restricting • Medical issues may include ketones in urine; increased bacterial infections; and effects on kidneys, vision, and muscle integrity.
Orthorexia	• Obsession with eating healthy food and avoiding unhealthy foods • Perceptions of healthy vs unhealthy food are skewed • Not recognized as a clinical eating disorder; however, if left untreated, it can progress into an eating disorder
Muscle dysmorphia (reverse anorexia or bigorexia)	• Form of body dysmorphia in which the patient is preoccupied with masculinity, believing their muscles are small or weak no matter how large they are • Patients' self-perception of their bodies is not reality-based, and they also develop a range of eating rituals
Compensatory	• Characterized by a variety of behaviors meant to compensate for or "undo" eating to relieve guilt associated with eating or enjoyment • After eating, a patient may purge, fast, restrict, use diet pills, chew and spit food, and/or exercise
Rumination[a]	Now a part of *DSM-5*; characterized by repeating regurgitation or chewing and spitting of food.[a]
Body/gender dysphoria/identity	Characterized by feelings of social anxiety, guilt for not fulfilling expectations of self and others, low self-esteem, feelings of anger or rejection, not feeling accepted, or tension with family and friends
PANDAS	Anorexia nervosa in patients believed to be linked to Group A and β hemolytic *Streptococcus* spp.
Autism spectrum	• Patient may present as an eating disorder • May be a result of developmental issues as well as obsessive-compulsive disorder or anxiety behaviors

Disordered-Eating Type	Characteristics
	• May binge eat, restrict, limit food choices, or purge without a desire for body changes or have negative body image
Psychosis/schizophrenia	• Characterized by fear of food because of auditory or visual hallucinations • May also present as restricting due to paranoid thoughts or general fear of people and surroundings
Comorbid psychiatric diagnosis	• Comorbidity of multiple psychiatric diagnoses may confound eating issues and body image due to cognitive and/or mental status. • In some cases, medication-induced eating issues arise (eg, anorexia with stimulant medications)

Abbreviations: *DSM-5*, *Diagnostic and Statistical Manual of Mental Disorders* (5th ed); PANDAS, pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections.

[a] See Table 17-1.

Psychiatric comorbidities, such as obsessive-compulsive disorder and affective disorder, are common and should be treated along with the eating disorder.[8] Major depression is the most common comorbid disease among persons with anorexia nervosa.[9] Substance abuse prevalence is estimated at 30% to 70% in persons with bulimia,[7,10] and is on the rise in all types of eating disorders. Other common comorbid psychiatric diagnoses include anxiety, attachment disorders, sexuality/gender identification, personality disorder, and trauma/posttraumatic stress disorder (including considerations of physical, emotional, sexual, and psychological abuse, or neglect). Eating disorders have been observed in children with psychosis and schizophrenia.[4,5]

Psychiatric comorbidities or medical problems such as ongoing dizziness, fatigue, or syncope; unintended weight loss or changes; social and physical behavior changes; prevailing illness or injuries; and isolation are often present to the physician prior to detection of an eating disorder.[5,7,11,12]

Binge-eating disorder has been associated with obesity and comorbid anxiety, depression, agitation, and food addiction. Within the assessment for treatment, it is important to clarify binge triggers and identify self-esteem and self-loathing issues (many children with eating disorders verbalize this as associated with guilt).[5,7,13] The treatment often encompasses the addiction to food binging and the feeling of being out of control, which is comparable to drug or alcohol addiction or other binging behaviors. The treatment program should be a didactic process that addresses brain and behavioral thought processes.

Avoidant/restrictive food intake disorder (ARFID) can be diagnosed along with comorbid behavioral health issues but it is difficult to identify as a primary diagnosis. The most common subtypes of ARFID are the following:

- *Avoidant:* Fear-based phobia related to choking, nausea, vomiting, or pain (medical)
- *Aversion:* Sensory-based response; consuming a limited variety of foods because of sensory or texture issues, paranoid thinking, or food jags; possibly a sensory disorder
- *Restrictive:* Lower appetite and low drive for eating because of extreme pickiness, forgetfulness, or autism
- *Mixed:* Any combination, initially restricting, that usually moves to other comorbid types[1,5,13]

Refeeding syndrome may not occur in children with an ARFID eating disorder, but it should be monitored with parameters of assessment, treatment, and interdisciplinary team review.

DSM-5 Axis Definitions

Although the updated *DSM* format does not require Axes I–V, the information is still commonly reported within the psychiatric progress note or assessment and helps in planning nutrition treatment as well as understanding the individual's needs.

- Axis I—Clinical syndromes: Typically thought of as the *DSM* diagnosis (eg, depression, social phobia, mood disorder, anxiety, posttraumatic stress disorder, and/or eating disorders)

- Axis II—Developmental disorders (including autism and intellectual disability with evidence) and personality disorders
- Axis III—Physical conditions (especially those that play a role in the exacerbation of Axes I and II (eg, side effects of eating disorders, brain injury, HIV infection, AIDS, cancer, diabetes)
- Axis IV—Severity of psychosocial stressors: Stressful events in a person's life (eg, death of a loved one, leaving for college)
- Axis V—Highest level of functioning (clinicians rate the person's level of functioning, known as a global assessment of functioning)[5]

Physical Presentation

The physical presentation of a person with anorexia nervosa includes the following:

- weight loss significant to hospital/*DSM-5* guidelines
- dehydration
- mental/physical lethargy
- hair loss
- muscle wasting
- dry skin
- signs of malnutrition in the body
- abnormal laboratory values
- cyanosis of extremities
- bradycardia <60 beats/min
- lanugo-type hair
- cachexia

When anorexia develops in childhood, the first clinical sign may be failure to maintain weight gain or linear growth velocity. In addition, children with anorexia may not achieve age-specific maturation goals, thus growth charts should be evaluated for growth patterns.[4,5,14]

Physical signs and symptoms of a person with bulimia nervosa are more difficult to detect but may include parotid gland enlargement, scarring of the hand used to stimulate gag reflux (referred to as Russell's sign), erosion of dental enamel with increased dental caries, and sore red throat secondary to excessive purging.[15,16] Other signs include swollen or reddened gums,

darkened circles under the eyes, swollen cheeks, scratches on knuckles or hands, broken nails, and dry skin around nose and mouth areas. Depending on the degree of purging or other compensatory behaviors, and if any additional food restriction is observed, a child with bulimia nervosa may meet all expected weight gains and track normally along the growth charts.

Etiology of Eating Disorders

The etiology of eating disorders is complex, but they appear to originate from predisposed genetic factors along with serotonin dysfunction and psychological factors surrounding childhood abuse and/or trauma.[7,13,16] A 17-year longitudinal study of 800 children found that eating conflicts, struggles with food, and unpleasant meals were additional risk factors for the development of an eating disorder in this population.[17] The role of heredity is still unclear because twin studies, which are often utilized in familial studies to differentiate between genetic and environmental factors, have reported mixed data, some of which indicated a strong correlation, and some found little correlation.[1,5,16]

The Eating Recovery Center's limited ARFID research indicates that interview questions are not robust enough to capture intake or eating issues. The questions did, however, highlight various ARFID-related symptoms spanning age and comorbidity (eg, young children with behavioral diagnoses, adults diagnosed with trauma but not disordered eating, patients on the autism spectrum).[5,13,18]

Nutrition in Eating Disorders

Although nutrition rehabilitation and weight stabilization are essential components in the treatment of and recovery from eating disorders, research remains limited. The following recommendations should be used as guidelines and not definitive treatment protocols.[19,20]

Nutrition Assessment

Establishing trust with a patient is of paramount importance to complete a nutrition assessment and set parameters for treatment as well as the continuum of care. Individuals with eating disorders often have limited

cognitive abilities, poor memory due to malnutrition/poor intake, comorbid psychiatric issues, trust issues, and fears of being overfed.

When interviewing a child with an eating disorder (see Exhibit 17-1), speak in calm, low tones. The interviewer should attempt to establish trust and rapport, although initially this may be limited depending on the child's affect and history. Posture should be non-threatening, with an attempt to elevate eye contact as needed. The interviewer should concentrate on open-ended questions, and interactions should be firm but empathetic. Avoid showing disappointment or acting surprised about responses. A trauma history frequently influences effect during the interview, assessment, and treatment. Observe physical attributes during the interview such as posture, signs of malnutrition/dehydration, nonverbal cues, signs of self-harm, and overall cognitive level. It is important to evaluate whether the interview should be one-on-one rather than include family to ascertain the most accurate information.[5,7,20]

EXHIBIT 17-1. Interview Process Template Guide Decision Tree

1. Ask the patient what brings them into the clinical setting (eg, hospital or office). If patient responds about eating issues, continue to Route A.

   Route A

   - Ask the patient to describe what is currently going on with their intake and health.
   - Determine how long it has been an issue and explore practices/concerns/struggles.
   - Inquire when the last time the practice (restriction, purging, etc) occurred.
   - Acquire physical parameters, asking about dizziness, headaches, gastrointestinal distress, bowel movements, regular periods, time of last period, and sleep patterns.
   - Ask the patient to describe any triggers or sentinel event that initiated the practice.
   - Acquire any intake recall for a typical day (attempt to get quantities and brand information), eg, when the patient ate, what was eaten, types/amounts of fluids, any food avoidances, food allergies, new diet plans or new diet practices (eg, vegetarian or gluten free) Ask for intake on both "normal"/previous days and days with struggles.
   - Ask for information on supplements, vitamins, herbs, supplements, and medications.
   - Inquire about the patient's usual weight and any changes in weight/appetite history.
   - Ask the patient how he or she views his or her body: Do you have a negative body image? What do you see in a mirror?
   - Inquire about participation in sports and other activities, including amount of time spent in practice, games, clubs (eg band, dance, or drama), or competition or in

exercise.

- Determine the patient's goals for hospitalization/treatment.
- Review any substance use, vaping, tobacco, self-harm, depression, anxiety, suicidal thoughts, or other trauma.
- For patients with posttraumatic stress disorder, consider briefly reviewing the influence of trauma on eating issues.

2. If the patient does not respond about eating issue, but one is suspected, start with Route B.

   Route B

   - Ask about any recent changes in appetite or weight, and explore the patient's answers.
   - Inquire whether the patient's habits about how he or she eats or sees food changed; again, explore the answers in nonthreatening manner.
   - Determine whether the patients is able to eat in front of others and explore the parameters.
   - Gauge the direction of information before asking if the patient ever restricts, gets sick after eating, or can't stop eating or is addicted to certain foods; explore the responses.
   - In cases of binging, inquire about hoarding, triggers, challenging situations, history, and where/when binges occur.
   - In cases of purging, inquire about the number of times, history, locations, and triggers.
   - In cases of restricting, inquire on trigger, history, challenge foods, and challenge situations.

3. Continue with Route A, starting with acquiring physical parameters and continuing to the end.

During the entire assessment process, practitioners should assess for signs and symptoms of malnutrition along with a thorough nutrition-focused physical exam (NFPE). The practitioner should specifically check for the previously mentioned indicators of disordered eating, starting from the beginning of the interview, continuing into the formal NFPE. Assess the following:

- gait/balance
- overall body skin integrity
- stores
- capillary refill on nails
- hydration
- inner eye lids

- hair integrity/growth history
- swelling
- areas with poor healing or dryness
- edema
- status of teeth, gums, tongue
- changes in taste or smell
- orbit and temporal areas
- stores in extremities
- integrity of the knees, legs, ankles, and feet[14]

Gathering additional information regarding the child's weight and development , along with family history (trauma, illnesses, addiction, food security, social factors, caregivers, growth parameters) are some factors to consider (if available) and include in the assessment and treatment.[1,6,14]

In addition to physical, medical, and social information obtained from the medical record, key interview points should include the following:

- history of eating issues, trauma history, and sentinel events
- changes in medical conditions (eg, emesis, changes in bowel habits, sleep patterns, hair loss, dizziness/headache)
- changes in food acceptance, food or activity rituals, food jags, or diet
- body image perceptions
- intake recall
- any comorbid behavioral issues or suicidal ideation
- activity levels
- current goals[1,6,14,20]

Identifying social influences within the assessment can provide critical information for formulating a treatment plan. Teens and those in the developing years can be influenced by external factors, specific trauma, or feelings of insecurity. Factors to explore include the following:

- genetics/family history
- distorted body image
- severe family issues/problems
- history of abuse (eg, sexual, physical)
- substance use

- sexual/gender identity
- self-harm
- social pressures from peers or those implied from media
- pressure from activities to increase performance
- pressure from coaches, peers, family, parents, or self

See Appendices 17-1 through 17-4 for case studies.[5,16,20]

Nutrition Requirements

The needs of each child with an eating disorder should be addressed individually because of varying levels of medical conditions, cardiac and laboratory status, probability of refeeding, and prior intake. Therefore, the following ranges may be a general guideline unless your hospital policy/program dictates otherwise:[1,6,7,16,23]

Macronutrients

ENERGY REQUIREMENTS Initial energy requirements for anorexia nervosa are 20–40 kcal/kg of current body weight.[6,23] Energy intake can be advanced by 200 calories every other day, but if it is not tolerated, it is necessary to adjust advancement. Elevated diet-induced thermogenesis has been reported in anorexia nervosa.[1,16,23] In children with an eating disorder and elevated diet-induced thermogenesis or in extremely anxious patients energy requirements may be as high as 80 to 100 kcal/kg before weight gain can be achieved.[6] If higher energy intake is required for a child with anorexia nervosa due to poor weight gain, the child should be evaluated for manipulation of the intake. In children with bulimia nervosa or binge-eating disorder, initial energy requirements for weight maintenance may start at 1.2 to 1.3 times the measured resting energy expenditure for sedentary activity.[20] Avoiding caloric levels that promote weight loss is recommended until the eating pattern is stabilized because restricting calories in such a patient may trigger a binging episode.

PROTEIN REQUIREMENTS Recommended protein intake is the recommended dietary allowance in grams per kilogram ideal body weight for age (0.8–1.5 g/kg) or 15%–20% of total calories from a high biologic value source.[6,19,23] During treatment and follow-up, evaluation parameters should be monitored and reassessed.

FAT REQUIREMENTS Recommended fat intake is 25% to 30% of total daily calories from fat, with appropriate sources of essential fatty acids.[6,20,23]

WATER REQUIREMENTS The pulse values of a child with an eating disorder should be monitored while lying down, sitting, and standing. If the split is greater than 30 points, the patient requires monitoring for fluid needs and advancement. Monitoring the patient's blood pressure values and pulse provides orthostatic parameters for fluid advancement. Some references suggest initially starting the caloric energy amount in milliliters and advancing by 200 to 250 mL daily as tolerated to an estimated goal of 2000 to 2500 mL or following hospital/program guidelines.[6,7,23] See Table 17-3 for more information on fluid intake.

TABLE 17-3. Timeline for Prevention of and Therapy for Refeeding Syndrome

Energy/Nutrient	Days 1–3	Days 4–7	Days 8–14
Calories	50% of goal, or 15–20 kcal/kg/d	Advance by 200–300 kcal if electrolytes and orthostatic measures are stable	Advance every 3 d by 200–300 kcal if electrolytes and orthostatic measures remain stable
Carbohydrate	2–3 g/kg/d	Advance to meet daily calorie adjustments	Advance to meet daily calorie adjustments
Protein	1–1.5 g/kg/d	1–1.5 g/kg/d	1–1.5 g/kg/d
Fat	1 g/kg/d	1 g/kg/d	1 g/kg/d
Fluid	800–1000 mL/d	Advance with calories if electrolytes stable and no clinical signs of fluid overload	Advance with calories if electrolytes stable and no clinical signs of fluid overload
Phosphorus	0.3–0.6 mmol/kg/d for normal serum levels; correct low serum levels aggressively with 9–18 mmol over 2–12 h as indicated	0.3–0.6 mmol/kg/d; continue to correct low serum levels as necessary	0.3–0.6 mmol/kg/d; continue to correct low serum levels as necessary
Potassium	2–4 mmol/kg/d; correct low serum levels as necessary	2–4 mmol/kg/d; correct low serum levels as necessary	2–4 mmol/kg/d; correct low serum levels as necessary
Magnesium	0.2 mmol/kg/d; correct moderately low serum levels with 0.5 mmol/kg × 24 h; correct severely low levels with 24 mmol over 6 h	0.2 mmol/kg/d if stable; 0.25 mmol/kg/d for patients who have been hypomagnesemic	0.2 mmol/kg/d
Thiamin	200–300 mg/d	200–300 mg/d	200–300 mg/d until day 10
Other vitamins/minerals	Multivitamin/mineral supplement daily	Multivitamin/mineral supplement daily	Multivitamin/mineral supplement daily

Data from the National Eating Disorders Association,[1] Findley,[2] Konek and Becker,[16] Malone et al,[26] Kraft et al,[28] Itokaiva et al,[29] and Reuler et al.[30]

Micronutrients

Micronutrient deficiencies occur in children with eating disorders. In both anorexia nervosa and bulimia nervosa, zinc deficiency is common and has been documented as resulting from suboptimal intake attributed to severe caloric restriction, the avoidance of red meat, and/or the adoption of an inadequate vegetarian lifestyle.[21] Additionally, deficiencies in riboflavin, thiamin, and other B vitamins as well as calcium and magnesium are well documented and are of concern in both anorexia nervosa and bulimia

nervosa, especially with comorbid drug or alcohol addictions or a history of restrictive nutrient intakes.[16] Routine screening is recommended with subsequent supplementation for anorexic children with thiamin and magnesium deficiencies in addition to any other identified deficiencies.[22] At the onset of intervention, providing a 100% recommended dietary allowance multivitamin with minerals is recommended.[20] Remember to account for any gross deficiencies as evidenced by intake report/history, NFPE, or laboratory data.

Laboratory Assessment

A detailed laboratory assessment is recommended at the time of initial assessment. Although a complete blood count and chemistry profile are recommended, these traditional tests are typically normal and may underestimate the physical damage and degree of malnutrition. Tests are recommended, with an extensive history of restriction, limited nutrient intake like that found in vegan/vegetarian types, co-morbid substance use, and in some cases, trauma or food insecurity to include zinc, iron, 25-OH vitamin D, and thiamin.[23] Other laboratory values recommended for review are an electrolyte panel, glucose (for hypoglycemia or hyperglycemia), magnesium, phosphorus, insulin, calcium, and liver panel.

Children with anorexia often have elevated serum cholesterol and abnormal lipoprotein profiles regardless of prior consumption of extremely low-fat and low-cholesterol diets. Arden et al postulated that mild hepatic dysfunction, decreased bile acid secretion, and/or hypothalamic dysfunction may contribute to these abnormalities. [24]

Nutrition Support in Eating Disorders

Milieu Management

The treatment milieu, when it is set up effectively, provides a safe environment and leads to improved outcomes. The milieu includes the following suggestions:

- Monitor clothing to ensure patients cannot hide food (no hoodies or super baggy clothes).

- Set observation order as the patient may need 1:1 or constant observation as needed.
- Ensure that a room/bathroom precaution (not allowed in room alone) is followed for at least 1 hour post meal or snack; also remove any containers that can hide food or emesis.
- Monitor bathroom if indicated.
- Establish meal and snack timeline (eg, 20−30 min to complete intake).
- Monitor for exercise and emesis in the room, including in showers (emesis, water loading, or exercise in a shower) as well as excessive use of energy such as walking and tensing muscles while sitting or standing.
- Monitor for active fears of eating in front of others as well as food challenges/triggers that hamper intake and may increase anxiety.
- Monitor for maintenance of foodstuffs as needed to ensure the patient does not hand off foods, move them around, hide them in clothes, or throw them away.

The interdisciplinary team's focal point should be providing a unified treatment plan. The team communication paradigm will guide the continuum of care and support the patient and family. Many teams benefit from having members including but not limited to a psychiatrist, medical support specialist, registered nurse, registered dietitian (and registered dietetic technician, as needed), licensed social worker, advanced practice nurse, care manager, teacher, behavioral specialist, occupational therapist, art therapist, music therapy, chaplain, and speech therapist.[2,6,16,34]

Treatment plans for children with an eating disorder should include observation, which is an important part of treatment and includes monitoring social interactions, eating requirements, and independent situations. Seeing how a child with an eating disorder interacts and noting the child's responses and triggers lends valuable insights into the severity of the illness as well as other factors to consider for treatment. The goal is to build a treatment toolbox that will aid the child with an eating disorder in developing strategies toward the remission of symptoms and will treat the mental health aspects of the disorder.

Documentation should be based on evidence and behavior to help advance treatment as well as meet the needs of a clinical review for coverage of treatment. Guidelines differ from region to region and from

country to country. Documentation should include the interventions with family, nutrition education, and cognitive behavioral therapy as well as other therapeutic programs.[4,5]

Nutrition Support Order Set

A general order set is dependent on hospital policies but should include the following:

(a) monitoring intakes and outputs
(b) tracking calories
(c) taking blind weights in gown after void in the morning
(d) restricting physical activity
(e) monitoring lab values
(f) monitoring orthostatic measures
(g) keeping a behavior plan on allotted time for eating
(h) monitoring at meal/snack time
(i) calorie control plan with advancement plan
(j) offering vitamin supplements
(k) offering a supplement replacement plan[2,6]

Oral Nutrition and Meal-Planning Guidelines

In all eating disorders, the ultimate nutrition treatment goals include nonrestrictive eating that incorporates variety and nutrition adequacy and an absence of purging or compensatory behaviors.[25] In bulimia, purging efforts are utilized in attempts to lose weight, and children will often request assistance during treatment to achieve weight-loss goals. Although long-term weight loss may be reasonable and/or recommended, the immediate goal for children with either bulimia or binge-eating disorder should be interruption of the binge or binge-purge cycle with stabilization of weight and health.[1,2,6]

For all eating disorder types, plan 4 to 6 eating opportunities per day. Allow no more than 4 hours between eating opportunities to prevent hypoglycemia, extreme hunger, and/or the temptation to binge.[25] Each meal and snack should contain a balance of sufficient carbohydrates to prevent craving, adequate protein and fat to promote satiety and fluids.[1,2,6]

For children with binge-eating disorder or bulimia, the initial meal plan should not include any foods that the patient is unwilling or unable to keep from vomiting. Provide support to the child during and after meals while encouraging the expression of feelings and use of coping skills. Many patients state that all foods are challenging, but the clinical provider should work with them and create a safe/acceptable list to initiate treatment.[6,16,18] Additionally, encourage the patient to remain out of the bathroom, as well as the bedroom, for up to 1 hour after meal and snack consumption.[25]

Treatment guidelines differ for food avoidance, food challenges, and triggers. Individual programs differ in treatment plan approaches that utilize behavioral specialists, a feeding team, or other ancillary professionals. Exposure therapy and food chaining techniques may also be utilized around food presentation and possible acceptance in treatment and at home.[6,13]

Enteral Nutrition Support and Route of Feeding

The decision to initiate enteral nutrition (EN) in a child with an eating disorder is a complex one and should consider the child's immediate physical and psychological health. EN support is indicated if a patient is refusing any oral intake, rapid weight loss continues despite improved oral intake, or the patient is hypermetabolic and unable to meet nutrition needs orally.[23,26] When choosing a route for EN, the nasogastric route is preferred for the relative ease of administration; as part of the eating plan, however, a nasojejunal placement may alleviate discomfort from delayed gastric emptying.[20] If long-term enteral support is needed, the tube end should be placed in the duodenum to avoid problems with gastric reflux and purging by the patient.[23]

When utilizing EN in a child with an eating disorder, providing the supplementation in a manner that permits identifying natural hunger cues is encouraged. In a patient with bulimia nervosa, continuous drip tube feeding is often recommended because bolus feeding may cause involuntary vomiting and is more easily purged.[20] For anorectic patients, several options are appropriate: bolus feeding appropriate supplemental calories only at mealtimes, bolus feeding only uneaten calories to meet mealtime goal, or nighttime continuous feedings of uneaten or excessive calories.[25]

When EN is utilized, an isotonic, fiber-containing polymeric formula is usually sufficient for nutrition repletion unless impaired digestion or absorption indicates the need for an elemental or peptide-based product. There is a high risk of refeeding syndrome (discussed in the "Refeeding Syndrome" section in this chapter) in an anorectic patient. The initial rate, volume, and advancement may differ per hospital/program, but the *ASPEN Enteral Nutrition Handbook* suggests 25 to 30 mL/h that should be gradually increased 20 to 30 mL every 4 to 8 hours as tolerated until goal feeds are achieved.[25,26] Monitor free water inclusion as well as pulse and blood pressure.

Manipulation behaviors may arise when utilizing EN for a patient with an eating disorder, so precautions need to be taken. Sample behaviors used in tube feeding manipulation include lowering the delivery rate on the feeding pump, unplugging the pump, and using sharp objects to poke holes in the feeding tube.[2,6]

Parenteral Nutrition

Parenteral nutrition (PN) is only indicated in cases of digestive inability because it leads to a continued loss of hunger cues in patients with an eating disorder.[25] Use caution when initiating PN in severely malnourished patients because of the potential high risk of refeeding syndrome. (Refer to the "Refeeding Syndrome" section in this chapter for definitions and guidelines.) Monitoring of laboratory values should be established during treatment, depending on the patient's treatment plan or hospital policy parameters.

Monitoring Nutrition Interventions

The anthropometric status of patients with eating disorders should be assessed and monitored regularly. Rehydration and replenished glycogen stores contribute to weight gain during the initial refeeding; thereafter, weight gain results from increased lean and fat stores.[1,2,23] In hospitalized patients for whom weight restoration is a goal, 2 to 3 lb/wk is reasonable, although lower goals are normal with acute malnutrition, medical crisis, or refeeding.[1,2,7,23]

The hospitalized individual should be weighed daily, gowned, blinded (ie, weighed while turned away from the scale number when indicated in treatment), preprandial, and postvoid, preferably in the morning/same time. For a child with an eating disorder who still has growth potential, baseline height and growth history should be obtained and monitored every 1 to2 months. Baseline anthropometric measurements (skinfolds, midarm circumference, midarm muscle circumference) should be obtained at the onset of intervention and monitored as medically indicated.[14,20]

Refeeding Syndrome

Definition and Incidence

Refeeding syndrome can be described as a cascade of potentially fatal complications caused by shifts in fluids and electrolytes as nutrition is reintroduced into the body, taxing wasted and weakened tissues and demanding more nutrients than are readily available.[26,27] The syndrome is manifested in an assemblage of symptoms that result from rapidly and inappropriately refeeding (via an oral, enteral, or parenteral route) individuals who have been malnourished or starved for a period of time, usually exceeding 7 to 10 days.[28] Additional symptoms of refeeding syndrome include cardiac dysfunction, edema, and neurological changes.[29] Hypophosphatemia is the hallmark clinical sign of refeeding syndrome, but hypomagnesemia and hypokalemia are also common indicators. Glucose intolerance and thiamin deficiency are often present as well.[30]

The exact incidence of refeeding syndrome is unknown, due in part to the lack of a universal definition[26] and there is poor recognition of the condition. It is known that 30% to 38% of previously unfed patients receiving PN containing phosphorus experience hypophosphatemia,[31] and 100% of these patients develop hypophosphatemia when no phosphorus has been added to the PN solution. It has also been documented that when malnourished patients were vigorously refed, 80% experienced hypokalemia, hypomagnesemia, and/or hypophosphatemia.[32]

Pathophysiology and Characteristics of Starvation and Refeeding

In a normal fed state, glucose and fatty acids are the preferred energy substrates for the human body. During periods of starvation exceeding 3 to 5 days, the body shifts glucose metabolism to fat and protein metabolism and enters a state of ketosis. The brain switches from glucose to ketones as an energy source. The liver visceral protein stores and vital organs, adipose tissue, and fluids also become depleted. The wasting of muscle affects vital organ function, including both respiratory capacity and cardiac mass and output.[26,29]

During starvation, the kidneys' role is to decrease the excretion of minerals as the body's stores become depleted. Serum electrolyte levels are maintained by decreased excretion through the kidneys and by volume constriction as fluid shifts from extracellular to intracellular spaces.[26] In addition, because electrolytes (especially phosphorus) play a major role in glucose metabolism, electrolyte demands are diminished during ketosis and starvation.[33]

As nutrition is reintroduced to the body, a rapid spike of insulin accompanies the introduction of carbohydrate, which seems to be the driving force of refeeding syndrome.[1] Insulin promotes the uptake of glucose, water, and electrolytes by the cells, and thus glycogen, protein, and fat synthesis resume. Water and sodium are retained causing extracellular fluid overload, which can lead to pulmonary edema and cardiac decompensation.[27] Hyperglycemia may result from excess carbohydrate administration and inadequate insulin output. Hyperglycemic complications include osmotic diuresis, dehydration, metabolic acidosis, and ketoacidosis.[26] Anabolism is triggered by macronutrient intake, and places demands on the body for a myriad of other nutrients including phosphorus, potassium, magnesium, and water-soluble vitamins. These nutrients are now in short supply after their depletion during the prolonged fasting period, and the body's remaining stores are exhausted quickly.[26] Thus, hypophosphatemia, hypokalemia, hypomagnesemia, and thiamin deficiency may present clinically.

Phosphorous is involved in the intracellular processes and structural integrity of all cells.[26] It is also required for the production of energy in the

form of adenosine triphosphate (ATP) and is a structural component of 2,3-diphosphoglycerate (2,3-DPG).[30] Hypophosphatemia may cause clinical symptoms when serum levels reach 1.5 mg/dL, and severe hypophosphatemia (≤ 1 mg/dL) can have devastating effects on multiple systems.[27] Serum phosphorus levels typically reach a nadir around 2 to 3 days of refeeding.[1] Cardiovascularly, ATP depletion and cardiac atrophy contribute to hypercontractility and ventricular arrhythmia, which is complicated by volume overload. Skeletal muscle weakness and sarcolemmal disruption lead to rhabdomyolysis. Myopathy causes difficulty with ambulation and may additionally contribute to respiratory dysfunction due to accessory muscle and diaphragmatic weakness/catabolism. Hypophosphatemia affects the hemoimmunologic system by inducing bone marrow dysfunction, which can lead to decreased immune function evidenced by hemolytic anemia, thrombocytopenia, hemolysis, and decreased oxygen delivery to peripheral tissue. Hypophosphatemia influences the nervous system via inadequate 2,3-DPG and/or ATP deficiency, which may contribute to the incidence of delirium, coma, hallucinations, seizures, tetany, weakness, and parasthesias.[30]

Hypokalemia may result as anabolism resumes and cells take up potassium during fluid and electrolyte shifts. Serum potassium levels <2.5 mg/dL may cause devastating paralysis, respiratory dysfunction, rhabdomyolysis, muscle necrosis, and changes in myocardial contraction and signal conduction.[27] Serum magnesium levels <1 mg/dL can cause electrocardiographic changes, tetany, convulsions, and seizures.[34]

All vitamins may be deficient as a result of long-term inadequate nutrition intake; however, because of their role in carbohydrate metabolism, thiamin (vitamin B_1) is of particular importance. Thiamin is a structural component of nervous system membranes,[35] and thus its deficiency may present with symptoms of beriberi, such as paresthesia, hypoesthesia, anesthesia, and lower extremity weakness[6]; Wernicke's encephalopathy (ocular abnormalities, ataxia, confusion, hypothermia, coma); or Korsakoff's psychosis (retrograde and anterograde amnesia, confabulation).[36]

Prevention and Therapy

Prevention of refeeding syndrome is the most effective factor in its management; therefore, an awareness and ability to identify high-risk patients is key.[27] Patients with a weight loss of ≥10% within 2 to 3 months or those at or below 70% ideal body weight are at the greatest risk.[27] Categories of patients who may meet these criteria include those with anorexia nervosa, alcoholism, cancer, uncontrolled diabetes, marasmus, malabsorptive syndrome (eg, pancreatitis, cystic fibrosis, short bowel), prolonged fasting, morbid obesity with profound weight loss, body dysmorphia, prolonged antacid use (due to binding of phosphorus), and long-term diuretic use (due to electrolyte losses), as well as postoperative patients, elderly patients, and patients allowed nothing by mouth for longer than 5 to 7 days.[26]

If a patient meets the preceding high-risk criteria for refeeding syndrome, several acceptable approaches exist for preventing or treating refeeding (see Table 17-3). Importantly, baseline electrolytes (including potassium, phosphorus, magnesium, calcium) should be obtained (and corrected if they are low), before feeding is initiated.[1] Depending on the severity of malnutrition, electrolyte monitoring should continue 1 to 4 times per day for the first 3 days.[29] During this time, calories may be introduced at 50% of goal, not exceeding 20–25 kcal/kg/d.[1,26,27,29] Macronutrient distribution should limit carbohydrate intake to 2–3 g/kg/d based on actual body weight. No restriction is necessary for protein or fat intake, and common recommendations for each are 1–1.5 g/kg/d[1,27,29] and 1 g/kg/d, respectively.[1] Fluid should be restricted to 800–1000 mL/d due to the potential risk of fluid overload and cardiac decompensation.[27,29]

During these first few days of renourishment, electrolytes (if low) should be corrected aggressively. Potassium phosphate (preferably) or sodium phosphate in the presence of normal serum potassium can be given intravenously for moderate-to-severe hypophosphatemia.[30] Different references recommend infusing 9 to 18 mmol for a duration of anywhere from 2 to 12 hours.[26,30] For orally fed patients with mild-to-moderate hypophosphatemia, cow's milk is an excellent source of both phosphorus and potassium[30] and can be used to treat mild electrolyte derangements.

Oral sodium phosphate can also be used, at 500 mg 4 times per day until serum phosphorus is stable, then decreased to 250 mg 3 times per day for maintenance.[27] Mild-to-moderate hypomagnesemia can be treated with an initial dose of 0.5 mmol/kg over a 24-hour infusion, then maintained at 0.25 mmol/kg/d for the next 5 days to maintain serum levels.[26] For severe hypomagnesemia, infuse 24 mmol over 6 hours, then follow with 0.25 mmol/kg/d for the next 5 days.[26]

Patients at risk of refeeding should receive a daily multivitamin/mineral supplement and their macronutrients and electrolytes should be monitored closely. Any signs or symptoms of thiamin deficiency can be treated with 200 to 300 mg of oral thiamin daily for 10 days to correct deficiency.[26]

After electrolytes have stabilized and the patient has received ≥ 72 hours of nutrition at 50% of goal, calories can gradually be increased every 3 days by 200 to 300 kcal.[27,29] As feedings progress, continue to monitor and correct electrolytes for the duration of the first 2 weeks of feeding.[26]

With awareness and proper monitoring, refeeding syndrome can be prevented or managed appropriately to prevent serious complications and the potential of death. Monitoring and correction of electrolytes, nutrient supplementation, and conservative carbohydrate and fluid administration can save the lives of those at the highest risk for refeeding.

Behavioral Health Considerations

Consideration of the patient's behavioral health in the nutrition care process is imperative for assessment and treatment. It is important to understand the behavioral health effects on the overall health status and comorbid diagnoses. Therefore, the practitioner should assess for the following:

- comorbid features (as suggested throughout the chapter)
- substance use
- trauma
- economic status
- food insecurity
- thinking errors
- gender/sexual identity

- effects of COVID on health/mental health (physical attributes, smell, taste, appetite, depression, fatigue)
- access to prior treatment, providers, and therapies

Many patients are unable to access treatment because of location/travel. Additionally, some areas experience supply challenges even with the advent of telehealth. Insurance companies continue to put treatment constraints on many patients and families. Some families have complications around general support and the ability for follow-up. Thoughtful provision of nutrition education, counseling, and follow-up has increased success when these barriers are identified as early as possible during treatment.[35]

As part of treatment, it is important to provide support/resources for the patient and family. Addressing cultural needs that may exist around feeding, beliefs about supplemental formulas, or medical procedures; types of foods, family rituals, habits, or status can also improve outcomes of refeeding. Improving the provision of information and offering education to and collaboration with the interdisciplinary team increases positive outcomes and creates a continuum of care.[35]

Conclusion

Disordered eating is a complex treatment modality requiring supportive and thorough assessment, treatment plans, nutrition support, and continuity of care. An interdisciplinary team approach with daily review addressing food acceptance, thinking errors, health/weight parameters, monitoring of orthostatic measures, laboratory values, and behavioral advances are factors for improved outcomes. The patient and family benefit from active and joint treatment and support, including a stable aftercare plan to ensure a continuum of care. Support for both nutrition as well as medical and overall mental health should be included.

Test Your Knowledge Questions

1. Which of the following are common physical signs and symptoms of anorexia nervosa?

A. Lanugo-type hair, cyanosis of the extremities, and erosion of the dental enamel
B. Cyanosis of the extremities, erosion of the dental enamel, and Russell's sign
C. Cachexia, cyanosis of the extremities, and muscle wasting
D. Cachexia, Russell's sign, and sore red throat

2. Which of the following should you do when interviewing an individual with a newly diagnosed eating disorder?
   A. Be judgmental and show no empathy; do not assess physical issues
   B. Be calm, empathic, and nonjudgmental
   C. Establish trust with the patient and offer reassurance; assess for nonverbal information
   D. Both A and C
   E. Both B and C
3. Which of the following describes persons at greatest risk for refeeding syndrome?
   A. Weight loss ≥ 10% within 2 to 3 months or those at or below 70% ideal body weight
   B. Weight loss ≥ 10% within 6 to 8 months or those at or below 70% ideal body weight
   C. Weight loss ≥ 7% within 2 to 3 months or those at or below 75% ideal body weight
   D. Weight loss ≥ 7% within 2 to 3 months or those at or below 70% ideal body weight

References

1. National Eating Disorders Association (NEDA). Accessed July 6, 2022. http://www.nationaleatingdisorders.org
2. Findley, MP. Eating disorders. In: Corkins MR, ed. *The A.S.P.E.N. Pediatric Nutrition Support Core Curriculum*. 2nd ed. American Society for Parenteral and Enteral Nutrition; 2015:275–287.
3. Perez M, Ohrt TK, Hoek HW. Prevalence and treatment of eating disorders among Hispanics/Latino Americans in the United States.

Curr Opin Psychiatry, 2016; 29(6):378–382. https://doi.org/10.1097/yco.0000000000000277

4. American Psychiatric Association. *Practice Guideline for the Treatment of Patients With Eating Disorders*. 4th ed. American Psychiatric Association Publishing; 2023.
5. American Psychiatric Association. Feeding and eating disorders. In: *Diagnostic and Statistical Manual of Mental Disorders.* 5th Ed. (DSM-5-TR) American Psychiatric Association Publishing; 2022:329–354.
6. Stenick, J. *The Eating Disorders Clinical Pocket Guide.* 2nd ed. Snack Time Press; 2013.
7. Stenick, J. *Academy of Nutrition and Dietetics Pocket Guide to Eating Disorders.* 2nd ed. Academy of Nutrition and Dietetics; 2017.
8. Vastag B. What's the connection? No easy answers for people with eating disorders and drug abuse. *JAMA.* 2001;285:1006–1007. https://doi.org/10.1001/jama.285.8.1006-JMN0228-3-1
9. Mahan LK, Escott-Stump S. *Krause's Food, Nutrition, & Diet Therapy.* 11th ed. WB Saunders Co; 2004.
10. Russell GFM. The changing nature of anorexia nervosa. *J Psychiatr Res*. 1985;19:101–109. https://doi.org/10.1016/0022-3956(85)90005-6
11. Patrick L. Eating disorders: a review of the literature with emphasis on medical complications and clinical nutrition. *Altern Med Rev*. 2002;7(3):184–202.
12. Kotler LA, Cohen P, Davies M, Pine DS, Walsh BT. Longitudinal relationships between childhood, adolescent, and adult eating disorders. *J Am Acad Child Adolesc Psychiatry*. 2001;40(12):1434–1440. https://doi.org/10.1097/00004583-200112000-00014
13. Eating Recovery Center Webinar and Materials. Accessed November 30, 2023. https://www.eatingrecovery.com
14. Hamilton C, ed. *Nutrition-Focused Physical Exam: An Illustrated Guide.* American Society for Parenteral and Enteral Nutrition; 2022.
15. The Royal College of Psychiatrists. *Guidelines for the nutritional management of anorexia nervosa*. Published July 2005. Accessed December 15, 2008. https://www.rcpsych.ac.uk/docs/default-source/improving-care/better-mh-policy/college-reports/college-report-cr130.pdf?sfvrsnc4aad5e3_2

16. Konek S, Becker P. *Pediatric Nutrition in Clinical Care.* 5th Ed. Jones and Barrett Learning; 2019:523–548.
17. Winston AP, Jamieson CP, Madira W, et al. Prevalence of thiamin deficiency in anorexia nervosa. *Int J Eat Disord*. 2000;28:451–454. https://doi.org/10.1002/1098-108x(200012)28:4<<451::AID-EAT14>>3.0.CO;2-I
18. Vuillier L, Carter Z, Teixeira AR, Moseley RL. Alexithymia may explain the relationship between autistic traits and eating disorder psychopathology. *Molecular Autism.* 2020;11(63):1–19. https://doi.org/10.1186/s13229-020-00364-z
19. Woosley M. *Eating Disorders: A Clinical Guide to Counseling and Treatment*. American Dietetic Association; 2002.
20. Setnick JS. *The Eating Disorders Clinical Pocket Guide: Quick Reference for Healthcare Professionals*. Snack Time Press; 2005.
21. Mehanna HM, Moledina J, Travis J. Refeeding syndrome: what it is, and how to prevent and treat it. *BMJ.* 2008;336:1495–1498. https://doi.org/10.1136%2Fbmj.a301
22. Tresley J, Sheean PM. Refeeding syndrome: recognition is the key to prevention and management. *J Am Diet Assoc*. 2008;108:2105–2108. https://doi.org/10.1016/j.jada.2008.09.015
23. Da Silva JSV, Seres DS, Sabino K, et al. ASPEN Consensus Recommendations for Refeeding Syndrome. *Nutr Clin Prac*. 2020;35(2):178–195. https://doi.org/10.1002/ncp.10474
24. McCray S, Walker S, Parrish CR. Much ado about refeeding. *Pract Gastroenterol.* 2005;23:26–44.
25. Marinella MA. The refeeding syndrome and hypophosphatemia. *Nutr Rev*. 2003;61:320–323. https://doi.org/10.1301/nr.2003.sept.320-323
26. Malone A, Carney LN, Carrera AL, Mays A. *ASPEN Enteral Nutrition Handbook.* 2nd ed. American Society for Parenteral and Enteral Nutrition; 2019.
27. Yantis M, Velander R. How to recognize and respond to refeeding syndrome. *Nursing*. 2008;38:34–39. https://doi.org/10.1097/01.nurse.0000317679.01914.a4
28. Crosbie C, Sterling W. *How to Nourish your Child Through an Eating Disorder.* The Experiment; 2016.

29. Kraft MD, Btaiche IF, Sacks GS. Review of the refeeding syndrome. *Nutr Clin Pract*. 2005;20:625–633. https://doi.org/10.1177/0115426505020006625
30. Itokaiva Y, Schulz RA, Cooper JR. Thiamine in nerve membranes. *Biochem Biophys Acta*. 1972;266:293–299. https://doi.org/10.1016/0005-2736(72)90144-7
31. Reuler JB, Girard DE, Cooney TG. Wernicke's encephalopathy. *N Engl J Med*. 1985;312:1035–1039. https://doi.org/10.1056/nejm198504183121606
32. Dwyer K, Barone JE, Rogers JF. Severe hypophosphatemia in postoperative patients. *Nutr Clin Pract*. 1992;7:279–283. https://doi.org/10.1177/0115426592007006279
33. Klein CJ, Stanek GS, Wiles CE. Overfeeding macronutrients to critically ill adults—metabolic complications. *J Am Diet Assoc.* 1998;98:795–806. https://doi.org/10.1016/s0002-8223(98)00179-5
34. Turon-Findley, MP. *Healthy Bites Build Better Nutrition in Mental Health and Disorder Eating.* Support Line. Academy of Nutrition and Dietetics; 2022.

Test Your Knowledge Answers

1. The correct answer is **C**. The physical presentation of a person with anorexia nervosa includes lanugo-type hair, muscle wasting, dry skin, cyanosis of extremities, bradycardia less than 60 beats/min, and cachexia. When anorexia develops in childhood, the first clinical sign may be failure to make weight gains while continuing to grow in height as opposed to documented weight loss. Growth charts should be evaluated for typical growth patterns of the individual.
2. The correct answer is **E**. Paramount to good treatment and interventions for a patient with a newly diagnosed eating disorder is gaining trust and assessing cognitive, emotional, and physical parameters in the absence of judgment.
3. The correct answer is **A**. Patients with a weight loss of ≥10% within 2 to 3 months or those at or below 70% ideal body weight are at the greatest risk. Categories of patients who may meet these criteria

include those with anorexia nervosa, alcoholism, cancer, uncontrolled diabetes, marasmus, prolonged fasting, morbid obesity with profound weight loss, malabsorptive syndrome (such as pancreatitis, cystic fibrosis, short bowel), prolonged antacid use (due to binding of phosphorus), or long-term diuretic use (due to electrolyte losses). Additional groups include those with no oral intake for longer than 5 to 7 days, postoperative patients, and older patients.

APPENDIX 17-1. Eating Disorder Case Study 1

NG, a girl who is 16 years and 5 months old, was admitted with a 15-lb weight loss during the previous 4 weeks due to restrictive intake. She describes a usual day's food intake as follows:

Breakfast: 2–3 fruits, 1 cup vegetables, 8–12 oz of coffee

Snack: Vegetables (vague report)

Lunch: Cut-up vegetables, 6 oz of low-fat yogurt, fruit, 2 diet pops

Dinner: 6–8 oz of cod with fat-free butter spray, salad (no dressing)

Snack: Air-popped popcorn

Limited fluid intake throughout the day

NG was 68 lb 2 years ago when her eating issues began. At the time, she was active in dance, ballet, and tennis. She currently has dizziness when standing, fatigue, occasional blurred vision, and hair loss. She passed out in the gym last week and notes a "cold that just won't go away." She is cold "all the time." She has dry skin, and her nails appear brittle. Her hair is falling out "a lot." She has not had a period in 2 months (she is not pregnant per urine test). She implies she sometimes gets "sick" (vomits) at home when alone—the last time was a week ago.

NG's admission weight was 37.7 kg (82.94 lb; <3rd percentile) at 162.5 cm (25th–50th percentile) with a body mass index (BMI) of 14.3 (<3rd percentile). She does not see herself as "too thin," but people tell her that constantly. She is pale and has a 48-point pulse split. She also has infrequent bowel movements. During the interview, she was incessantly swinging her legs and tapping her feet. Results from her laboratory tests are as follows (with normal ranges for comparison): sodium, 131 mEq/L (135–145 mEq/L); potassium, 3.3 mEq/L (3.6–5.0 mEq/L); blood urea nitrogen, 6 mg/dL (7–20 mg/dL); chloride, 111 mmol/L (98–107 mmol/L); glucose, 117 mg/dL (70–110 mg/dL); hemoglobin, 10.8 g/dL (12.1–15.6 g/dL); and hematocrit, 31% (34%–45%) with elevated liver labs.

NG's mother admits to having a negative body image, and NG's grandmother was hospitalized in her 20s for consistently being ill and having poor bone healing. The mother seemed to think she may have had an eating disorder also.

During the interview: Using the interview tree, you establish the previous information on physical signs and symptoms. NG indicates that her mom and grandmother put pressure on her to excel at both ballet and tennis. Mom also demands good grades, and NG sometimes takes pills to stay awake to do homework. Dad is often out of town for work, and NG worries that he will be disappointed in her for poor grades and not dancing well. Her schoolwork has been more difficult lately. NG has been underweight for age as long as 2 years, and she notes "everyone is very thin in my family."

Tentative plan:

- Start menu at 1000 calories with 1200 mL of fluids. Suggest 5 feedings a day. If tolerated, food intake increases 200–250 calories per day.

- Take weight daily in the morning in gown after void, with NG turned away from scale numbers.
- Monitor at mealtime; only allow 20 minutes to eat. Redirect her not to get up or move her legs during meal and snack time.
- Observe her for 1 hour post intake and restrict her from her room and bathroom.

Note that NG has activity restrictions.

- Use a meal/snack supplement replacement if NG does not eat all of her meals/snack/fluids. She has a calorie count, intakes and outputs, orthostatic measures, and reassessment of laboratory values, pulse, and blood pressure each shift. Patient receives a K-Phos packet twice a day.

Long-term treatment: Work with NG on food challenges and concerns. Start cognitive and therapeutic interventions, and work with family during family meetings. Provide support and offer outpatient menu planning for passes and family meal practices. Monitor laboratory values, pulse, blood pressure, weight, and lab values.

APPENDIX 17-2. Eating Disorder Case Study 2

ER, a boy who is 15 years and 6 months old, was admitted with a >20-lb weight loss over the past month due to restricting and excessive exercise. He states his usual day's intake is as follows:

Breakfast: Not eaten lately, but sometimes a handful of nuts

Lunch: Packed lunch with soy milk and a vegan item (vague)

Snack: Sometimes water and another handful of nuts or a fruit

Dinner: Sometimes skips; aunt and uncle try to provide a vegetarian entrée and vegetables

Snack: Sometimes has a protein drink and some soy milk or vegetables

His fluid intake is limited. He noted he adopted a vegan diet about 2 months ago.

He changed his intake to become healthy and get more muscular. He noted he used to be 125 lb. He admits to trying to become muscular and fit after he was "dumped" by a girl at a dance. He is dizzy all the time; has bradycardia, orthostasis, and pallor; and is tired and cold "all the time." Fingernails are down to stubs. Skin is very dry, and he notes his hair falls out. He lives with his aunt and uncle; his dad works 8 hours away and has limited contact, and his mom is in jail.

Admission weight is 48.9 kg (107.8 lb; 10th–25th percentile) at 166 cm (65.4 in; 25th–50th percentile); BMI 17.7 (10th–25th percentile). He doesn't see that he is thin and just wants muscle. Electrolytes were all abnormally low, pulse split was 55 points, glucose was 60 mg/dL, and liver panel laboratory values were abnormal.

Treatment interview intervention: ER was very guarded and needed to slowly review questions because his cognitive understanding was impaired. He was started on 1200

calories with 1200 mL of fluids for 5 feedings with a meal/calorie supplement plan. He had to eat in 20 minutes and was monitored for 1 h post intake. Calorie count, intakes and outputs, and orthostatic measures were assessed during each shift. His diet advancement goal was 200–250 cal/200 mL daily. Fluid goals were set at 2000–2500 mL/d, and the calorie goal was 2500 daily. Weight was measured daily in the morning in a gown, after voiding, with ER turned away from the scale. Exercise was restricted.

Treatment: A lot of effort went into keeping the menu plan vegetarian and working with ER's aunt and uncle about parameters to monitor at home. Family meetings included therapy and trauma work around losses and neglect that ER felt. ER worked on coping skills, positive affirmations, and family interventions. He was encouraged to continue outpatient follow-up and started on a behavior medication for mood and sleep as well as a multivitamin with zinc and K-Phos packets twice a day until laboratory values stabilized.

APPENDIX 17-3. Eating Disorder Case Study 3

B, a 14-year 1-month-old male-female transgender was admitted for suicidal ideation with reported 15-lb weight loss, self-harm, language impairment, depression, and possible autism. Poor intake with reported nausea with eating, some reported emesis when "getting overheated," but denies purging.

Patient states having a high metabolism as well as negative body image for about 3–4 months.

Breakfast: Cereal with milk or chocolate muffin, or donuts on Friday

Lunch: Full school lunch on weekdays with sweet tea (caffeinated); sandwich and sweet tea on weekends

Snack: Chips or popcorn with sweet tea, reports "I love sweet tea"

Dinner: Usually what mom cooks (entrée, 2 sides) or Door Dash; "sometimes" snacks during the night

Patient/she/them changes intake due to increase in nausea when eating possibly due to anxiety over acceptance and body dissatisfaction. Wrapped in blanket and often cold. Good gait and balance although slow pace, hair growing but dull/lackluster, eyes clear, pale inner lids, chapped lips, nails growing, polished, cannot check capillary refill, no tenting of skin, skin pale and dry, limited adipose and muscle stores, limited orbit and temporal stores, limited dental care, tartar and slightly inflamed gums, no cuts on knuckles or corners of mouth, no swelling under eyes or on neck.

Admission weight: 53.8 kg (59% z score +0.23 for bio/cis gender), height: 181.5 cm (99% z score +2.20 for bio/cis gender); BMI: 16.3(>5% z score − 1.43 for bio/cis gender)

Glucose, electrolytes, Ca, lipids, Hgb/Hct are normal.

Treatment interview intervention: Patient guarded initially and reporting negative body image and struggling to acknowledge the effects the disordered eating has on comorbid issues. Due to recent poor intake, patient struggled with some of the interview questions. She was started on 1500 cal with 1500 mL fluids; offered milkshake meal or snack replacements. Monitored intake, out of room for 30 min post intake, monitored orthostatic measures, blinded weight in gown in morning after void. Advanced 200 cal/200 mL every other day as tolerated. Exercise restricted.

Treatment: Key to success was support during meal and snack times in the milieu; patient needed family therapy around identity acceptance and accommodation of social and school needs to decrease anxiety and improve self-esteem. Follow-up in outpatient eating disorders clinic.

Complications: Family struggled with complexity of identity changes and, based on culture and religion, pulled patient against medical advice (AMA) after first family therapy session. A report was made to family services because of AMA; family working with a liaison to start working through treatment and attempt to compromise with patient and their beliefs.

APPENDIX 17-4. Eating Disorder Case 4

AJ, a 14-year 7-month-old male was admitted for autism spectrum disorder (ASD), cerebral palsy, self-harm, and GERD in addition to multiple other medical needs. Poor intake and reported constipation along with chronic low weight. Patient is nonverbal. Has food allergies to beef, milk (although can have foods cooked with regular dairy), and tomato, needing food cut into bite-sized pieces. Some history of emesis without known trigger; no purging noted.

Breakfast: Usually likes cut-up hash browns; will drink almond milk and take some small bites (never a strong meal)

Lunch: Will consume most of entrée and sides with almond milk; likes items dipped in sauces/condiments

Snack: At 3 p.m. and bedtime; softened cereal or soft food items and water

Dinner: Similar to lunch with almond milk or water

Patient intake is difficult to gauge due to limited ability to report needs. Patient has limited food preferences and will become upset and self-harm when given foods or fluids he does not like. Additionally, parents want limited fluids later in the day due to night urination. Limited NFPE due to possible aggression, done with aid of staff; eyes clear, cannot check nail refill or inner lids, pale and dry skin, rash from drool on face and chin, limited muscle and adipose stores, limited orbit or temporal stores, contractor on right hand/wrist, lips chapped.

Current weight: 36.7kg (<1% z score − 2.38); height: 153.7 cm (5% z score − 1.63; old height data point); BMI: unable to calculate due to missing current height data point. No

updated laboratory values.

Treatment interview intervention: Due to patient being aggressive at times and non-verbal, most of the interview was based on staff report, observing at a meal and snack and general observation. Because the true intake was difficult to ascertain, did a calorie count for 3 days. Started commercial supplement at each meal plus almond milk. Monitored for acceptance. When commercial supplement noted as accepted, plans to move to a higher calorie supplement.

Treatment: Due to the complexity of this case and family needs, the team waited for 2 weeks of improved intake of commercial supplement to move to the high-calorie formulation at each meal plus almond milk and preferred foods. Patient presents as ARFID/ASD type along with poor hunger cues. With improved fluid intake and improved bowel regimen, patient began having bowel movements daily. Also, with increased nutrition, patient is more active physically without as much aggression but is still slow to gain weight. Laboratory values normal.

Long-term treatment comments: Patient will be followed in outpatient nutrition clinic while medications for medical and behaviors continue to be worked on. RD suggests a gastrostomy tube if patient does not respond to further therapy due to self-harm.

The author of this chapter appreciates support from the Cincinnati Children's Hospital Medical Center for its continued education and practice opportunities.

18

Food Allergies

Mary Beth Feuling, MS, RD, CSP, CD; Leslie M. Gimenez, MD; Nicole M. Martin, RD, CSP, CD; and Praveen S. Goday, MBBS

Learning Objectives

1. Understand the epidemiology, pathophysiology, and clinical presentation of pediatric food allergies.
2. Describe the nutrition assessment of children with food allergies.
3. Apply nutrition management to children with food allergies.
4. Identify the food-allergy and nonfood-allergy issues that may impact the provision of nutrition support to children with food allergies.

Introduction

Adverse reactions to foods are a rapidly growing public health concern in the Western world. Food allergies are a greater problem in children than in adults, with significant food allergies being associated with poorer nutrition outcomes in children. This chapter discusses the epidemiology, pathophysiology, clinical presentation, management, and prognosis of children with food allergies.

Definitions

Several terms may be used when defining adverse reactions to foods. An abnormal response to a food may include “allergy,” “hypersensitivity,” or “intolerance.” Tolerance usually refers to the ability to consume food that may have the potential for allergy or a food that previously caused allergy and is now consumed without sequelae. Adverse reactions to foods may occur within a spectrum of reactions ranging from immune-mediated (IgE or non-IgE) to non–immune-mediated mechanisms. In general, allergy or hypersensitivity refers to immune-mediated events, and intolerance refers to non–immune-mediated events. Other important definitions that will be used in this chapter are outlined in Table 18-1.

TABLE 18-1. Common Terms Frequently Used With Food Allergies

Term	Definition
Adverse food reaction	Any undesired response to a food regardless of mechanism.
Allergen	A substance foreign to the body that interacts with the immune system and causes an allergic reaction.
Anaphylaxis	An acute, often severe, and sometimes fatal immune response that may affect one or more organ systems.
Antibodies	Immunoglobulins produced in response to an antigen or allergen.
Antigen	Any substance (such as a toxin or enzyme) that stimulates an immune response in the body, especially the production of antibodies.
Atopic dermatitis (eczema)	A disease characterized by chronic inflammation of the skin that is atopic, hereditary, and noncontagious.
Atopy	A tendency toward the development of allergic diseases, determined genetically.
Elimination diet	An eating plan that omits one or more foods suspected of causing an adverse food reaction.
Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA)/Food Allergy Safety, Treatment, Education, and Research Act of 2021 (FASTER)	The laws that govern food allergen labeling in the United States. The 8 most common food allergens (did not include sesame) must be identified on food products. This includes dietary supplements, infant formulas, and imported food products. Raw agricultural products, medications, lotions, and cosmetics are excluded from this law. The FASTER Act identified sesame as a major food allergen and required it to be identified on food labels beginning January 1, 2023.
Food allergy (hypersensitivity)	An adverse food reaction mediated by an immunologic mechanism; the reaction occurs consistently after consumption of a particular food and causes functional changes in target organs.
Food challenge	Administration of food in increasing amounts to establish whether a patient is orally tolerant. This may be performed in an open, single-blind, or double-blind fashion.
Food and symptom diary	A subjective tool for recording food and drink consumed and onset, intensity, and duration of symptoms.

Term	Definition
Food intolerance	An adverse reaction to a food caused by toxic, pharmacologic, metabolic, or idiosyncratic reactions to the food or chemical substances in the food.
Mast cells	Tissue cells that release histamine and other mediators that cause allergic symptoms.
Skin prick test	A test in which an antigen is applied directly to the skin and is pricked with a specifically designed device. The localized histamine and mediator release correlates to the presence of allergen-specific IgE.
Tolerance	Ability to consume food that may have the potential for allergy or a food that previously caused allergy and is now consumed without sequelae.
Top food allergens	Top 8 food allergens are cow's milk, soy, egg, wheat, fish, shellfish, tree nuts, and peanut (referred to as the top 6 food allergens when fish and shellfish as well as peanuts and tree nuts are considered together instead of separately). With the addition of sesame, there are now 9 top food allergens.

For many clinicians, defining a food reaction as "IgE mediated" or "non-IgE mediated" has great utility. IgE-mediated reactions are well understood and chemically described as a cascade of events arising from mast cell or basophil degranulation at mucosal surfaces or the skin. Because IgE can be quantitatively measured, levels of a food-specific IgE antibody may aid in the diagnosis of IgE-mediated food allergy, and serial food-specific IgE levels may be followed to help determine the development of clinical tolerance.

Food intolerance is a nonimmunologic reaction due to the effects of other components within food (eg, lactose, seafood toxins, or naturally occurring pharmacologically active compounds such as tyramine). These substances may cause an adverse reaction, but they are differentiated from true food allergy because they do not involve the IgE cascade.

Gastrointestinal diseases related to foods may also be caused by IgE and non-IgE immune-mediated mechanisms. Some diseases such as

eosinophilic esophagitis (EoE) may have both an IgE and a non-IgE immune component. These diseases are characterized in Table 18-2.

TABLE 18-2. Clinical Food Allergy Syndromes Associated With IgE or Non-IgE Immune-Mediated Mechanisms

IgE-Mediated Syndromes	Mixed IgE and Non-IgE Immune-Mediated Syndromes	Non-IgE Immune-Mediated Syndromes
Oral allergy syndrome	Eosinophilic esophagitis	Protein-induced enterocolitis
		Allergic proctocolitis
Anaphylaxis	Eosinophilic gastritis	Protein-induced enteropathy
Urticaria	Eosinophilic gastroenteritis	Food protein–induced enterocolitis syndrome
Angioedema	Atopic dermatitis	Dermatitis herpetiformis, celiac disease
		Heiner syndrome (pulmonary hemosiderosis)

Epidemiology

The prevalence of food allergies has increased in the last few decades in the United States and other parts of the world. It is estimated that about 8% of children in Western countries have an IgE-mediated food allergy.[13] In a 2015–2016 U.S. household survey with 38,408 responses for children, the overall estimated prevalence of IgE-mediated food allergy was 7.6%. About one-third of the children with a convincing food allergy did not have a physician-confirmed diagnosis. Typically, these children are from families earning less than $50,000/y. Even in those with physician-diagnosed food allergy, the study found the diagnosis is often not complete and may exclude additional reported food allergies. The highest prevalence is in infancy and childhood, with 2.8% in infants under 1 year and a peak of 10% in children 2 years of age. The prevalence decreases to 7.1% in adolescents ages 14 to 17 years.

In approximately 50% of children with food allergies who are <1 year old, cow's milk is the most common food allergy. Among children ages 6 to

10 years, peanut surpasses cow's milk in allergy prevalence. By early adolescence, tree nut and shellfish allergies also exceed cow's milk allergy in prevalence.[2,4] Other studies from Europe and the United States reported the prevalence rate of tree nut allergy to be less than 2%. The rate of fish allergy varies from 0% to 7%, and the rate of shellfish allergy varies from 0% to 10.3%.[3] As the prevalence has increased, so has the number of hospitalizations for food-induced anaphylaxis. A study by Pousell et al shows that foods cause 37% of intensive care unit admissions for anaphylaxis and 79% of recurrent anaphylaxis.[1]

A significant rise in atopic conditions has also occurred in Western countries during the last few decades. The NHANES III (1988−1994) study, which measured the prevalence of positive allergy skin prick test (SPT) responses to common food and nonfood allergens in the U.S. population from 1988 to 1994, showed a significant rise in SPT reactivity compared to the NHANES II (1976−1980) study Another study using stored sera, however, found that sensitization to common food allergens did not increase from NHANES III to NHANES 2005–2006 in subjects ages 6 to 19 years.[6] Interestingly, Hispanic children had a lower prevalence of food allergy (3.6%) compared with non-Hispanic White and non-Hispanic Black children.[7]

Children with food allergies are more likely to have other allergic conditions, including asthma and atopic dermatitis, compared to children without food allergies. Asthma has been reported in 29% of children with food allergies (vs 12% of children without food allergies); respiratory allergy is noted in over 30% of children with food allergies (vs 9% of children without food allergies), and eczema is present in 27% of children with food allergies (vs 8% of children without food allergies).[5] Patients with peanut allergy have asthma and atopic dermatitis prevalence rates of 46% and 50%, respectively.[8] Moreover, several studies have indicated that food allergy may be a risk for problematic asthma, and asthma may be a risk for severe or fatal food allergy.[9] A 2011 study found that 30.4% of children with reported food allergy have multiple food allergies.[10]

Other reported risk factors for food allergy offer new insights. The 2005–2006 NHANES found that vitamin D levels of <15 ng/mL compared with >30 ng/mL were associated with an increased risk of peanut

sensitization.[12] However, not all studies support this theory.[11] Many studies implicate the following risk factors in food allergy development: atopic dermatitis, the Western diet, delayed introduction of specific foods, and low microbial exposure (eg, small families, limited animal exposure, frequent antibiotic use).[3]

Pathophysiology

The production of IgE antibodies may occur in the genetically predisposed individual through mechanisms that involve multiple factors. Once allergen-specific IgE is produced, binding to the high-affinity IgE receptor that is present in mast cells and basophils occurs. Low-affinity IgE receptors are present in eosinophils, monocytes, and macrophages.[18]

Multiple host, antigen, and allergen factors may be involved in the IgE-sensitization cascade, which may result in the subsequent development of clinical allergy. These factors include the host genetics, immunologic competence at the mucosal level, and allergen presentation by intact antigen-processing cells, as well as the route of exposure to the allergen. Sensitization is defined as the production of specific IgE to food allergens. Sensitization may occur via ingestion, inhalation of airborne residue (eg, steam droplets carrying antigen), or by skin contact. There is increasing evidence that early life allergen exposure through the skin causes food allergy.

Early-onset severe atopic dermatitis markedly increases the risk of food allergy.[19] In atopic dermatitis, the breakdown in the epithelial barrier facilitates early food allergen exposure through the skin that can lead to sensitization. In the sensitization phase, specific resident dendritic cell subsets capture allergens in the skin, airway, or gut and transport allergens to draining lymph nodes, where they are processed and presented to naïve CD4+ T cells. The T cells differentiate into allergen-specific CD4+ T cells producing cytokines favoring the B-cell isotype class switch to specific IgE. As B cells mature, they differentiate into plasma cells and produce large amounts of allergen-specific IgE, which bind to high-affinity FceRI receptors on mast cells and basophils.[19]

In the effector phase, IgE-mediated degranulation of effector cells occurs after the food allergen contacts the food-specific IgE antibodies. Cross-linking of the IgE antibodies present on the surface of these cells results in mediator release of histamine, leukotrienes, and prostaglandins. These mediators cause the clinical manifestations of immediate hypersensitivity reactions, including pruritus, vasodilatation, smooth muscle contraction, mucus production, and inflammatory cell recruitment to tissues.[19]

The allergenic properties of foods may be affected by product processing (eg, heating or enzymatic digestion), which may alter the antigenic epitope conformation. This alteration may render a food more or less allergenic. Studies have observed that 73% of children with cow's milk–allergy were able to tolerate baked cow's milk and 64% of children allergic to egg could tolerate baked egg.[20,21] The allergen threshold dose, which is the dose that triggers a systemic allergic reaction in the host, involves many factors and is an area of current research interest.

Major Food Allergens

Almost every major food allergen identified is a protein or glycoprotein. These allergens tend to resist denaturation by heat or acid and may be common depending on the society or ethnicity of the population observed. In the United States, milk, soy, egg, wheat, peanut, tree nuts, fish, shellfish, and sesame are the top 9 most common allergens.[18] However, poppy seeds, sunflower seeds, pine nuts, some spices, and other legumes are increasingly important allergens because allergies to them are becoming more prevalent.

Clinical Presentation

IgE-Mediated Diseases

The major IgE-mediated allergic diseases are oral allergy syndrome, anaphylaxis, urticaria, and angioedema.

The pollen-associated oral allergy syndrome, or pollen food allergy syndrome, presents with pruritus of the lips, palate, tongue, and oropharynx following oral mucosal contact with fresh fruits and vegetables.[13] The reaction usually does not occur following a cooking process because the

cross-reactive allergen is very heat-sensitive. These symptoms usually resolve without treatment and generally do not become systemic. Cross-reactivity between plant pollens and fruits is responsible for the clinical syndrome. Specifically, patients with ragweed sensitivity may have these symptoms after ingesting watermelon, cantaloupe, banana, or honeydew melon, while patients sensitive to birch pollen may notice symptoms with apple, pear, celery, carrot, or peach.

Food-induced *anaphylaxis* is the most severe form of immediate hypersensitivity reaction and symptoms may include hypotension; urticaria; angioedema; respiratory compromise (including laryngeal edema); and gastrointestinal symptoms of pain, vomiting, and diarrhea; however, it can occur without any skin manifestations. Near-fatal and fatal reactions often occur in patients between the teenage years and the 35-year age range and are associated with a history of asthma, accidental ingestion of a known allergen, and delayed epinephrine administration. Peanut, tree nut, or seafood are the usual implications.[22]

Food allergy to mammalian meat (ie, beef, pork, lamb) has been described and allergic symptoms, including anaphylaxis, typically occur 2 to 6 hours after the meat is ingested instead of immediately. Mammalian meat food allergy has been linked to IgE sensitization to the carbohydrate galactose-α-1,3-galactose rather than allergenic protein. The route of sensitization appears to be from tick bites.[11]

Mixed IgE and Non-IgE Immune–Mediated Diseases

The gastrointestinal eosinophilic disorders listed in Table 18-2 have features that may best be described as mixed IgE and non-IgE disorders. Evidence of IgE may be present (eg, positive SPTs or serologic in vitro IgE to the offending food), but other mechanisms may be involved. These disorders are characterized by eosinophilic infiltration of the esophageal, gastric, or intestinal mucosa. These patients often present with vomiting, abdominal pain, weight loss, or malnutrition. Diagnosis is confirmed by endoscopic examination and biopsy. EoE is discussed in the “Eosinophilic Esophagitis” section of this chapter.

Non-IgE Immune–Mediated Diseases

Efforts to define the mechanisms underlying the non-IgE immune–mediated diseases listed in Table 18-2 have shown varying results. These conditions are thought to be caused by other immunologic mechanisms not involving IgE. Typical symptoms may include recurrent vomiting or diarrhea. In infancy, this is most commonly related to cow's milk or soy protein. This condition, called *food protein–induced enterocolitis syndrome* (FPIES), is discussed in detail in the "Food Protein–Induced Enterocolitis Syndrome" section of this chapter.

Allergy Testing

Allergy SPT is commonly used by allergist-immunologists to determine the presence of IgE in specific foods. Clinical correlation of the patient's history to the testing results is important. The skin prick technique is highly reproducible, and extracts for these tests are commercially available for hundreds of airborne and food allergens. These tests are performed by applying the extracts by a prick or puncture technique to the palmar surface of the forearm or upper back. The allergy prick test is a localized mediator-release phenomenon that occurs following allergen presentation to skin mast cells. The reaction is a nearly immediate wheal-and-flare reaction characteristic of IgE-mediated allergy.

The test is read within 20 minutes and correlates closely with the presence of specific IgE to the suspected allergen. Positive tests indicate the presence of IgE or sensitization but not clinical reactivity, with an estimated false-positive rate of approximately 50% if used for screening or with a low pretest probability of IgE food allergy based on clinical history. In children with a history of previous reactions, mean wheal size cutoffs with a 95% positive predictive value have been established for peanut, egg, milk, and fish, which can increase the specificity of SPT.[1,3,23] A negative test has a high negative predictive value of nearly 95%, thus excluding the role of IgE.[24]

Radioallergosorbent tests (RASTs) are the first in-vitro blood tests for determining allergen–specific IgE (sIgE) with close correlation to SPT results. Like SPT, a positive sIgE indicates sensitization or IgE presence but

not clinical reactivity, with similar false-positive rates if used for screening. Undetectable values of sIgE are associated with a low risk (10%–25%) of reaction to the food, while the risk increases with a rise in the levels of sIgE.[3]

The ImmunoCAP system (fluorometric enzyme immunoassay) improved the sensitivity and predictive value of diagnosing clinical allergy. ImmunoCAP was studied with food challenge results and yielded a >95% predictive value for reactions to peanut, egg, and milk for children with a previous reaction. A small number of false-negative ImmunoCAP tests occurred for peanuts.[25] A recent study defined sIgE thresholds that had a positive predictive value (PPV) >95% for almond, cashew, egg, milk, peanut, pecan, walnut, and wheat.[26]

Clinicians can use established values to determine when a food challenge may be safe to perform for a patient with IgE-mediated food allergy.[25] More tests are being developed that can offer greater specificity and aid in diagnosing food allergy without the need for a food challenge. Determination of specific IgE to a single allergen, known as component-resolved diagnosis is a major area of investigation. Researchers are trying to use this test to better distinguish sensitization to food from clinical allergy.[9,27]

In component testing, IgE binding to various, specific protein components of an allergen is measured. Studies have addressed the utility of component testing for allergies to egg, milk, wheat, soy, fruits, hazelnut, cashew, walnut, pistachio, pecan, almond, Brazil nut, and peanut.[26,28] Peanut allergy has had the most attention. IgE specific to peanut seed storage proteins (Ara h2, Ara h1, Ara h3, and Ara h6) are more predictive of peanut allergy, with Ara h2–specific IgE documented to have greater predictive performance for the peanut-specific IgE.[29] Hazelnut components Cor a 9 and Cor a 14 are associated with systemic reactions.[26]

Epitope-specific IgE is a new diagnostic technique under research. There are specific regions or epitopes on allergens for which IgE binding seems to have more clinical relevance and prognostic value. Most of the studies have investigated the epitope of cow's milk and peanut. Further studies are needed to identify relevant epitopes and develop and validate diagnostic and prognostic algorithms for each food allergen.[30]

The basophil activation test (BAT) could improve diagnostic accuracy in children with equivocal SPT and sIgE. Basophil exposure to allergens cross-links the surface IgE, leading to basophil activation and the release of inflammatory mediators. In peanut allergy, BAT has been shown to identify clinically reactive versus tolerant individuals.[29] BAT to peanut indicated 96% and 100% specificity in a discovery and validation cohort, respectively.[26] BAT to milk, egg, sesame, and other tree nuts have shown improved sensitivity and specificity. Diagnostic cutoffs with PPVs ranging from 75% to 100% have been published. The BAT is not yet available in most clinical settings and further studies on standardization are needed.

Management

Currently, no cure exists for food allergies. Strict avoidance of allergy-causing foods is the only way to prevent a reaction. A proactive approach under investigation is immunotherapy, which involves gradual increments of exposure to the allergenic food to develop tolerance. There are 3 major forms of immunotherapy: oral, sublingual, and epicutaneous. Most food allergy immunotherapy has been focused on peanut, cow's milk, and egg. Peanut oral immunotherapy (OIT) has shown high efficacy in achieving desensitization. Palforzia is the first OIT for peanut allergy that is approved by the U.S. Food and Drug Administration (FDA). Trials demonstrated that 67.2% of Palforzia recipients tolerated 600 mg of peanut protein compared to 4% on placebo.[18,31] Peanut OIT is not a cure but does offer protection against accidental peanut ingestion and improves quality of life.[32] Disadvantages of peanut OIT include frequent side effects and risk of anaphylaxis, especially during the initial dose escalation. Sublingual and epicutaneous immunotherapy have a better safety profile, but their efficacy is lower than peanut OIT.[33] Combining oral immunotherapy with anti-IgE monoclonal antibody therapy may further facilitate desensitization.[28] Additional trials evaluating efficacy and safety are needed to clarify the potential of these therapeutic strategies.

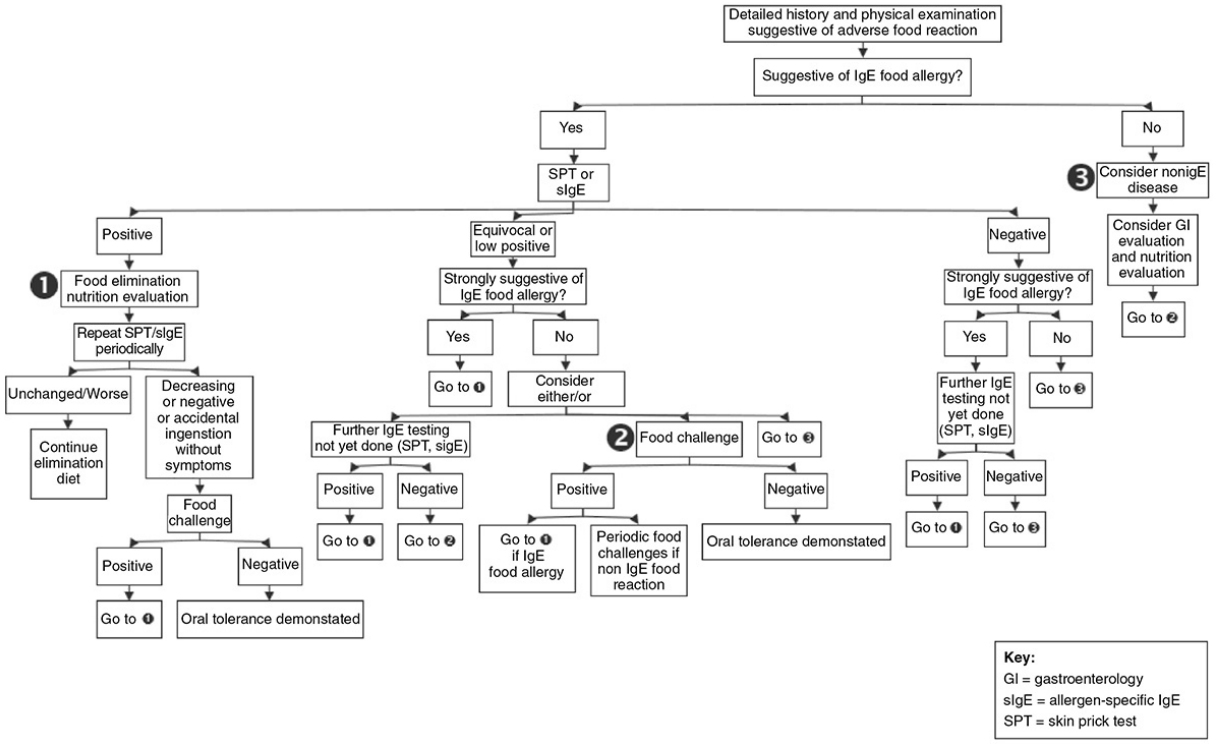
Exclusion of foods may lead to nutrition problems that require the expertise of a qualified dietitian. All patients with anaphylaxis to foods (or other allergens) and patients with severe food allergies should be educated

regarding the use of injectable epinephrine, which can be lifesaving in the event of accidental exposure. All children with multiple food allergies should be co-managed by an allergist and a dietitian as recommended by the national guidelines for the management of food allergy in the United States.[34] Because avoidance is the only proven treatment,[35] children with food allergies need to avoid the foods to which they are allergic. Thus, dietitians have 2 goals: (1) provide families and patients with guidelines, education, and suggestions for avoiding allergenic foods, and (2) monitor the child to ensure a nutritionally adequate diet is followed that will promote appropriate weight gain and growth. Optimally, a multidisciplinary approach is adopted in conjunction with the allergist with

- accurate diagnosis of causative foods,
- assessment of nutrition status,
- institution of a diet that eliminates the offending foods (elimination diet),
- prevention of adverse reactions,
- development of proper emergency treatment with an "action plan" in place, and
- treatment of associated atopic disorders.

There should be ongoing care by both the allergist, who periodically determines whether the child has developed tolerance to any of the offending foods, and the dietitian, who continues to monitor the nutrition status and growth of the child. Figure 18-1 proposes an algorithm for managing children with food allergies.

FIGURE 18-1. Algorithm for the Evaluation of Suspected Food Reactions



Food Allergy Prevention

Preventing the development of food allergy is a topic of great interest. Of the known modifiable risk factors for food allergy, research is actively focused on controlling atopic dermatitis and timing of the introduction of solid foods.[15] Based on the evidence that sensitization occurs through the skin, a pilot study demonstrated a trend toward a reduction in atopic dermatitis and food sensitization in infants treated with trilipid emollient therapy for 6 months.[36] A retrospective study conducted in 2019 indicated that early (<4 mo) versus later (>4 mo) proactive use of topical steroids in infants with atopic dermatitis resulted in a 45% reduction in food allergy at 2 years of age.[37] In contrast, 2 large randomized control trials in 2020 using a preventative emollient did not have a significant effect on the prevention of atopic dermatitis for food allergy.[19] This lack of effect may be partially explained by the age at which emollients were applied and the rate of adherence

Delayed food introduction may increase the risk of food allergy.[16] In general, it is recommended that complementary foods be started at 4 to 6 months of age, including potentially highly allergenic foods.[17] Once a few typical complementary foods have been tolerated, it is suggested that highly allergenic foods be introduced one at a time at home. The Learning Early About Peanut study showed that early consumption of peanut in high-risk infants (with severe eczema and/or egg allergy) reduced the development of peanut allergy by 86% by 5 years of age.[39] The benefits of early peanut introduction persisted after 12 months of cessation of peanut consumption in a follow-up study. Based on these findings, updated guidelines endorsed by the American Academy of Pediatrics outline a new approach to reducing the risk of peanut allergy[40] (see Table 18-3). The EAT study reviewed the early introduction of several food allergens (eg, peanut, egg, cow's milk, sesame, white fish, and wheat) in the general population,[41] and the data leaned toward significance in peanut and egg allergy prevention.

TABLE 18-3. Early Peanut Introduction Guidelines

Infant Criteria	Recommendations	Earliest Age of Peanut Introduction
Severe eczema, egg allergy, or both	• Strongly consider evaluation by sIgE measurement or SPT and, if necessary, an OFC • Based on results, introduce peanut-containing foods	4–6 mo
Mild to moderate eczema	Introduce peanut-containing foods	Around 6 mo
No eczema or any food allergy	Introduce peanut-containing foods	Age-appropriate and per family preferences and cultural practices

Breastfeeding provides many health benefits for both mother and child. However, it is not certain whether exclusive breastfeeding for any length of time offers protection against food allergy development. For high-risk

infants who are not exclusively breastfed, the use of hydrolyzed formula might offer some protection against allergic disease. However, these effects appear weak and are generally limited to the development of atopic dermatitis.[42] In a study of breastfed newborns, Sakihara et al found that concomitant daily ingestion of at least 10 ml of cow's milk formula between 1 and 2 months of age prevents cow's milk allergy development.[42]

Nutrition Assessment

Restricting a child's diet in response to a food allergy diagnosis may severely impact the child's nutrition intake. Along with providing guidelines for a comprehensive nutrition assessment, this section offers a practical approach to identifying the risk factors that can lead to nutrition deficiencies, undernutrition, and poor growth.

Because strict avoidance of the causative food is necessary, clearly defining the avoidance list is critical. The nutrition risk increases as the number of foods to be avoided increases, which compounds the challenge of providing a nutritionally complete diet. Any additional problems associated with feeding further exacerbate the risk. Collaboration among the dietitian, allergist, and the family is crucial to clearly define the foods to avoid and prevent any unnecessary restrictions. Exhibit 18-1 outlines methods that can be used to ascertain the degree of nutrition risk.

EXHIBIT 18-1. Important Questions for Determining the Degree of Nutrition Risk in Children With Food Allergies

1. **How many foods need to be avoided?**
   Risk increases with more foods being/needing to be avoided
2. **What is the impact on nutrients?**
   Risk increases with more of the following nutrients being impacted or fewer nutrients being severely impacted
   - Calories
   - Protein
   - Fat
   - Micronutrients

3. **Are there other concerns about food intake?**

   Risk increases with other medical and psychological diagnoses affecting intake, such as the following:

   - Swallowing/chewing difficulties
   - Feeding disorder associated with a concurrent medical condition, sensory food aversion, or lack of appetite, which results in low volume and/or limited variety of food intake

---

When a food allergy has been diagnosed, medical nutrition therapy with scheduled follow-up visits can provide a way to monitor the overall health effects of food elimination. Identifying individuals at risk may protect and possibly improve the patient's nutrition and overall health status. Medical nutrition therapy that provides appropriate food substitutions and resources allows patients with food allergies to focus on improved nutrition self-care and avoidance of food allergens.[43]

Caregivers of children with food allergy often experience significant anxiety, which affects the quality of life for both the child and the entire family. These anxieties may in turn lead to avoidance of nonallergenic foods and, potentially, a pediatric feeding disorder. Referrals to other specialists (eg, speech-language pathologists, gastroenterologists, psychologists, occupational therapists) or a team of interdisciplinary specialists may be necessary to address concerns related to food intake.

Table 18-4 provides a case scenario presenting 3 toddler diets. The first diet is a typical unrestricted diet. For a toddler diagnosed with milk, egg, and peanut allergies, the second diet imposes a high risk for malnutrition and micronutrient deficiencies. The third diet provides vital food substitutions (for the foods that the child must avoid) to ensure adequate nutrition.

TABLE 18-4. Case Scenario

Diet 1			Diet 2[a]			Diet 3		
Breakfast	**Lunch**	**Dinner**	**Breakfast**	**Lunch**	**Dinner**	**Breakfast**	**Lunch**	**Dinner**
Whole milk	Whole milk	Whole milk	~~Whole milk~~	~~Whole milk~~	~~Whole milk~~	Enriched soy milk	Enriched soy milk	Enriched soy milk
Fortified breakfast cereal	Peanut butter and jelly sandwich	Meatloaf	Fortified breakfast cereal	~~Peanut butter and jelly sandwich~~	~~Meatloaf~~	Fortified breakfast cereal	Sunflower seed butter and jelly sandwich	Milk-free, egg-free meatloaf
Banana	Cooked carrots with butter	Peas	Banana	Cooked carrots ~~with butter~~	Peas	Banana	Cooked carrots with milk-free margarine	Peas
	Strawberries	Mashed potatoes		Strawberries	~~Mashed potatoes~~		Strawberries	Mashed potatoes made with chicken broth
		Roll with butter			~~Roll with butter~~			Milk-free roll with milk-free margarine
Snack	**Snack**	**Snack**	**Snack**	**Snack**	**Snack**	**Snack**	**Snack**	**Snack**
Granola bar	Yogurt drink	Ice cream	~~Granola Bar~~	~~Yogurt drink~~	~~Ice cream~~	Graham crackers	Soy yogurt	Soy ice cream
Juice	Chocolate chip cookie	400 IU vitamin D	Juice	~~Chocolate chip cookie~~	400 IU vitamin D	Juice	Milk-free, egg-free, and peanut-free chocolate chip cookie	400 IU vitamin D
Nutritional Analysis of Diet 1			**Nutritional Analysis of Diet 2**			**Nutritional Analysis of Diet 3**		
Nutrient		**% Goal[b]**	**Nutrient**		**% goal[b]**	**Nutrient**		**% goal[b]**
Calories	1420 kcal	>100	Calories	232 kcal	25	Calories	1425 kcal	>100
Protein	46 g	>100	Protein	5 g	41	Protein	43 g	>100
Fat	52 g	32% of total calories	Fat	2 g	6% of total calories	Fat	51 g	32% of total calories
Calcium	955 mg	136	Calcium	94 mg	13	Calcium	920 mg	132
Vitamin D	615 IU	103	Vitamin D	420 IU	70	Vitamin D	547 IU	91
Iron	10 mg	146	Iron	6 mg	89	Iron	12 mg	181
Zinc	6.4 mg	213	Zinc	3 mg	100	Zinc	4.9 mg	165

[a] Strike-through text indicates that these foods are eliminated because of the child's allergies.

[b] Based on recommended dietary allowance for age.[30]

Diet 1: Sample menu for an 18-month-old child before diagnosis of food allergy.

Diet 2: Nutritionally depleted sample menu for the same child who has been diagnosed with milk, egg, and peanut allergies.

Diet 3: Revised nutritionally adequate menu with acceptable food substitutions for the child.

Nutrient intake needs change over time and throughout the life cycle. These changes include macronutrient, micronutrient, and fluid needs, all of which play a key role in a developing child. Nutrient requirements for infants and children with food allergies are the same as the requirements for other children. Occasionally, they require increased energy intake to

provide catch-up growth due to poor growth often associated with allergen–necessitated diet restriction. In addition, children with moderate to severe atopic dermatitis may have higher energy and protein needs based on the degree of skin involvement. Other nutrition needs may arise for children who face medical complexities beyond food allergies.

Clinical and Laboratory Assessment

Studies have shown that nutrient intake and growth are affected in children with food allergies. Children with food allergies have lower height and weight than children without food allergies.[44] Specifically, children with more than 2 food allergies have a lower height, weight, and body mass index than those with 1 food allergy, and children with 3 or more food allergies are smaller than children with 2 or fewer food allergies.[44,45] Children diagnosed with food allergies often have poor growth because of a lack of caregiver knowledge about nutrition needs, inadequate intake because of a lack of guidance for substitutions to meet nutrition needs, and increased anxiety associated with feeding. Failure to achieve normal growth rates or growth velocity indicates the need for medical nutrition therapy.

A multidisciplinary approach involving a dietitian at the time of food allergy diagnosis may prevent or attenuate problems associated with growth. Accurate anthropometric data and the use of growth charts are critical for evaluating these children. Based on the patient's diet and feeding history, clinicians must review the risk of micronutrient deficiency. Table 18-5 summarizes the micronutrients found in the top 9 allergens and lists common food substitutions.

TABLE 18-5. Key Micronutrients of Common Food Allergens and Alternative Food Substitutes

Allergenic Foods	Micronutrients Provided	Appropriate Food Substitutes
Milk[33]	Vitamin A, vitamin B1, vitamin B2 (riboflavin), vitamin B12, vitamin D, vitamin B5 (pantothenic acid), calcium, magnesium, selenium, zinc, potassium, phosphorus	Meats, legumes, whole grains, nuts, mushrooms, fortified foods/beverages (fortified with B vitamins, calcium, and vitamin D), fish, bright yellow and orange vegetables
Egg	Vitamin B12, vitamin B2 (riboflavin), vitamin B5 (pantothenic acid), biotin, selenium, iron, folic acid, vitamin E, chromium	Meats, legumes, beans, lentils, whole grains, nuts, leafy green vegetables, fish, dried fruit
Soy	Thiamin, vitamin B2 (riboflavin), pyridoxine, folic acid, calcium, phosphorus, magnesium, iron, zinc	Meats, legumes, enriched whole grain bread products, egg, nuts, peas, seeds, milk, dried fruit
Wheat	Thiamin, vitamin B2 (riboflavin), niacin, iron, zinc, selenium, chromium, folic acid if fortified	Alternative fortified grains (barley, rice, oat, corn, rye, quinoa, amaranth, farina), soybean, legumes, egg, milk, nuts, seeds, apples, banana, spinach, potatoes
Peanut/tree nut	Vitamin E, biotin, copper, folic acid, niacin, magnesium, manganese, chromium	Whole grains, vegetable oils, soybean, egg, other legumes
Fish/shellfish	Vitamin B6, vitamin E, niacin, phosphorus, selenium, omega-3 fatty acids, folic acid, copper, zinc, potassium, vitamin A	Fortified whole grains, meats, oils, soybean, seeds, nuts, milk, egg
Sesame	Vitamin B1, phosphorus, iron, magnesium calcium, manganese, copper, zinc	Meat, legumes, whole grains, milk, nuts, mushrooms, fortified foods/beverages (fortified with B vitamins, calcium), fish, mussels, wheat germ, tofu, sweet potatoes, brown rice, lima beans, chickpeas, spinach, pineapple

Many children with multiple food allergies are at high risk for inadequate intake of essential amino acids and essential fatty acids. Refer to Chapter 5 ("Protein Digestion, Absorption, and Metabolism") and Chapter 4 ("Fats") for a complete discussion of the goals for the pediatric population. Often, protein hydrolysate–based and/or amino acid–based (elemental) formulas can supplement the diet to meet these nutrition needs. Patients who present after being on prolonged significantly restricted diets without concomitant multivitamin-multimineral use and patients who present with significant malnutrition should be considered for laboratory testing for micronutrient adequacy. The clinical scenario should guide which laboratory tests are obtained (eg, a vegetarian child who is sustained on rice milk should be tested for anemia and zinc, essential fatty acid, and vitamin D deficiencies if the rice milk is not enriched). Most patients in the United States with minimal dietary restrictions can be managed without laboratory testing through judicious use of a multivitamin-multimineral supplement and careful food/beverage intake goals.

Nutrition Intervention

Education including information on dietary avoidance and resulting nutrition deficiencies provides families and patients a pathway to success with an elimination diet. In addition, it encompasses patient-specific nutrition goals for avoiding nutrition consequences of food allergies.[46] The family and patient must also be educated about resources for obtaining further information regarding living with food allergies (eg, how to prepare allergen-free foods, support groups, local retail establishments that sell allergen-free foods, tips for management at daycare and schools, cookbooks, food-labeling laws, and other helpful tips for the elimination diet).

A list of food allergy resources is provided in Table 18-6. Each caregiver of a child with food allergies must be given a list of food substitutions to be successful with strict avoidance of the food allergens. In addition, a nutritionally complete formula or beverage, if possible, should be recommended. This type of information assists the patient and family/caregivers in living a normal and well-nourished life despite the

patient's food allergies. Without education, the recommendation of an elimination diet can be overwhelming and unsuccessful as families struggle to find accurate and useful information, and it may result in unnecessary medical consequences.

TABLE 18-6. Food Allergy Resources

Resource	Website
Food Allergy Research and Education	https://www.foodallergy.org
American Academy of Allergy, Asthma, and Immunology	https://www.aaaai.org
Academy of Nutrition and Dietetics	https://www.eatright.org
Asthma and Allergy Foundation of America	https://www.aafa.org
American Partnership for Eosinophilic Disorders	https://www.apfed.org
American College of Allergy, Asthma, and Immunology	https://www.acaai.org
Food Allergy Research and Resource Program, University of Nebraska–Lincoln	https://farrp.unl.edu
National Institute of Allergy and Infectious Diseases	https://www.niaid.nih.gov
National Association of School Nurses	https://nasn.org
Food Allergies, Centers for Disease Control and Prevention	https://www.cdc.gov/healthyschools/foodallergies/index.htm
Food Allergies, U.S. Food and Drug Administration	https://www.fda.gov/food/food-labeling-nutrition/food-allergies

With the changing practice of managing cow's milk and egg allergy, evaluating patients for tolerance of baked products containing these ingredients has become more common. Nutrition counseling for this recommendation can be challenging but is a critical part of care. Considering published guidelines for incorporating baked milk and egg into the diet is important because it may increase the number of allowed foods based on individual preferences.[46]

Nutritionally Complete Formulas

Identifying the most appropriate formulas depends on the known food allergens. Most standard formulas are free of wheat, egg, peanut, tree nuts, fish, shellfish, and sesame. Careful review of the ingredients of any standard formula is critical before recommending use. It is common to substitute a soy protein–based formula for patients allergic to cow's milk protein, and for patients who are allergic to both cow's milk and soy, a protein hydrolysate or elemental formula is recommended. These formulas exploit the concept that intact proteins are allergenic, and with the increased breakdown of intact protein, the allergenicity can be reduced. Protein hydrolysates are made by hydrolysis of proteins into mostly dipeptides and tripeptides and can be tolerated by the vast majority (~90%) of patients with milk and soy allergies.[47,48] Elemental formulas comprise individual amino acids and are tolerated by the small fraction of children who are also allergic to the protein hydrolysates.[45]

Both of these types of formulas are generally less palatable than standard formulas and are considerably more expensive. Significant advances have been made to the flavor and acceptability of these formulas, which has improved the adherence to incorporating them as supplemental oral nutrition. The major categories of formulas are enumerated in Table 18-7.

TABLE 18-7. Major Types of Pediatric Formulas

Formula	Protein	Comments
Cow's milk	Casein, whey	Most postinfant formulas for children >1 y are lactose-free
Lactose-free		
Soy	Soy	Postinfant soy formulas can be hard to obtain in the USA
Food-based formula		Food-based formulas can contain major allergens other than cow's milk or soy (eg, fish, legumes)
Hydrolysate	Peptides, amino acids	—
Elemental	Amino acids	—

Pediatric food-based formulas are available and may be appropriate for children with food allergies, depending on whether they contain any of the top 9 most common allergens. These formulas may be considered nutritionally complete and/or palatable for oral intake. Homemade or commercially prepared food-based formulas are increasingly being used as tube feedings to replace formulas and should be used cautiously in children with food allergies.

The degree of complete nutrition will vary based on allowed foods and/or recipes used for tube- feeding preparation. Homemade tube feeding requires close nutritional monitoring in conjunction with a dietitian who is familiar with the preparation of food-based tube feedings. Because of the increase in commercially available food-based formula (also known as commercial blenderized tube feeding [CBTF]), caregivers can avoid having to prepare formula at home. Instead, a registered dietitian can review the commercially available options and identify a nutritionally complete alternative that does not require preparation. Common reasons for using CBTF include:

- improved feeding tolerance
- a desire to provide whole foods
- evidence for increasing oral intake
- avoidance of known food allergens
- promotion of microbial biodiversity

- potentially increased cost effectiveness[49]

The advancement of food-based formulas provides more alternatives for patients, however, risks remain, and a complete nutrition assessment should be performed frequently to ensure nutritional adequacy. No standard definitions exist regarding what constitutes a nutritionally complete food-based CBTF product. The increased use of nontraditional plant proteins (eg, rice, pea), has led to considerable debate regarding whether they are nutritionally adequate and if there are any nutrition risks to address.

Most food allergies in children can be managed through judicious food substitutions. When faced with an extensive array of food allergies that span multiple food groups, protein hydrolysate and elemental formulas become the primary options. Infants under the age of 4 months (sometimes up to 6 months) usually accept these less-palatable formulas without difficulty, but with increasing age, they are less accepting of them. When elemental formulas are the sole or major nutrition source for toddlers or preschool children and they will not consume enough to sustain nutrition, tube feeding may become necessary.

Patients who are extremely malnourished at presentation may need to be admitted to the hospital to monitor for refeeding syndrome (see Chapter 17, "Eating Disorders"); otherwise, most patients with food allergies can be managed in outpatient settings.

Milk Substitutes/Beverages

Milk substitutes/beverages must be used in combination with nutrition assessment and monitoring. Many different "milk" products are available in the marketplace that provide alternatives for patients with allergies. However, these products should only be used after careful consideration of nutritional quality because a wide range of differences exist among products both for macronutrients and micronutrients.[50] Many provide adequate micronutrients such as vitamin D, calcium, and B vitamins; however, most provide minimal fat and protein. Children under the age of 2 years are at high risk for malnutrition if one of the incomplete milk substitutes is used in place of whole cow's milk. Table 18-8 provides nutritional constituents of various milk substitutes.

TABLE 18-8. Nutrient Comparison of Enriched Unflavored Milk Substitutes/Beverages[a]

Nutrients (per 8 Oz)	Coconut Milk	Almond Milk	Rice Milk	Soy Milk	Whole Milk	Pediasure	Hemp Milk	Almond Coconut Blend	Coconut, Almond, and Chia Blend
Calories	70–80	60–70	120	80–130	150	240	70	50	70
Protein (g)	0[b]	1–5[b]	1[b]	7–11	8	7	2–3[b]	<1[b]	<1[b]
Carbohydrate (g)	7–8	7–8	23	7–13	11	33	1	5	8
Fat (g)	4–5	2–4	2.5	2.5–4.5	8	9	5–6	3	4
Saturated fat (g)	4–5	0	0	0–0.5	5	1	0.5	1	2.5
Calcium (mg)	100–450	100–450	300	200–450	294	250	300	450	300
Iron (mg)	0.4–0.7	0.4–0.7	0.7	0.7–1.8	0.1	2.7	1.1–1.8	0.4	0.4
Vitamin A (IU)	500	500	500	500–1500	300	500	500	500	500
Vitamin D (IU)	100–120	100–120	100	40–140	100	160	100–120	100	100

[a] These are typical nutritional values for various milk substitutes/beverages using enriched, unflavored versions. Individual brands may have varying amounts of nutrients.

[b] Protein source is not a complete protein.

When evaluating milk substitutes for patients, it is important to read the food label of the specific product that will be consumed because the nutrient content of milk substitutes varies by the type (food source) of "milk" (see Table 18-8) and also by brand and versions within the brand. Milk substitutes with added flavors may have higher calorie content than unflavored versions, and some milk substitutes are not enriched. Nonenriched products often contain <100 mg of calcium per 8-oz (~240 mL) serving and do not contain vitamin D.

Food Allergy Education and Labeling

Food allergy diagnosis impacts the patient and family/caregivers in many ways, including grocery shopping, cooking, socializing, travel/vacations,

eating out, and family relationships. Providing education on all these topics is essential. One of the cornerstones of management is education about reading food labels.[51] Labels must be reviewed every time a food product is purchased because the ingredients may change without warning. Labels must also be reviewed for supplements, medications, bath products, lotions, pet foods, and cosmetics because young children may accidentally or voluntarily consume these products.

The Food Allergen and Consumer Protection Act of 2004 (FALCPA) along with the Food Allergy Safety, Treatment, Education and Research Act of 2021 (FASTER) are the amendments to the Food, Drug, and Cosmetic Act, requiring that food containing an ingredient that is 1 of the 9 major food allergens (or contains a protein of these allergens) be listed on the food label.[52,53] This requirement includes the presence of the 9 major food allergens in spices, flavorings, and other ingredients. The law applies to all food regulated by the FDA, including many packaged food products, dietary supplements, and infant formula. The U.S. Department of Agriculture in collaboration with the Federal Safety and Inspection Service regulates food products consisting primarily of meat, poultry, and egg and they support the voluntary addition of allergen statements (eg, "contains" statements) on meat, poultry, and egg product labels.[54] FALCPA and FASTER do not apply to medications, cosmetics, or lotions. Consumers should read the ingredient list of all products carefully to ensure that they are allergen-free.

Voluntary allergen advisories or "may contain" statements are appearing on an increasing number of products.[55] Food-processing companies determine when to use these statements and what language to use. The allergen advisories are used by some food processors to indicate a possible risk of cross-contact with an allergen from another product. Recent efforts to increase public awareness and improvements in food product labeling are encouraging. However, there is concern that food processors may make voluntary allergen advisories regarding cross-contact to avoid accidental allergen exposure, which decreases the choices for patients with food allergies. Table 18-9 provides some examples of "hidden" food allergens in common foods.

TABLE 18-9. Common Sources of Hidden Food Allergens

Egg	Milk	Nuts	Soy	Wheat	Rice	Sesame
Pasta	Cakes/muffins	Breakfast cereals/ granola bars	Bread/bread crumbs	Cereals	Baby food	Asian cuisine
Bread/bread crumbs	Breakfast cereals	Egg rolls	Waffles	Oatmeal cookies	Bread/bread crumbs	Baked goods
Egg Beaters	Frozen desserts	Cakes/cookies	Crackers	Chicken hot dogs/low-fat beef franks	Cake/muffin mixes	Chips, dipping sauces
Candy/chocolate	Candy/ chocolate	Frozen desserts	Chicken hot dogs/low-fat beef franks	Soy sauce	Waffles	Dressings, gravies, marinades and sauces
Marshmallows	Canned tuna	Nut butters	Cakes/muffins	Barbecue-flavored potato chips	Soups	Flavored rice, noodles, risotto, shish kebabs, stews and stir fry
Waffles	Processed meats	Sauces/chili	Bouillon cubes	Modified food starch	Food marketed as free of the 9 most common food allergens	Protein and energy bars

In 2014, the FDA issued a regulation that defines the term "gluten free" for food labeling.[56] This law standardizes the definition of "gluten-free" on food labels. The FDA set the gluten limit as <20 parts per million for foods labeled "gluten free," "no gluten," "free of gluten," or "without gluten." Because the use of the "gluten-free" claim is voluntary, it may not appear on a food label even if the food is actually gluten free.

Micronutrient Supplementation

The benefit of early nutrition intervention is to avoid micronutrient deficiency by recommending adequate substitutions and supplementation. The dietary reference intakes for vitamins, minerals, and trace elements can be used for children with food allergies because the vast majority of these children are healthy except for their food allergies and atopic conditions.[57] Chapter 6 ("Minerals"), Chapter 7 ("Water-Soluble Vitamins and Related Compounds"), and Chapter 8 ("Fat-Soluble Vitamins") discuss these topics. Recommendations for supplements should be made based on foods that need to be eliminated and the patient's nutrition status. Several hypoallergenic multivitamin-multimineral supplements are appropriate for children with food allergies (see Table 18-10). Two of the most common micronutrient supplements recommended for children with food allergies are calcium and vitamin D (see Table 18-11).

TABLE 18-10. Allergen-Free Multivitamins[a]

For Children	For Teenagers/Young Adults
Garden of Life Vitamin Code Kids[b,c]	One A Day Teen Advantage for Him or Her Multivitamin[b]
Vitaflo FruitiVits Powder Multivitamin[b,d]	Nature's Plus Source of Life Power Teen Multivitamin
Up & Up Kids' Complete Multivitamin Chewable Tablets	Active Health Teen Multivitamin from Rainbow Light
NanoVM powder (1–3 y and 4–8 y)[b,d] Multivitamin	
Nature's Plus Animal Parade Gold Children's Liquid Multivitamin[b]	
Nature's Plus Animal Parade Sugar-Free Children's Chewable Multivitamin	

[a] All of these products are free of milk, soy, egg, wheat, peanut, tree nuts, fish, and shellfish; however, products can change at any time, so it is important to check labels before use. Store brands and generic brands may also be allergen-free.

[b] This allergen-free vitamin contains selenium.

[c] This product does not contain iron.

[d] This product is only available online.

TABLE 18-11. Allergen-Free Calcium and Vitamin D Supplements

Supplement Name[a]	Serving Size	Calcium (mg)	Vitamin D (mcg)
L'il Critters Calcium with Vitamin D	2 gummy bears	200	5.5
FitFormula Calcium + Vitamin D3 Supplement (formerly Cal EZ) Powder Packets	1 packet/d	1000	25
Tums Regular Strength	1 tablet	200	0
D-Vi-Sol	1 mL daily	0	10
Kids First Vitamin D Gummies	1 gummy	0	25
Rainbow Light Vitamin D3 400 IU Sunny Gummies	1 gummy	0	10

[a] All of these products are free of milk, soy, egg, wheat, peanut, tree nuts, fish, shellfish, and sesame; however, products can change at any time, so it is important to check labels before use.

Special Scenarios

Cow's Milk–Protein Allergy

Cow's milk–protein allergy (CMPA) is one of the most common food allergies in pediatric patients. Cow's milk–protein is the first and only dietary antigen introduced into the diet before the introduction of other foods. Therefore, CMPA occurs mainly in infants during the first year of life. Although it can be difficult to assess the real prevalence of CMPA, it has increased over recent years,[58] affecting approximately 2% of children under 4 years of age.

In the 2015 EuroPrevall birth cohort study, 12,049 children were evaluated and the overall incidence of challenge-proven CMPA was 0.54% and showed differences in national incidences, ranging from 1% (Netherlands and UK) to <0.3% (Lithuania, Germany, and Greece).[59] Reported prevalence is between 2% to 7.5%.[60] CMPA can present with a wide range of clinical symptoms depending on the underlying mechanism. Clinical symptoms often appear during the first few months of life, within days or weeks after the introduction of cow's milk–based formula.

If there is enough cow's milk–protein transmitted from the maternal diet to human milk, symptoms may occur in exclusively breastfed infants. The majority, about 60%, of CMPA are IgE mediated.[59] IgE-mediated CMPA presents immediately after ingestion with symptoms that may include urticaria, angioedema, wheezing, vomiting, diarrhea, and anaphylaxis. The remaining 40% of CMPA are non-IgE mediated or mixed IgE and non-IgE mediated. Non-IgE-mediated CMPA is typically a delayed reaction occurring more than 2 hours after ingestion.

Food-protein proctitis or proctolitis may cause blood-streaked, mucousy, loose stools in children under 6 months of age. FPIES is another non-IgE-mediated CMPA, which will be discussed in the "Food-Protein-Induced Enterocolitis Syndrome" section. Finally, mixed IgE- and non-IgE-mediated CMPA can present with acute or chronic symptoms such as seen with atopic dermatitis or allergic eosinophilic gastrointestinal disorders.

Diagnosis of CMPA relies on a thorough clinical history, where eliciting pertinent details is crucial for determining the underlying mechanism. Further tests such as allergy tests and endoscopic biopsy may need to be done for suspected IgE- and some non-IgE-mediated reactions, respectively.

Avoiding cow's milk is recommended no matter the mechanism. Up to 90% of these infants will do well with a protein hydrolysate, and the rest will require an elemental formula.[61] In breastfed infants with food-protein proctitis/proctocolitis, the mother should initially avoid cow's milk; if no improvement is seen, she may also need to exclude other common food allergens. There is consensus that soy formulas should not be used for infants with food allergy who are under 6 months of age.[14] Children older than 6 months can be tried on soy formula, particularly after a clinical challenge; however, children with IgE-mediated cow milk allergy are more likely to tolerate soy than those with non-IgE-mediate allergy.[14]

These children, particularly infants with gastrointestinal symptoms, have a good prognosis. Approximately 50% of infants can tolerate cow's milk by the age of 1 year and the vast majority remit by the age of 3 years.[62]

Eosinophilic Esophagitis

EoE is a disorder of the esophagus characterized by upper gastrointestinal tract symptoms in association with esophageal mucosal eosinophilia.[63] EoE

is generally a chronic disease with persistent or relapsing symptoms, and its prevalence appears to be increasing.

Children under the age of 5 years commonly present with food refusal, regurgitation, and emesis. Abdominal pain and malnutrition may also be seen. Dysphagia and food impaction tend to be increasingly common with age. A strong association exists between EoE and allergic rhinitis, asthma, and eczema as well as food allergies. All patients with EoE must be managed with coordinated care between a gastroenterologist, allergist, and dietitian.

Systemic and topical corticosteroids effectively resolve acute features of EoE; however, when they are discontinued, the disease generally recurs. Despite this, EoE can be maintained in remission in a vast majority of patients with the use of topical corticosteroids. Nutrition intervention can be used as an adjunct to corticosteroid therapy or as the sole therapy for EoE. Three types of nutrition intervention have met with varying degrees of success in EoE.

1. An allergy-directed elimination diet involves removing foods based on allergy testing, which has an efficacy of <50%, reflecting the poor specificity of such testing to predict EoE food allergens.[53] Even when allergy testing does not reveal specific food allergens, elimination diets can be used. Simply removing the 8 most common allergenic foods (ie, milk, soy, egg, wheat, peanut, tree nuts, fish, shellfish) from the diet has significant efficacy,[64] which has been reported to be around 70%. The role of sesame in this elimination process is unclear.
2. Decreasing the number of eliminated foods and step-up empiric diet elimination are being trialed to reduce nutrient restriction and improve patient quality of life and adherence. The success rates vary from 54% for eliminating cow's milk alone to 64% for eliminating 4 foods simultaneously (ie, milk, soy, egg, wheat).
3. A 100% amino acid–based formula diet removes all potential food allergens and has been extremely effective.[60,61] The roles of long-term diet therapy, including relapse risk despite strict adherence, and food reintroduction are unknown.

Hence, medical nutrition therapy should be considered an effective treatment for all children diagnosed with EoE. When deciding on a specific nutrition therapy, the patient's lifestyle and family resources also need to be considered, considering comprehensive education and nutrition monitoring by a dietitian.[62]

Food Protein−Induced Enterocolitis Syndrome

FPIES is classified as a non-IgE-mediated allergic disorder, triggered by the ingestion of certain food proteins.[63] Patients with this disorder do not present with urticaria, angioedema, or respiratory compromise. Three clinical phenotypes of FPIES have been described in children[64]:

1. Acute
2. Chronic
3. Atypical

In acute FPIES, children usually present at <12 months of age with delayed vomiting and/or diarrhea within 2 to 4 hours of the ingestion of the causative food. In a moribund state, children present with shock and metabolic acidosis secondary to their gastrointestinal symptoms,[65] which typically resolve within 48 to 72 hours after removal of the suspected antigen.[66] Typically, the offending food is either cow's milk, soy, or rice,[67,68,69] although other grains, poultry, fruits, and vegetables have also been implicated.[65]

Chronic FPIES typically occurs in infants <4 months old whose trigger food, such as cow's milk or soy formula, is ingested regularly. It is characterized by frequent vomiting and diarrhea over days to weeks, leading to poor weight gain or weight loss. It may take up to 2 weeks for symptoms to resolve once the trigger food is eliminated.

Lastly, atypical FPIES presents with a clinical history consistent with FPIES and positive IgE to the trigger food. Some may develop IgE-mediated−food allergic reactions with reexposure to the trigger food. Except for patients with atypical FPIES, tests for food-specific IgE by either SPT or serologic in-vitro methods are negative.[70] Awareness of the entity is important because the clinical presentation can be confused with other life-threatening conditions. It is normal for multiple presentations to

occur before the true diagnosis is determined. Early diagnosis should be based on the clinical history and presentation, and removal of the offending food antigen serves as a simple and effective therapy. The age at which oral tolerance develops varies.

Medical nutrition therapy for FPIES is similar to that for food allergies. The dietitian should seek advice from the physician about which foods to avoid and which to introduce. The dietitian can help the physician focus on specific food groups that will provide necessary nutrients based on the nutrition assessment. Breastfeeding is recommended because reactions to human milk are rare, however, some have been reported.[71,72] Formula-fed patients who do not tolerate milk may tolerate soy formula, but a food challenge should be considered because there is a high incidence of concomitant milk and soy FPIES.[69] FPIES patients may tolerate extensively hydrolyzed formula, however, up to 20% of patients require amino acid–based formula.[69]

For infants and toddlers with a history of reactions to certain solid foods, practitioners may recommend delaying the introduction of other solid foods, which in turn may lead to the development of feeding difficulties. Practitioners must be attentive to the interruption of this sensitive period for feeding development and provide strategies for enhancing feeding skills to avoid the development of a more severe feeding disorder.

Prognosis and Follow-Up

Many young children diagnosed with allergies to foods such as milk, egg, wheat, and soy will outgrow the sensitivity after several years.[73] Non–IgE-mediated milk allergy tends to be outgrown more quickly than IgE-mediated allergy, both having a good prognosis.[73] Resolution of an IgE-mediated milk allergy occurs in about 80% of patients by 5 years of age. More recent studies suggest a slower rate of resolution. Wood et al observed that about half of infants diagnosed with milk allergy between ages 3 and 15 months experienced resolution of the allergy at a median age of ~5 years.[74] Egg allergy has a similarly slow resolution. In a cohort of infants diagnosed with egg allergy between the ages of 3 and 15 months, 49% experienced allergy resolution at a median age of 6 years.[75]

Factors associated with outgrowing an IgE allergy include having a mild-to-moderate reaction history, being allergic to only 1 food, having eczema as the sole allergy symptom, and being Caucasian.[76] Studies reviewing the history of egg and milk allergy indicated that baseline sIgE, SPT wheal size, and severity of eczema were important predictors of the likelihood of resolution.[74,75] Children who develop a food allergy after 3 years of age are less likely to lose the food reactivity over several years.[77] Peanut allergy is a lifelong disorder for most but not all patients.[37] About 20% of children with a peanut allergy may tolerate peanut later in life.[38] A smaller percentage of those with tree nut allergy seem to develop tolerance.[78] While data for individuals with fish allergies are unavailable, seafood allergies appear to be permanent.[40] Table 18-12 indicates the ages at which tolerances are likely to develop for common food allergens.

TABLE 18-12. Ages for Tolerance of Common Food Allergens

Food[a]	Age (y)	Tolerance (%)	References
Milk	4	19	Wood,[73] Skripak et al[93]
	5	52.6	
	12	64	
	16	79	
Egg	4	12	Sicherer et al,[75] Savage et al[94]
	6	37, 49.3	
	10	68	
Wheat	4	29	Keet et al[95]
	8	56	
	12	65	
Soy	4	25	Savage et al[96]
	6	45	
	10	69	
Peanut	5	21[b]	Ho et al[78]
Tree nuts		9[c]	Fleischer et al[97]

[a] Natural history data for fish allergy are unavailable, and shellfish allergy is considered to be persistent.[26]

[b] Predictors of persistent allergy: skin prick test wheal size >6 mm and allergen-specific IgE (sIgE) >3 kUA/L before age 2 y.

[c] The percentage is 63% with sIgE < 2kUA/L and passed oral challenge.

Follow-up visits with the allergist-immunologist are important for the management of food allergies. Because children have the potential to outgrow a food allergy, the follow-up visits allow clinicians to reassess the allergic status and determine if any food allergens may be reintroduced. Reintroduction of food allergens should only be considered if managed and directed by the allergist. Introducing previously avoided allergens may increase food options, decrease cost if the patient is drinking a specialty

formula and/or eating specialty allergen-free foods, and decrease caregiver stress around preparing meals for the child.

Food Allergies and Nutrition Support

Two scenarios are possible when food allergies are associated with nutrition support: (1) when a child with known food allergies requires nutrition support, and (2) when allergies to formula or parenteral nutrition components become apparent only after nutrition support has commenced.

Enteral Nutrition

Enteral nutrition support for children presenting with food allergies can be straightforward. Because most standard enteral formulas contain cow's milk–protein, children with CMPA can be managed with soy-based, commercial blenderized food-based, protein hydrolysate, or elemental formula using the principles outlined earlier in this chapter. Some formula intolerances that occur in young children receiving nutrition support are probably secondary to food allergies and are usually not recognized at first. Because one of the management strategies for formula intolerances during nutrition support includes a transition to a protein hydrolysate or elemental formula, the acute situation usually resolves. Often, food allergy is diagnosed retrospectively when the child cannot be transitioned back to a more standard formula.

Parenteral Nutrition

A variety of allergies to parenteral nutrition (PN) have been described through case reports in the literature.[8288] A systematic review of hypersensitivity to PN estimated that the rate of such hypersensitivity in the United States may be around 1.5 per million patients who are provided PN.[89] As with other allergies, they appear to be more common in children but can occur at any age. [83,84,86] The majority of these reactions occur at the first administration but can occur after several days of administration or after reinstitution following a hiatus. Skin rashes appear to be the most common manifestation. However, patients can present with dyspnea, cyanosis, nausea, vomiting, headache, flushing, fever, and chest pain.

Anaphylaxis can occur.[84,86,90] Severe reactions are most likely within the first hour of PN initiation. The agents most frequently implicated in PN hypersensitivity are intravenous fat emulsion (IVFE) and the multivitamin solution (either stabilizers and emulsifiers in the M.V.I. Pediatric or due to thiamine, vitamin B complex, or vitamin K) but have been attributed to crystalline amino acid solutions[86] as well.

Limited data are available on PN support in children with documented food allergies. Egg allergy can be a cause for concern because these proteins are found in IVFE. Patients with documented allergies to eggs have several options:

(a) Consult with an allergist who may do a SPT
(b) Use fat-free PN
(c) Use a fish oil–based lipid emulsion (eg, Omegaven) or combination lipids such as Smoflipid or Clinolipid (all of which still contain some egg phospholipid).[79]

A risk exists for extremely soy-allergic patients needing PN. Patients may tolerate IV soy-based fat emulsion, but the first 2 options should be considered.

Two case reports regarding soy allergy and PN present directly opposing views. In the first, no detectable soy allergen was found in the 20% Intralipid emulsion preparation.[80] In the second report, a patient with soy allergy developed systemic signs of anaphylaxis after receiving a test dose of Intralipid.[81] This patient was successfully maintained on the fish oil–based lipid emulsion as the sole source of fat for 45 days.[81]

Fish oil−based IVFE should either be avoided or used cautiously for patients with fish allergy for 2 reasons: (1) the likelihood that patients with a food allergy to one fish will react to another fish is relatively high, and (2) manufacturers are unlikely to be able to identify which types of fish are the sources of fish oil in a given IVFE.[79] On the other hand, patients with hypersensitivity to only a single legume (particularly peanut or soy) are unlikely to have an allergy to a different legume-based emulsion product (eg, a person with isolated peanut allergy reacting to soy-based product).[79] Despite this and the lack of clear evidence that such a reaction is likely to occur, the manufacturer of Smoflipid lists peanut allergy as a

contraindication to the product. Intralipid, which contains a higher concentration of soybean oil, does not declare a contraindication.[79]

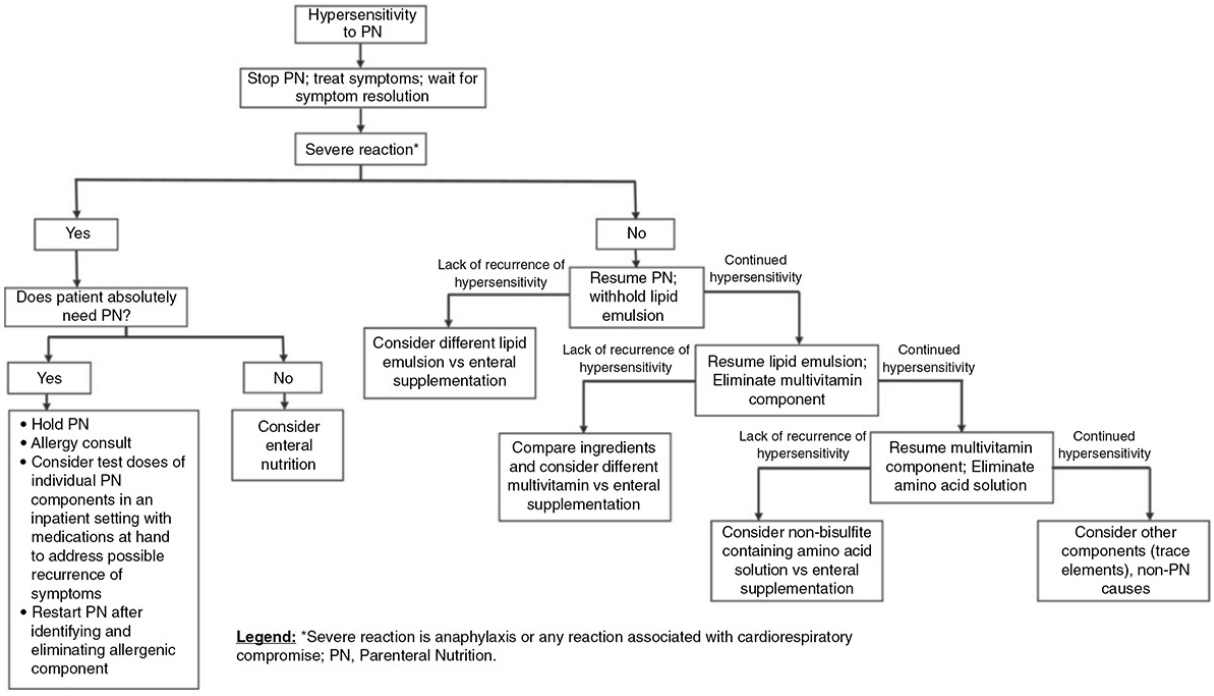
During PN administration, a perceived allergy to PN may actually be to components of the PN, such as other chemicals or devices to which the patient is exposed. Such reactions have been described for chlorhexidine gluconate (when used as a skin disinfectant), nickel (from an eyelet in an intravenous needle), and latex (from the latex stopper on the IV fat emulsion).[89] Considering these and other exposures is critical when encountering a patient with possible PN hypersensitivity.

These reactions have been attributed to IV fat emulsions[75,83] and multivitamin mixtures.[78,81,82,84,85] For example, a neonate presents with allergic manifestations from Trophamine amino acid solution containing PN, but the symptoms did not occur with Premasol amino acid solution. The reaction is thus presumed to be a response to bisulfite, which is present in the former solution but not in the latter.[86] Latex allergy can also present with allergic manifestations each time PN is commenced.[87]

When these reactions occur, PN must be stopped and appropriate drug treatment for the allergic reaction should be administered. See Figure 18-2 for the general schema on how to manage such an allergic reaction. If the reaction is severe and the patient will continue to require PN, a multidisciplinary approach involving an allergist, pharmacist, nutrition-support physician, and/or dietitian should be pursued. Two approaches may be considered when the reaction is mild and resolves after PN is discontinued:

1. Perform SPT for the fat emulsion, multivitamin, and amino acid components, subsequently removing the offending agent(s) before restarting PN.
2. Identify the offending agent through trial and error. In severe reactions, using IV desensitization in the intensive care unit has been described; however, the effectiveness of this method is unclear.[80]

FIGURE 18-2. Suggested Algorithm for the Management of Hypersensitivity to Parenteral Nutrition



IV Iron is one micronutrient that may be added to PN solutions, but it can cause significant allergic reactions. All 3 parenteral iron compounds (ie, iron dextran, sodium ferric gluconate complex in sucrose, and iron sucrose) can be associated with allergic reactions.[91,92] Iron sucrose has the lowest risk of allergy.[49,91] Iron dextran is the least expensive preparation, and a test dose should always be given while routinely pretreating patients with diphenhydramine and acetaminophen to minimize adverse reactions. Both sodium ferric gluconate and iron sucrose offer safe alternatives to patients who are intolerant of iron dextran but at a higher cost.[91,92] Patients who are sensitive to iron dextran and patients with multiple allergies who receive one of the newer preparations should receive test doses before starting therapy.

Conclusion

Practitioners should be aware of the most common food allergens and the manifestations of the different types of food allergies. Because the management of food allergies involves avoidance of the offending allergens, malnutrition and nutrient deficiencies may result. A dietitian is needed to educate families about how to avoid specific allergens and how to replace the nutrients lost by avoiding those allergens. Finally, specific protocols can aid in allergies that are uncommonly encountered during the provision of nutrition support therapy.

Test Your Knowledge Questions

1. A 7-year-old boy with an enterocutaneous fistula develops an urticarial rash the day that he is started on PN. Which of the following PN constituents would NOT cause the rash?
   A. Intravenous fat emulsion
   B. Amino acid solution
   C. Pediatric multivitamin solution
   D. Dextrose
2. An 18-month-old vegetarian girl with presumed milk and soy protein allergy is drinking 32 oz of enriched rice milk per day. She also eats rice, wheat, corn, fruits, and vegetables but does not consume any egg or meat products. She does not receive any vitamin or mineral supplementation. Which of the following is NOT a concern regarding her intake?
   A. Fat
   B. Vitamin D
   C. Energy
   D. Zinc
3. A 6-year-old boy is seen by a dietitian for follow-up nutrition assessment and education. His parents report he is allergic to milk, soy, and peanuts. He has a history of anaphylaxis while eating peanut butter 1 year ago. His current intake includes tofu stir-fry and milk chocolate candy bars and he eats these foods at least once a week without any

problems. He does not drink a milk substitute. Which of the following should NOT be done or considered at this visit?

A. Assess growth and nutrient intake
B. Suggest an age-appropriate beverage
C. Recommendfollow-up with an allergist (since the patient is tolerating milk and soy)
D. Suggest peanut butter food challenge at home

4. A 6-month-old breastfed infant has significant vomiting and diarrhea within hours of receiving a bottle of cow's milk–based formula. His mother reports that this has happened each time he received the formula. No skin rashes were present. A SPT for IgE directed against cow's milk−protein was negative. Which of the following is false?

A. This is consistent with IgE-mediated anaphylaxis.
B. This is most likely food protein-induced enterocolitis syndrome.
C. Cow's milk protein must be eliminated from the child's diet.
D. In addition to breastfeeding, a protein hydrolysate formula may be appropriate.

References

1. Peters RL, Krawiek M, Koplin JJ, Santos AF. Update on food allergy. *Pediatr Allergy Immunol*. 2021;32:647–657. https://doi.org/10.1111/pai.13443
2. Galic I, Warren CM, Jiang J, Tobin MC. Parent report of physician diagnosis in pediatric food allergy: an update. *J Allergy Clin Immunol Pract*. 2021;9(1):542–546. https://doi.org/10.1016/j.jaip.2020.09.033
3. Barni S, Liccioli G, Sarti L, et al. Immunoglobulin E (IgE)-mediated food allergy in children: epidemiology, pathogenesis, diagnosis, prevention, and management. *Medicina*. 2020;56(111):1–16. https://doi.org/10.3390/medicina56030111
4. Sicherer SH, Warren CM, Dant C, et al. Food allergy from infancy through adulthood. *J Allergy Clin Immunol Pract*. 2020;8(6):1854–1864. https://doi.org/10.1016/j.jaip.2020.02.010
5. Arbes SJ Jr, Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population:

results from the third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol*. 2005;116(2):377–383. https://doi.org/10.1016/j.jaci.2005.05.017
6. McGowan EC, Peng RD, Salo PM, Zeldin DC. Changes in food-specific IgE over time in the National Health and Nutrition Examination Survey (NHANES). *J Allergy Clin Immunol Pract*. 2016;4(4):713–720. https://doi.org/10.1016/j.jaip.2016.01.017
7. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997–2011. *NCHS Data Brief*. 2013; (121):1–8.
8. Sicherer SH, Furlong TJ, Muñoz-Furlong A, Burks AW, Sampson HA. A voluntary registry for peanut and tree nut allergy: characteristics of the first 5149 registrants. *J Allergy Clin Immunol*. 2001;108(1):128–132. https://doi.org/10.1067/mai.2001.115755
9. Sicherer SH. Epidemiology of food allergy. *J Allergy Clin Immunol*. 2011;127(3):594–602. https://doi.org/10.1016/j.jaci.2010.11.044
10. Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics*. 2011;128(1):e9–e17. https://doi.org/10.1542/peds.2011-0204
11. Sicherer SH, Sampson HA. Food allergy: epidemiology, pathogenesis, diagnosis, and treatment. *J Allergy Clin Immunol*. 2014;133(2):291–307. quiz 308. https://doi.org/10.1016/j.jaci.2013.11.020
12. Brough HA, Nadeau KC, Sindher SB, et al. Epicutaneous sensitization in the development of food allergy: what is the evidence and how can this be prevented? *Allergy*. 2020; 75:2185–2205. https://doi.org/10.1111/all.14304
13. Mehr S, Turner PJ, Joshi P, Wong M, Campbell DE. Safety and clinical predictors of reacting to extensively heated cow's milk challenge in cow's milk-allergic children. *Ann Allergy Asthma Immunol*. 2014;113(4):425–429. https://doi.org/10.1016/j.anai.2014.06.023
14. Turner PJ, Mehr S, Joshi P, et al. Safety of food challenges to extensively heated egg in egg-allergic children: a prospective cohort study. *Pediatr Allergy Immunol*. 2013;24(5):450–455. https://doi.org/10.1111/pai.12093

15. Elghoudi A, March H. Food allergy in children—the current status and the way forward. *World J Clin Pediatr*. 2022; 11(3):253–269. https://doi.org/10.5409/wjcp.v11.i3.253
16. Bock SA, Muñoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol*. 2001;107(1):191–193. https://doi.org/10.1067/mai.2001.112031
17. Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update—2014. *J Allergy Clin Immunol*. 2014;134(5):P1016–1025.E43. https://doi.org/10.1016/j.jaci.2014.05.013
18. Bock SA, Lee WY, Remigio L, Holst A, May CD. Appraisal of skin tests with food extracts for diagnosis of food hypersensitivity. *Clin Allergy*. 1978;8(6):559–564. https://doi.org/10.1111/j.1365-2222.1978.tb01509.x
19. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol*. 2001;107(5):891–896. https://doi.org/10.1067/mai.2001.114708
20. Foong R, Dantzer JA, Wood RA, Santos AF. Improving Diagnostic Accuracy in Food Allergy. *J Allergy Clin Immunol Pract*. 2021;9(1):71–80. https://doi.org/10.1016/j.jaip.2020.09.037
21. Liu AH, Jaramillo R, Sicherer SH, et al. National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005–2006. *J Allergy Clin Immunol*. 2010;126(4):798–806.e713. https://doi.org/10.1016/j.jaci.2010.07.026
22. Sicherer SH, Leung DY. Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects in 2013. *J Allergy Clin Immunol*. 2014;133(2):324–334. https://doi.org/10.1016/j.jaci.2013.11.013
23. Patil SU, Bunyanavich S, Berin MC. Emerging food allergy biomarkers. *J Allergy Clin Immunol Pract*. 2020;8(8):2516–2524. https://doi.org/10.1016/j.jaip.2020.04.054
24. Santos AF, Kulis MD, Sampson HA. Bringing the next generation of food allergy diagnostics into clinic. *J Allergy Clin Immunol Pract*. 2022;10(1):1–9. https://doi.org/10.1016/j.jaip.2021.09.009
25. PALISADE Group of Clinical Investigators, Vickery BP, Vereda A. AR101 oral immunotherapy for peanut allergy. *N Engl J Med*.

2018;379(21):1991–2001. https://doi.org/10.1056/nejmoa1812856
26. Jones SM, Kim EH, Nadeau KC, et al. Efficacy and safety of oral immunotherapy in children aged 1–3 years with peanut allergy (the Immune Tolerance Network IMPACT trial): a randomised placebo-controlled study. *Lancet*. 2022;399(10322):359–371. https://doi.org/10.1016/S0140-6736(21)02390-4
27. Fleischer DM, Greenhawt M, Sussman G, et al. Effect of epicutaneous immunotherapy vs placebo on reaction to peanut protein ingestion among children with peanut allergy: the PEPITES randomized clinical trial. *JAMA*. 2019;321(10):946–955. https://doi.org/10.1001/jama.2019.1113
28. Panel NI-SE, Boyce JA, Assa'ad A, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010;126(suppl 6):S1–S58. https://doi.org/10.1016/j.jaci.2010.10.007
29. Sicherer SH. Diagnosis and management of childhood food allergy. *Curr Probl Pediatr*. 2001;31(2):35–57. https://doi.org/10.1016/s1538-5442(01)70030-2
30. Lowe AJ, Su JC, Allen MJ, et al. A randomized trial of a barrier lipid replacement strategy for the prevention of atomic dermatitis and allergic sensitization: the PEBBLES pilot study. *Br J Dermatol*. 2018;178:19–21. https://doi.org/10.1111/bjd.15747
31. Miyaji Y, Yang L, Yamamoto-Hanada K, et al. Earlier aggressive treatment to shorten the duration of eczema in infants resulted in fewer food allergies at 2 years of age. *J Allergy Clin Immunol Pract*. 2020;8(50):1721–1724. https://doi.org/10.1016/j.jaip.2019.11.036
32. Waserman S, Begin P, Watson W. IgE-mediated food allergy. *Allergy Asthma Clin Immunol*. 2018;14(Suppl 2):71–81. https://doi.org/10.1186/s13223-018-0284-3
33. Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States. *JAAPA*. 2017;30(3):1–5. https://doi.org/10.1097/01.JAA.0000512231.15808.66
34. Du Toit G, Tsakok T, Lack S, Lack G. Prevention of food allergy. *J Allergy Clin Immunol.* 2016;137(4):998–1010. https://doi.org/10.1016/j.jaci.2016.02.005

35. Sakihara T, Otsuji K, Arakaki Y, et al. Randomized trial of early infant formula introduction to prevent cow's milk allergy. *J Allergy Clin Immunol*. 2021;147(1):224–232. https://doi.org/10.1016/j.jaci.2020.08.021
36. D'auria E, Abrahams M, Zuccotti GV, Venter C. Personalized nutrition approach in food allergy: is it prime time yet? *Nutrients*. 2019;11:E359. https://doi.org/10.3390/nu11020359
37. Flammarion S, Santos C, Guimber D, et al. Diet and nutritional status of children with food allergies. *Pediatr Allergy Immunol*. 2011;22(2):161–165. https://doi.org/10.1111/j.1399-3038.2010.01028.x
38. Christie L, Hine RJ, Parker JG, Burks W. Food allergies in children affect nutrient intake and growth. *J Am Diet Assoc*. 2002;102(11):1648–1651. https://doi.org/10.1016/s0002-8223(02)90351-2
39. Venter C, Groetch M, Netting M, Meyer R. A patient-specific approach to develop an exclusion diet to manage food allergy in infants and children *Clin Exp Allergy*. 2018;48(2):121–137. https://doi.org/10.1111/cea.13087
40. Groetch M, Nowak-Wegrzyn A. Practical approach to nutrition and dietary intervention in pediatric food allergy. *Pediatr Allergy Immunol*. 2013;24(3):212–221. https://doi.org/10.1111/pai.12035
41. ESPGAN Committee on Nutrition. Antigen-reduced infant formulae. *Acta Paediatr*. 1993;82(12):1087–1088. https://doi.org/10.1111/j.1651-2227.1993.tb12671.x
42. Sampson HA, Bernhisel-Broadbent J, Yang E, Scanlon SM. Safety of casein hydrolysate formula in children with cow milk allergy. *J Pediatr*. 1991;118(4 Pt 1):520–525. https://doi.org/10.1016/s0022-3476(05)90001-2
43. Bennett, K., Hjelmgren, B. and Piazza, J. (2020), Blenderized tube feeding: health outcomes and review of homemade and commercially prepared products. *Nutr in Clin Pract*. 2012;35:417–431. https://doi.org/10.1002/ncp.10493
44. Fructuoso I, Romão B, Han H, et al. An overview on nutritional aspects of plant-based beverages used as substitutes for cow's milk. *Nutrients*. 2021;13(8):2650. https://doi.org/10.3390/nu13082650

45. Joshi P, Mofidi S, Sicherer SH. Interpretation of commercial food ingredient labels by parents of food-allergic children. *J Allergy Clin Immunol*. 2002;109(6):1019–1021. https://doi.org/10.1067/mai.2002.123305
46. U.S. Food and Drug Administration. Food allergen labeling and Consumer Protection Act of 2004. Accessed September 15, 2022. https://www.fda.gov/food/food-allergensgluten-free-guidance-documents-regulatory-information/food-allergen-labeling-and-consumer-protection-act-2004-falcpa.
47. Food Allergy Safety, Treatment, Education and Research Act of 2021 (FASTER) 117th U.S. Congress (April 23, 2021). Public Law 117–11. Accessed April 18, 2024. https://www.congress.gov/bill/117th-congress/senate-bill/578/text
48. Food Safety and Inspection Service. *FSIS compliance guidelines allergens and ingredients of public health concern: identification, prevention and control, and declaration through labeling*. Published April 2014. Accessed September 15, 2022. http://www.fsis.usda.gov/wps/wcm/connect/f9cbb0e9-6b4d-4132-ae27-53e0b52e840e/Allergens-Ingredients.pdf?MOD=AJPERES
49. Food Allergy Issues Alliance. *Food Allergen Labeling Guidelines*. National Food Processors Association; 2001.
50. U.S. Food and Drug Administration. *Food labeling; gluten-free labeling of foods*. Published August 5, 2013. Accessed September 15, 2022. https://www.federalregister.gov/articles/2013/08/05/2013-18813/food-labeling-glutenfree-labeling-of-foods
51. Dietary guidance. National Agricultural Library, U.S. Department of Agriculture. Accessed December 3, 2023. https://www.nal.usda.gov/human-nutrition-and-food-safety/dietary-guidance
52. Vandenplas, Brough HA, Fiocchi A, et al. Current guidelines and future strategies for the management of cow's milk allergy. *J Asthma and Allergy*. 2021;14:1243–1256.
53. Giannetti A, Vaspasiani GT, Ricci G, Miniaci A, di Palmo E, Pession A. Cow's milk protein allergy as a model of food allergies. *Nutrients*. 2021;13(1525):1–21. https://doi.org/10.3390/nu13051525

54. Sackesen C, Altintas DU, Bingol A, et al. Current trends in tolerance induction in cow's milk allergy: from passive to proactive strategies. *Front Pediatr*. 2019;7:372. https://doi.org/10.3389/fped.2019.00372
55. Atkins D. Food allergy: diagnosis and management. *Prim Care*. 2008;35(1):119–140.vii. https://doi.org/10.1016/j.pop.2007.09.003
56. Meyer R, Groetch M, Venter C. When should infants with cow's milk protein allergy use an amino acid formula? a practical guide. *J Allergy Clin Immunol Pract* 2018;6:383. https://doi.org/10.1016/j.jaip.2017.09.003
57. Host A. Cow's milk protein allergy and intolerance in infancy: some clinical, epidemiological and immunological aspects. *Pediatr Allergy Immunol*. 1994;5(suppl 5):1–36. https://doi.org/10.1111/j.1399-3038.1994.tb00352.x
58. Furuta GT, Liacouras CA, Collins MH, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology*. 2007;133(4):1342–1363. https://doi.org/10.1053/j.gastro.2007.08.017
59. Kagalwalla AF, Sentongo TA, Ritz S, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2006;4(9):1097–1102. https://doi.org/10.1016/j.cgh.2006.05.026
60. Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology*. 1995;109(5):1503–1512. https://doi.org/10.1016/0016-5085(95)90637-1
61. Markowitz JE, Spergel JM, Ruchelli E, Liacouras CA. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. *Am J Gastroenterol*. 2003;98(4):777–782. https://doi.org/10.1111/j.1572-0241.2003.07390.x
62. Feuling MB, Noel RJ. Medical and nutrition management of eosinophilic esophagitis in children. *Nutr Clin Pract*. 2010;25(2):166–174. https://doi.org/10.1177/0884533610361608
63. Sicherer SH. Food protein-induced enterocolitis syndrome: clinical perspectives. *J Pediatr Gastroenterol Nutr*. 2000;30(suppl):S45–S49. https://doi.org/10.1097/00005176-200001001-00007

64. Bartnikas LM, Nowak-Wegrzyn A, Schultz F, et al. The evolution of FPIES: from a diagnosis that did not exist to a condition in need of answers. *Ann Allergy Asthma Immunol*. 2021;126(5):489–497. https://doi.org/10.1016%2Fj.anai.2021.01.001
65. Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food protein-induced enterocolitis syndrome. *J Pediatr*. 1998;133(2):214–219. https://doi.org/10.1016/s0022-3476(98)70222-7
66. Maloney J, Nowak-Wegrzyn A. Educational clinical case series for pediatric allergy and immunology: allergic proctocolitis, food protein-induced enterocolitis syndrome and allergic eosinophilic gastroenteritis with protein-losing gastroenteropathy as manifestations of non-IgE-mediated cow's milk allergy. *Pediatr Allergy Immunol*. 2007;18(4):360–367. https://doi.org/10.1111/j.1399-3038.2007.00561.x
67. Burks AW, Casteel HB, Fiedorek SC, Williams LW, Pumphrey CL. Prospective oral food challenge study of two soybean protein isolates in patients with possible milk or soy protein enterocolitis. *Pediatr Allergy Immunol*. 1994;5(1):40–45. https://doi.org/10.1111/j.1399-3038.1994.tb00217.x
68. Powell GK. Milk- and soy-induced enterocolitis of infancy. Clinical features and standardization of challenge. *J Pediatr*. 1978;93(4):553–560. https://doi.org/10.1016/s0022-3476(78)80887-7
69. Leonard SA, Nowak-Wegrzyn A. Clinical diagnosis and management of food protein-induced enterocolitis syndrome. *Curr Opin Pediatr*. 2012;24(6):739–745. https://doi.org/10.1097/mop.0b013e3283599ca1
70. Nowak-Wegrzyn A, Sampson HA, Wood RA, Sicherer SH. Food protein-induced enterocolitis syndrome caused by solid food proteins. *Pediatrics*. 2003;111(4 Pt 1):829–835. https://doi.org/10.1542/peds.111.4.829
71. Monti G, Castagno E, Liguori SA, et al. Food protein-induced enterocolitis syndrome by cow's milk proteins passed through breast milk. *J Allergy Clin Immunol*. 2011;127(3):679–680. https://doi.org/10.1016/j.jaci.2010.10.017
72. Tan J, Campbell D, Mehr S. Food protein-induced enterocolitis syndrome in an exclusively breast-fed infant—an uncommon entity. *J Allergy Clin Immunol*. 2012;129(3):873–874. https://doi.org/10.1016/j.jaci.2011.12.1000

73. Wood RA. The natural history of food allergy. *Pediatrics*. 2003;111(6 Pt 3):1631–1637. https://doi.org/10.1542/peds.111.S3.1631
74. Wood RA, Sicherer SH, Vickery BP, et al. The natural history of milk allergy in an observational cohort. *J Allergy Clin Immunol*. 2013;131(3):805–812. https://doi.org/10.1016/j.jaci.2012.10.060
75. Sicherer SH, Wood RA, Vickery BP, et al. The natural history of egg allergy in an observational cohort. *J Allergy Clin Immunol*. 2014;133(2):492–499. https://doi.org/10.1016/j.jaci.2013.12.1041
76. Gupta RS, Lau CH, Sita EE, Smith B, Greenhawt MJ. Factors associated with reported food allergy tolerance among US children. *Ann Allergy Asthma Immunol*. 2013;111(3):194–198.e194. https://doi.org/10.1016/j.anai.2013.06.026
77. Jones SM, Pons L, Roberts JL, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. *J Allergy Clin Immunol*. 2009;124(2):292–300.97. https://doi.org/10.1016/j.jaci.2009.05.022
78. Ho MH, Wong WH, Heine RG, Hosking CS, Hill DJ, Allen KJ. Early clinical predictors of remission of peanut allergy in children. *J Allergy Clin Immunol*. 2008;121(3):731–736. https://doi.org/10.1016/j.jaci.2007.11.024
79. Franz, N., Pleva, M. and Nordbeck, S. Lipid emulsion therapies and type 1 hypersensitivity reactions: risk assessment and management. *Nutr Clin Pract*. 2021;36:398–405. https://doi.org/10.1002/ncp.10443
80. Nicklas RA. Lack of allergenic soy in intralipid for total parenteral nutrition. *Ann Allergy Asthma Immunol*. 2013;111(5):423. https://doi.org/10.1016/j.anai.2013.08.009
81. Gura KM, Parsons SK, Bechard LJ, et al. Use of a fish oil-based lipid emulsion to treat essential fatty acid deficiency in a soy allergic patient receiving parenteral nutrition. *Clin Nutr*. 2005;24(5):839–847. https://doi.org/10.1016/j.clnu.2005.05.020
82. Buchman AL, Ament ME. Comparative hypersensitivity in intravenous lipid emulsions. *JPEN J Parenter Enteral Nutr*. 1991;15(3):345–346. https://doi.org/10.1177/0148607191015003345
83. Bullock L, Etchason E, Fitzgerald JF, McGuire WA. Case report of an allergic reaction to parenteral nutrition in a pediatric patient. *JPEN J Parenter Enteral Nutr*. 1990;14(1):98–100. https://doi.org/10.1177/014860719001400198

84. Market AD, Lew DB, Schropp KP, Hak EB. Parenteral nutrition-associated anaphylaxis in a 4-year-old child. *J Pediatr Gastroenterol Nutr*. 1998;26(2):229–231. https://doi.org/10.1097/00005176-199802000-00022
85. Nagata MJ. Hypersensitivity reactions associated with parenteral nutrition: case report and review of the literature. *Ann Pharmacother*. 1993;27(2):174–177. https://doi.org/10.1177/106002809302700207
86. Pomeranz S, Gimmon Z, Ben Zvi A, Katz S. Parenteral nutrition-induced anaphylaxis. *JPEN J Parenter Enteral Nutr*. 1987;11(3):314–315. https://doi.org/10.1177/0148607187011003314
87. Scolapio JS, Ferrone M, Gillham RA. Urticaria associated with parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2005;29(6):451–453. https://doi.org/10.1177/0148607105029006451
88. Weidmann B, Lepique C, Heider A, Schmitz A, Niederle N. Hypersensitivity reactions to parenteral lipid solutions. *Support Care Cancer*. 1997;5(6):504–505. https://doi.org/10.1007/s005200050120
89. Christian VJ, Tallar M, Walia CLS, Sieracki R, Goday PS. Systematic review of hypersensitivity to parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2018;42(8):1222–1229. https://doi.org/10.1002/jpen.1169
90. Andersen HL, Nissen I. Presumed anaphylactic shock after infusion of Lipofundin [in Danish]. *Ugeskr Laeger*. 1993;155(28):2210–2211.
91. Bailie GR, Clark JA, Lane CE, Lane PL. Hypersensitivity reactions and deaths associated with intravenous iron preparations. *Nephrol Dial Transplant*. 2005;20(7):1443–1449. https://doi.org/10.1093/ndt/gfh820
92. Silverstein SB, Rodgers GM. Parenteral iron therapy options. *Am J Hematol*. 2004;76(1):74–78. https://doi.org/10.1002/ajh.20056
93. Skripak JM, Matsui EC, Mudd K, Wood RA. The natural history of IgE-mediated cow's milk allergy. *J Allergy Clin Immunol.* 2007;120(5):1172–1177. https://doi.org/10.1016/j.jaci.2007.08.023
94. Savage JH, Matsui EC, Skripak JM, Wood RA. The natural history of egg allergy. *J Allergy Clin Immunol.* 2007;120(6):1413–1417. https://doi.org/10.1016/j.jaci.2007.09.040
95. Keet CA, Matsui EC, Dhillon G, Lenehan P, Paterakis M, Wood RA. The natural history of wheat allergy. *Ann Allergy Asthma Immunol.* 2009;102(5):410–415. https://doi.org/10.1016/s1081-1206(10)60513-3

96. Savage JH, Kaeding AJ, Matsui EC, Wood RA. The natural history of soy allergy. *JAllergy Clin Immunol.* 2010;125(3):683–686. https://doi.org/10.1016/j.jaci.2009.12.994
97. Fleischer DM, Conover-Walker MK, Matsui EC, Wood RA. The natural history of tree nut allergy. *J Allergy Clin Immunol.* 2005;116(5):1087–1093. https://doi.org/10.1016/j.jaci.2005.09.002

Test Your Knowledge Answers

1. The correct answer is **D**. Allergens are usually proteins or glycoproteins. Except for galactose-α-1,3-galactose sensitization in allergic reactions specific to meat, allergies do not develop to carbohydrates. Allergies to IVFE, amino acid solution, and multivitamin solution have all been described.
2. The correct answer is **B**. Children under 2 years of age avoiding milk and soy protein are at increased risk of consuming insufficient fat, protein, calcium, vitamin D, zinc, iron, and total energy. Enriched rice milk provides adequate vitamin D and calcium but does not provide appropriate fat, protein, and energy intake. An appropriate substitute for liquid intake would be a hydrolysate formula or, if that is not tolerated, an elemental formula.
3. The correct answer is **D**. In a patient with a history of anaphylaxis to a food, a food challenge at home should never be recommended. Follow-up with an allergist is the only safe way to assess if a patient has "outgrown" or developed tolerance to the food. Annual follow-up assessment with an allergist is recommended for children with food allergies. The nutrition assessment of these children should always review growth and nutrient intake. By obtaining a 24-hour recall and reviewing common foods consumed, exposures to food allergens can be identified. If a patient is tolerating exposures to foods that were allergenic, again the patient must follow up with the allergist to clarify the allergen list. Liberalizing a patient's diet will provide more options for improving the overall nutrition intake.
4. The correct answer is **A**. In IgE-mediated anaphylaxis, cutaneous signs such as an urticarial rash are typical. The absence of cow's milk–

specific IgE on a RAST makes an IgE-mediated mechanism unlikely. This clinical scenario is consistent with food protein–induced enterocolitis syndrome, and avoidance of cow's milk is the most important therapy. A protein hydrolysate formula would be an effective substitute or, if not tolerated, an elemental formula.

The authors of this chapter wish to thank Cassandra Walia, MS, RD, for her contribution to previous editions of this text.

19

Diabetes Mellitus and Other Endocrine Disorders

Michelle Reed, MS, RD, CSP, LDN, CDCES

Learning Objectives

1. Define the common types of diabetes mellitus that occur in childhood.
2. Discuss how to create a parenteral formulation or choose an enteral formula for a child with diabetes mellitus who is receiving nutrition support.
3. Report considerations for insulin administration in a child with diabetes on parenteral or enteral nutrition support.
4. Describe how to prevent hyponatremia or hypernatremia in a child with central diabetes insipidus on nutrition support.

Introduction

Diabetes mellitus is one of the most common chronic illnesses affecting the pediatric population. It results from an absolute or relative lack of insulin, with or without insulin resistance. While several different causes exist for diabetes in children, all forms of diabetes mellitus are associated with elevated plasma glucose, and most forms are associated with dyslipidemia, except for cystic fibrosis—related diabetes. In this chapter, we focus on the

most common types of diabetes (the less common types of diabetes are beyond the scope of this book).

Types of Diabetes

The most common types of diabetes are type 1, type 2, cystic fibrosis–related, and drug-induced.

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) remains the most common form of diabetes in children.[1] In T1DM, the autoimmune destruction of the β cells of the pancreas results in an absolute deficiency of insulin.[2] The etiology of T1DM is a combination of genetic predisposition with environmental triggers. The genetic predisposition could explain the increased risk of T1DM in siblings of individuals with the disease.[2–4] The incidence of T1DM in the United States and other Western countries has been increasing. In the United States, the prevalence of T1DM in children and adolescents ages 19 years and younger is 2 to 3 per 1000.[1] The incidence of T1DM is higher in non-Hispanic white children compared with other ethnicities in the United States.[1]

At the time of diagnosis, children with T1DM present with hyperglycemia (plasma glucose ≥ 200 mg/dL, hemoglobin A1c ≥ 6.5%), typically with characteristic symptoms including polyuria, polydipsia, nocturia, enuresis, weight loss, and fatigue. These symptoms resolve with the initiation of insulin therapy. One-third of youth present with diabetic ketoacidosis (DKA) at the time of diagnosis.[5] Children in DKA experience dangerous electrolyte depletion and a small portion will suffer from cerebral edema, which has a mortality rate of 21% to 25%.[5,6] Vascular complications are not present at the time of disease presentation because of the rapid escalation of glucose experienced over a short time before diagnosis.

Intensive insulin replacement using multiple daily injections or subcutaneous administration through an insulin pump is the recommended treatment for T1DM based on its safety and effectiveness compared with less intensive insulin regimens.[7] Intensive insulin replacement combines

rapid-acting boluses of insulin for carbohydrate intake and glucose correction with long-acting or continuous basal insulin. The basal-bolus regimen is designed to physiologically mimic the normal action of intrinsic insulin.[5]

Type 2 Diabetes Mellitus

A global epidemic of childhood obesity has occurred in the last few decades, associated with a marked increase in the incidence of children with type 2 diabetes mellitus (T2DM).[8–10] In recent years, rates of childhood obesity and T2DM escalated further as a result of widespread school closures and quarantine orders during the COVID-19 pandemic.[10–13] In the United States, T2DM accounts for one-third of new diabetes diagnoses in children and adolescents.[1] The incidence of T2DM varies by ethnic group, with the highest incidence in Native American and African American children, followed by Hispanic American and Pacific Islander/Asian children, and a relatively low incidence in White children.[1]

The development of youth-onset T2DM in children and adolescents is the result of insulin resistance combined with deteriorating β-cell function, driven by genetic, environmental, and metabolic causes rather than an autoimmune etiology.[9,14] In comparison to adults with T2DM, youth with T2DM experience worse insulin resistance and more rapid β-cell deterioration.[9,15–17] Approximately 6% of youth with T2DM present with DKA at diagnosis. Youth with T2DM are at greater risk of microvascular and macrovascular complications compared with those diagnosed as adults, and they can develop complications at a relatively young age that can be present at diagnosis.[15]

T2DM in youth is rarely diagnosed before the onset of puberty, and the diagnosis is made after presenting with a symptomatic hyperglycemic event or as a result of routine screening in the outpatient setting, often when the youth is asymptomatic. Screening for diabetes is recommended for youth aged > 10 years with a body mass index (BMI) > 85th percentile and at least one risk factor for developing T2DM. Risk factors include the following:

- maternal history of diabetes or gestational diabetes during the child's gestation,
- family history of T2DM,
- race or ethnicity associated with high T2DM incidence, and
- conditions associated with insulin resistance (eg, acanthosis nigricans, dyslipidemia, hypertension, polycystic ovary syndrome, history of being small for gestational age, or having intrauterine growth restriction).[18]

Screening can be performed with fasting plasma glucose, HgbA1c, or an oral glucose tolerance test.[18] Islet autoantibodies, the laboratory marker for autoimmunity in T1DM, should be assessed at diagnosis for all youth with diabetes, even those with presumed T2DM. Misdiagnosis of T2DM in a child with autoimmune T1DM can delay insulin initiation, leading to health deterioration and putting them at risk for developing DKA.

Treatment for T2DM in children includes lifestyle modifications (weight management, healthy diet pattern, regular exercise) and pharmacologic management (metformin, glucagon-like peptide 1 [GLP-1] receptor agonists, sodium-glucose transport protein 2 [SGLT2] inhibitors, and insulin).[15] Pharmacotherapy selection is dependent on the degree of hyperglycemia, mechanism of action, route of administration, side-effect risk, the impact of comorbidities and complications, and cost.[9] Insulin therapy is recommended for all youth with T2DM with a HgbA1c > 8.5%.[9,15] Depending on the severity of the hyperglycemia and the presence of acidosis and/or ketoacidosis, an intensive insulin regimen as previously described for T1DM may be prescribed.[15]

Cystic Fibrosis–Related Diabetes Mellitus

Cystic fibrosis (CF) is an autosomal recessive genetic disease with multiorgan involvement.[19] CF-related diabetes is the most common comorbidity in individuals with CF, affecting approximately 20% of adolescents and 40% to 50% of adults.[19,20] Individuals with CF-related diabetes exhibit both insulin deficiency from progressive β-cell dysfunction and intermittent periods of insulin resistance, such as during an acute pulmonary exacerbation or with systemic corticosteroid treatment.[19–21]

Children with CF-related diabetes may be asymptomatic for years, not exhibiting the classic symptoms of polyuria and polydipsia associated with other types of diabetes mellitus, and the diagnosis is not associated with diabetic ketoacidosis.[19–21] The diagnosis of CF-related diabetes is typically made during routine screening with an oral glucose tolerance test (recommended annually for ages > 10 years) or with plasma glucose monitoring during acute illness.[19,20] HgbA1c is not a reliable screening lab for CF-related diabetes.

For individuals with CF who have chronic malnutrition despite comprehensive interventions to increase oral intake, nocturnal continuous enteral feeds may be recommended.[22] Continuous enteral feeds can unveil underlying glucose dysregulation in this population. Glucose levels should be checked mid-feeding and immediately post-feeding when enteral feeds are initiated and then monthly thereafter.[20] The diagnosis of CF-related diabetes can be made with plasma glucose levels that exceed 200 mg/dL mid-feeding or postfeeding on 2 separate days.[20]

The diagnosis of CF-related diabetes is associated with a decline in pulmonary function, malnutrition, and increased mortality.[20,21] Microvascular complications occur at lower rates in CF-related diabetes compared with T1DM or T2DM, and macrovascular complications are uncommon.[19–21,23] Insulin is the only recommended treatment for CF−related diabetes and can range from just once daily basal insulin to intensive insulin replacement, depending on the degree of hyperglycemia.[20,21]

Drug-Induced Diabetes

Various medications have the adverse side effect of glucose dysregulation. The most common medications to cause drug-induced diabetes in pediatric patients are anti-inflammatory, antineoplastic, and immunomodulatory therapies.[24]

Acute lymphoblastic leukemia (ALL) is the most common form of cancer in children and adolescents, accounting for 20% of cancer diagnoses in individuals under 20 years of age.[25] L-asparaginase, a standard treatment for ALL, decreases insulin production, increases glucagon production, and

impairs insulin receptor function.[24] Additionally, pancreatitis is a known toxicity of L-asparaginase treatment, and it can result in β-cell destruction and long-term insulin-dependent diabetes.[24,26]

From 2018 to 2022, more than 9000 children and adolescents under 18 years of age were the recipients of solid organ transplants.[27] Immunosuppression is essential in the prevention and treatment of solid organ rejection. Several common immunosuppressants are associated with hyperglycemia. Calcineurin inhibitors (tacrolimus and cyclosporine) decrease insulin production and secretion. Tacrolimus promotes β-cell destruction in the pancreas and has a much stronger hyperglycemic effect compared with cyclosporine.[24,28] Sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, decreases peripheral insulin sensitivity and promotes β-cell destruction.[24,28]

Glucocorticoids are used for immunosuppression in transplant recipients and for the treatment of numerous conditions affecting pediatric patients, including hematologic malignancies, rheumatologic conditions, and inflammatory bowel disease. Glucocorticoids promote insulin resistance, increase gluconeogenesis, and reduce insulin production and secretion.[24,28] It is important to note that the hyperglycemic effect of glucocorticoids is only seen with systemic treatment. Inhaled glucocorticoids do not affect glucose regulation.

Glucose Control in Healthy Children With Diabetes

Complications of diabetes (nephropathy, retinopathy, neuropathy, and macrovascular disease) are the result of chronic hyperglycemia. Targets for glucose control are aimed at preventing these chronic complications. While glucose targets should be individualized for each child with diabetes, the American Diabetes Association and the International Society for Pediatric and Adolescent Diabetes both recommend a target HgbA1c of <7% (equivalent to an average glucose of <154 mg/dL).[15,29] Evidence indicates that achieving a HgbA1c < 7% through intensive diabetes management

significantly reduces the risk of developing vascular complications in adulthood.[30]

The pursuit of tight glucose control can increase the risk of hypoglycemia. Severe hypoglycemia can result in loss of consciousness, seizure, coma, or death.[15] Studies have reported lasting cognitive impairment in young children who experience severe hypoglycemia.[31,32] However, 2 multicenter studies, the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications, found no evidence of cognitive impairment in adults or adolescents who had experienced repeated severe hypoglycemic episodes.[33]

In recent years, the widespread utilization of advanced diabetes technologies has made it safer to pursue more stringent glucose targets in children.[15] Diabetes technologies include continuous glucose monitoring (CGM) devices and continuous subcutaneous insulin infusion (CSII) pump devices. The use of these technologies is now becoming the standard of care and has been associated with the achievement of HgbA1C levels of <7% in children and adolescents with T1DM.[34]

CGM devices are wearable technologies that continuously measure glucose levels in the interstitial fluid underneath the skin, providing real-time data to users on their smartphone device or a handheld receiver provided by the CGM manufacturer. The devices show updated glucose readings in intervals as short as 1 and 5 minutes, trend data to indicate if glucose level is rising or falling, and alarm for episodes of hypoglycemia or hyperglycemia.[35] CGM devices can provide detailed interpretation of glucose data, including the calculation of a glucose-control metric called "time in range," which is the percentage of time spent with glucose between 70 and 180 mg/dL. A time-in-range level of >70% is associated with comparably favorable outcomes to a HgbA1c of <7%.[36] CGM devices allow the safe pursuit of tight glycemic control in pediatrics given the ability to readily identify and quantify hypoglycemia. Time below range (<70 mg/dL) should be kept to <5%.[36]

CSII pump devices dispense insulin at a sustained basal rate, with intermittent boluses administered for carbohydrate coverage and hyperglycemia correction prompted by the user.[37] Compared to multiple

daily injections with long-acting and rapid-acting insulin, CSII pump therapy is much more comparable to the physiological insulin profile.[37] CSII pump devices are now designed to receive data from CGM devices to inform an algorithm in the system that will augment insulin delivery.[37,38] These systems that coordinate both diabetes technologies for enhanced insulin delivery are called automated insulin delivery (AID) systems.

The first generation of AIDs was designed to suspend insulin delivery in anticipation of hypoglycemia, reducing the frequency and severity of hypoglycemic events. The second-generation systems, or "hybrid closed-loop" technology, added automated basal rate adjustments with or without automated correction boluses to prevent and attenuate hyperglycemia.[38] Hybrid closed-loop systems are associated with a 5.5% to 14.0% increase in time in range, which translates to an additional 1.2 to 3.4 hours per day of blood glucose in the desired range.[38] The use of AID systems has been safe and effective in children, including preschool age and younger.[37–40]

Consequences of Hyperglycemia and Hypoglycemia in Critically Ill Children

Hyperglycemia appears to be common in pediatric intensive care units (ICUs) regardless of whether a child has known diabetes mellitus.[41-46] Reported rates of hyperglycemia in pediatric ICUs range from 37% to 83% of patients, but hyperglycemia definitions are not consistent across the literature, contributing to the variability.[41-46] The pathophysiology of hyperglycemia in critically ill patients in the pediatric population is multifactorial. Increased endogenous counter-regulatory hormone secretion (ie, epinephrine, norepinephrine, cortisol, glucagon) and proinflammatory mediators drive insulin resistance by interfering with normal insulin signaling in target cells. Simultaneously, this increase in hormones and proinflammatory cytokines reduces insulin secretion by inhibiting β-cell function.[46-48] Research suggests that β-cell dysfunction may contribute to glucose dysregulation in the pediatric population to a greater extent compared with critically ill adult patients.[47,48]

Acute glycemic fluctuations induce endothelial apoptosis and amplify endothelial dysfunction and oxidative stress responses.[49] Hyperglycemia has been shown to adversely impact outcomes in critically ill children. In one retrospective study involving 552 children in a pediatric ICU, initial blood glucose concentration >200 mg/dL upon admission to the ICU was associated with mortality.[41] In a smaller study of 170 critically ill pediatric patients, a dose–response relationship was observed between maximum blood glucose concentration during ICU admission (or during the first week of an extended ICU admission) and mortality, as well as multiple organ dysfunction.[42]

Hypoglycemia in critically ill children is also deleterious, but less common than hyperglycemia, with reported rates ranging from 10% to 33%.[41-46] The literature has a greater consensus for hypoglycemia cutoff, typically defined as <60 to 65 mg/dL. Critical illness shifts the body into a catabolic state, increasing carbohydrate metabolism and decreasing glucose production, which can result in hypoglycemia.[44] Inadequate nutrient delivery in the ICU setting further contributes to hypoglycemia occurrence.[44] Hypoglycemia may be associated with multiple organ dysfunction and severe hypoglycemia (<40–50 mg/dL) with increased mortality.[41,42]

Tight Glycemic Control in the Intensive Care Unit

The question of whether tight glycemic control is linked with better outcomes in critically ill pediatric patients is controversial. A randomized, prospective study of infants and children (ages 1–16 y) found that tight glycemic control (defined as 50–79 mg/dL and 70–99 mg/dL for infants and children, respectively) was associated with improved morbidity and mortality, attenuated inflammatory response, infection prevention, and reduced extended ICU stays compared with conventional glycemic control (180–214 mg/dL).[50]

Another randomized, prospective study of infants and children (ages <16 y) demonstrated shorter hospital length of stay (LOS) and reduced renal-

replacement therapy in patients in the tight glycemic control (72–126 mg/dL) group compared with the conventional glycemic control (<216 mg/dL) group but no differences in mortality or mechanical ventilation use.[51] A multicenter study in the same age group found no difference in mortality, ICU-free days, or infection rate between tight glycemic control (80–110 mg/dL) and conventional glycemic control (150–180 mg/dL).[52] In a study of infants and young children (0–36 mo) undergoing surgery with cardiopulmonary bypass, tight glycemic control (80–110 mg/dL) did not prove beneficial in any outcomes (mortality, infection rate, LOS, or measures of organ failure) compared with standard care in the cardiac ICU.[53]

Results are mixed as to whether tighter glycemic control in critically ill infants and children results in a greater occurrence of hypoglycemic events.[50–53] In studies with a significantly increased risk of hypoglycemia among the tight glycemic control group, it may have been the result of lowering the threshold of minimum desired blood glucose level below 80 mg/dL.[50,51] Acute hypoglycemia as a result of tight glycemic control in the ICU may have lasting consequences. In a long-term follow-up study of 214 pediatric patients who had been randomized to tight glycemic control (80–110 mg/dL) or higher-target glycemic control (150–180 mg/dL) during critical illness, no significant between-group differences in neurobehavioral and quality-of-life outcomes were observed 1 year after ICU discharge.[54] However, tighter glycemic control was associated with a high risk of hypoglycemic events in the ICU, and any episode of hypoglycemia was associated with long-term consequences for physical health and psychosocial impairment.[54] Another study found that critically ill children who experienced hypoglycemia in the ICU had executive functioning deficits at 4-year follow-up when compared with critically ill children without hypoglycemia.[55]

Glucose Control in Children With Diabetes

Mellitus on Enteral Nutrition

Choice of Formula

The use of enteral formulas designed for patients with diabetes has not been studied in children with diabetes or critically ill children with acute hyperglycemia. Diabetes-specific enteral formulas are lower in carbohydrates (30%–35% kcal) and typically higher in fat (45% kcal), often with an emphasis on monounsaturated fatty acids and added fiber.[56] A meta-analysis of research in critically ill adults found that diabetes-specific enteral formulas were significantly associated with improved glycemic control compared with standard enteral formulas, but there was no association with improved clinical outcomes.[56] Authors were unable to support or refute the effectiveness of therapeutic enteral formulas because of the overall low quality of the evidence: few trials, relatively low sample size, and heterogenous study design.[56]

The American Society for Parenteral and Enteral Nutrition does not recommend diabetes-specific formula in hospitalized adults with hyperglycemia because of insufficient evidence.[57] Due to inconclusive research in the adult population and an absolute lack of evidence in the pediatric population, standard age-appropriate formula (rather than diabetes-specific formula) should be used in patients with diabetes or acute hyperglycemia.

Administration of Insulin

Blood glucose concentrations in children with diabetes on enteral nutrition (EN) support can usually be adequately controlled with subcutaneous injections of insulin. Insulin dosing should always be individualized and adjusted based on careful monitoring of blood glucose concentration. Initiation of insulin at 0.3 to 0.6 units/kg/d is appropriate, with daily titration based on glucose levels, which should be obtained on a scheduled basis every 3 to 6 hours.[58] There are no guidelines for glycemic control in hospitalized pediatric patients receiving nutrition support, but the recommended target blood glucose range of 140 to 180 mg/dL in adults receiving nutrition support is an appropriate initial goal.[57,59]

If a patient is receiving bolus feedings, insulin can be dosed using a basal-bolus regimen, with rapid-acting insulin administered for the carbohydrate content at the start of each feed. With continuous feedings, there are several strategies of insulin dosing that can be considered: long-acting insulin, neutral protamin Hagedorn (NPH) insulin, or premixed NPH-regular insulin. In a small retrospective study in non-critically ill adults with diabetes receiving continuous enteral feeds, 70/30 NPH-regular insulin administration 3 times daily was associated with better blood glucose control (maintenance in target range of 140–180 mg/dL) compared with twice daily 70/30 NPH-regular insulin administration or basal-bolus regimen.[60] Time in range for the 3 regimens were 69%, 22%, and 24%, respectively.[60] In another retrospective study comparing non-critically ill adults with diabetes receiving continuous feeds, basal-bolus and NPH-insulin regimens were comparable in glucose control (22% vs 24% time-in-range of 140–180 mg/dL), although the NPH group lagged behind the basal-bolus group in time to achieve target blood glucose control (defined as time needed to achieve 3 successive blood glucose readings in target range; 4.3 + 2.4 days compared with 3.6 + 1.7 days).[61] There are no studies comparing insulin regimens among pediatric patients receiving continuous EN.

Regardless of the insulin regimen, it is important to consider active insulin before abrupt discontinuation of continuous EN. Otherwise, the patient is at risk for hypoglycemia when insulin remains active in the body while the administration of glucose is interrupted.[60] Similarly, the condensing of enteral feeds requires careful coordination among interdisciplinary team members including endocrine providers to ensure that the new feeding schedule is safely and adequately covered by the insulin regimen. Typical duration of action for NPH and 70/30 biphasic insulin are comparable, 12 to 18 hours and 14 to 18 hours, respectively. In a basal-bolus regimen, rapid-acting bolus insulin will be active for 2 to 4 hours while long-acting basal insulin is active for up to 24 hours. If enteral feeds are discontinued while insulin is active, close blood glucose monitoring should be performed to identify and treat hypoglycemic events in a timely manner.

Glucose Control in Children With Diabetes Mellitus on Parenteral Nutrition

Choice of Dextrose Solution

No data suggest that children with diabetes require a special formulation for parenteral nutrition (PN). The composition of the PN solution should be determined independent of whether the patient has diabetes. This includes the choice of the final concentration of dextrose. The minimum recommended glucose infusion rate (GIR) for age should be met even in the setting of hyperglycemia. It is reasonable to limit the administration of dextrose beyond the minimum GIR in the setting of hyperglycemia unless it prevents the adequate provision of calories. Insulin administration, rather than dextrose restriction, should be the intervention for hyperglycemia in the setting of PN.

Use of an Insulin Infusion

When an intravenous (IV) infusion containing a high concentration of dextrose is given to a child (or adult) with diabetes, blood glucose concentrations are most safely controlled using a separate IV insulin infusion.[62] If insulin is given intravenously, the infusion can easily be changed if the rate of IV glucose administration is changed. Using a syringe pump, the insulin infusion can be directly "piggybacked" into the IV line. A reasonable rate to begin such an infusion would be 0.02 to 0.05 U of regular insulin per kilogram body weight per hour, taking into consideration the patient's clinical status and the presence of urine ketones. The rate of insulin administration can be changed to optimize blood glucose control. Frequent blood glucose monitoring is required for those receiving IV insulin, often performed at least hourly in children until blood glucose concentrations appear to be stable. Blood glucose concentrations are easiest to control if the PN is given as a continuous infusion, rather than being cycled.

Addition of Insulin to PN Solutions

If a separate IV insulin infusion is used to control blood glucose concentrations and both the rate of insulin infusion and blood glucose

concentrations have remained stable for 24 hours, the separate insulin infusion can be discontinued and replaced with insulin added directly to the PN. However, it is important to note that the addition of insulin to PN solutions is controversial. In vitro data raise concerns regarding insulin availability and bioactivity after being added to PN solutions.[63,64] Higher insulin dosing has been associated with greater insulin availability, both immediately after the addition of insulin to the PN solution and 24 hours later.[64] The inclusion of intravenous lipid emulsion (ILE) and higher doses of ILE have been associated with greater insulin availability, potentially because ILE prevents a direct reaction between insulin and plastic surfaces.[64]

In vivo data suggest that insulin added to PN solutions can effectively manage hyperglycemia. In non-critically ill adult patients with T2DM, regular insulin added to PN and subcutaneous long-acting basal insulin can both be used to achieve comparable glycemic control.[65,66] There is no pediatric research available comparing insulin as an additive in PN with insulin administered intravenously.

Enteral Nutrition Support in Cystic Fibrosis–Related Diabetes

Choice of Formula

In children with CF, optimal growth is integral to supporting lung health. When optimal growth cannot be achieved, supplemental enteral tube feeding may be recommended by the CF team.[22] The Cystic Fibrosis Foundation recommends continuous nocturnal feeds for individuals receiving supplemental EN to allow for greater appetite and oral intake during the day.[22] The Cystic Fibrosis Foundation does not recommend for or against any specific type of formula, although higher-calorie formulas (1.5 kcal/mL) are likely required.[22] The added diagnosis of CF-related diabetes does not impact formula selection.[67]

Control of Blood Glucose

Blood glucose concentrations in children with CF-related diabetes receiving EN support can usually be managed with subcutaneous insulin. Premixed NPH/regular or NPH/rapid-acting insulin can be used to manage continuous nocturnal feeds.[68] AID systems offer a unique approach to safely dosing insulin for nocturnal enteral feeds. In the event of an unexpected disruption in the enteral feed, AID systems can suspend insulin before a serious hypoglycemic event occurs. AID systems vary between CSII pumps, and some may be preferable to others in the management of nocturnal feeds. The use of CSII pump technologies in adolescents and young adults with CF-related diabetes is less common compared with their T1DM counterparts.[69]

For individuals with CF-related diabetes receiving enteral tube feedings, the importance of optimal pancreatic enzyme replacement therapy (PERT) and its relationship to glucose control cannot be overlooked. Approximately 90% of individuals with CF are pancreatic insufficient and require exogenous PERT to properly digest fat, protein, and carbohydrates. Without PERT, individuals with CF experience rapid gastric emptying, accompanied by impaired secretion of incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) and an insulin response deficiency.[70,71] Subsequently, an exaggerated postprandial glycemic excursion is observed.[70,71] Although pancreatic enzyme supplementation does not fully normalize these physiological disturbances, it does greatly attenuate the effect.[70,71] A review of PERT in individuals with CF receiving enteral tube feedings can be found in Chapter 26, "Pulmonary Disorders."

Nutrition Support in Other Endocrine Conditions

Central Diabetes Insipidus

Central or neurogenic diabetes insipidus is a relatively rare condition in children and results from an inability to secrete active vasopressin from the posterior pituitary gland.[72] While genetic defects in vasopressin synthesis have been described, the usual etiology of this condition is a hypothalamic

or posterior pituitary lesion.[72] Multiple potential causes underlie this condition, including tumors, inflammatory lesions, vascular diseases, and cranial malformations.[72]

Outpatient treatment for central diabetes insipidus in children with intact thirst sensation involves giving an analogue of vasopressin either orally or intranasally. These children are allowed to drink to thirst. Fluid intake in children without an intact thirst mechanism must be monitored carefully to prevent hyponatremia or hypernatremia. Infants with central diabetes insipidus are at higher risk for electrolyte abnormalities when they receive vasopressin analogs because their caloric intake is fluid-based and they lack access to free water. Many of these patients are managed with a low-solute diet (human milk or low-solute formula) and the use of thiazide diuretics.[73]

There do not appear to be any published guidelines on managing nutrition support in a child with central diabetes insipidus who might require PN. Because of the large volumes of fluid associated with such therapy, the child is at risk for both hyponatremia and hypernatremia. One option for managing these patients is to use a low-dose IV infusion of aqueous vasopressin, as has been described for children who are receiving additional fluid as part of a chemotherapy regimen.[74] To maintain adequate hydration and serum sodium concentrations, a dilute infusion of aqueous vasopressin is given at a starting rate of 0.08 to 0.1 mU/kg/h. During the infusion, fluid intake, urine output, body weight, urine specific gravity, and serum electrolyte concentrations are monitored carefully.

Panhypopituitarism

Another relatively uncommon endocrine condition that might affect nutrition support is panhypopituitarism. Again, no guidelines exist for how to manage nutrition support in such patients. Children with panhypopituitarism are unable to secrete several anterior pituitary hormones, including growth hormone and corticotropin. This condition can be the result of intracranial surgery but can also be idiopathic.

Neonates with this condition often present with hypoglycemia and are at continued risk for low blood sugar. Hypoglycemia arises from the pituitary gland being unable to secrete the counter-regulatory hormones during fasting.[75] To prevent hypoglycemia in a critically ill child with this

condition, additional glucocorticoids are administered. In such patients, a strong case can also be made for administering nutrition support as a constant infusion rather than giving enteral feeds as boluses or cycled PN.

Conclusion and Future Research

Many of the existing recommendations for diabetes care of patients receiving nutrition support are extrapolated from adult recommendations. Future studies should focus on confirming pediatric-specific recommendations for the management of critically ill children with diabetes, as well as optimal insulin dosing for children receiving EN or PN. With advancements in diabetes technology, researchers should investigate the safety and efficacy of using such technology for children receiving nutrition support, including children with CF-related diabetes who are chronically supplemented with nocturnal continuous feeds. Research should also explore the safety and efficacy of CGM in the hospitalized pediatric population. Inpatient use of CGM devices would provide more comprehensive insights into glucose trends, which would be specifically advantageous for assessing the adequacy of insulin regimens in patients receiving nutrition support.

Test Your Knowledge Questions

1. When a parenteral formulation is created for use in a child with diabetes mellitus, the dextrose concentration should be which of the following?
   A. Kept to a minimum
   B. No greater than 15%
   C. At least 20%
   D. Chosen without regard to whether the child has diabetes mellitus
2. In children with diabetes mellitus on EN, insulin should usually be which of the following?
   A. Discontinued
   B. Given parenterally
   C. Given subcutaneously

D. Given enterally

3. Serum sodium concentrations can be safely maintained in a child with diabetes insipidus on PN support by which of the following?
   A. Limiting oral fluids
   B. Administering a vasopressin analogue orally
   C. Doubling the patient's usual dose of a vasopressin analogue
   D. Using an intravenous drip of aqueous vasopressin

References

1. Lawrence JM, Divers J, Isom S, et al. Trends in prevalence of type 1 and type 2 diabetes in children and adolescents in the US, 2001–2017. *JAMA*. 2021;326(8):717–727. https://doi.org/10.1001/jama.2021.11165
2. Libman I, Haynes A, Lyons S, et al. ISPAD clinical practice consensus guidelines 2022: definition, epidemiology, and classification of diabetes in children and adolescents. *Pediatr Diabetes*. 2022;23(8):1160–1174. https://doi.org/10.1111/pedi.13454
3. Turtinen M, Härkönen T, Parkkola A, et al. Characteristics of familial type 1 diabetes: effects of the relationship to the affected family member on phenotype and genotype at diagnosis. *Diabetologia*. 2019;62(11):2025–2039. https://doi.org/10.1007/s00125-019-4952-8
4. Gillespie KM, Gale EA, Bingley PJ. High familial risk and genetic susceptibility in early onset childhood diabetes. *Diabetes*. 2002;51:210–214. https://doi.org/10.2337/diabetes.51.1.210
5. Dabelea D, Rewers A, Stafford JM, et al. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for diabetes in youth study. *Pediatrics*. 2014;133(4), e938–945. https://doi.org/10.1542/peds.2013-2795
6. Wolfsdorf JI, Allgrove J, Craig ME, et al. ISPAD clinical practice consensus guidelines 2014: Diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Pediatr Diabetes*. 2014;15(suppl 20):154–179. https://doi.org/10.1111/pedi.12165
7. ElSayed NA, Aleppo G, Aroda VR, et al. 9. Pharmacological approaches to glycemic treatment: standards of care in diabetes—2023.

Diabetes Care. 2023;46(suppl 1):S140–S157. https://doi.org/10.2337/dc23-S009
8. Copeland KC, Silverstein J, Moore KR, et al. Management of newly diagnosed type 2 diabetes mellitus (T2DM) in children and adolescents. *Pediatrics*. 2013;131(2):364–382. https://doi.org/10.1542/peds.2012-3494
9. Shah AS, Zeitler PS, Wong J, et al. ISPAD clinical practice consensus guidelines 2022: type 2 diabetes mellitus in children and adolescents. *Pediatr Diabetes*. 2022;23(7):872–902. https://doi.org/10.1111/pedi.13409
10. Jebeile H, Kelly AS, O'Malley G, Baur LA. Obesity in children and adolescents: epidemiology, causes, assessment and management. *Lancet Diabetes Endocrinol*. 2022;10(5):351–365. https://doi.org/10.1016/s2213-8587(22)00047-x
11. La Fauci G, Montalti M, Di Valerio Z, et al. Obesity and COVID-19 in children and adolescents: reciprocal detrimental influence-systemic literature review and meta-analysis. *Int J Environ Res Public Health*. 2022;19(13):7603. https://doi.org/10.3390/ijerph19137603
12. Chambers MA, Mecham C, Arreola EV, Sinha M. Increase in the number of pediatric new-onset diabetes and diabetic ketoacidosis cases during the COVID-19 pandemic. *Endocr Pract*. 2022;28(5):479–485. https://doi.org/10.1016/j.eprac.2022.02.005
13. Schmitt JA, Ashraf AP, Becker DJ, Sen B. Changes in type 2 diabetes trends in children and adolescents during the COVID-19 pandemic. *J Clin Endocrinol Metab*. 2022;107(7):e2777–e2782. https://doi.org/10.1210/clinem/dgac209
14. Arslanian S, Bacha F, Grey M, Marcus MD, White NH, Zeitler P. Evaluation and management of youth-onset type 2 diabetes: a position statement by the American Diabetes Association. *Diabetes Care*. 2018;41(12):2648–2668. https://doi.org/10.2337/dci18-0052
15. ElSayed NA, Aleppo G, Aroda VR, et al. Children and adolescents: standards of care in diabetes—2023. *Diabetes Care*. 2023;46(suppl 1):S230–S253. https://doi.org/10.2337/dc23-s014
16. RISE Consortium. Metabolic Contrasts between youth and adults with impaired glucose tolerance or recently diagnosed type 2 diabetes: I.

observations using the hyperglycemic clamp. *Diabetes Care*. 2018;41(8):1696–1706. https://doi.org/10.2337/dc18-0244
17. RISE Consortium. Metabolic contrasts between youth and adults with impaired glucose tolerance or recently diagnosed type 2 diabetes: II. observations using the oral glucose tolerance test. *Diabetes Care*. 2018;41(8):1707–1716. https://doi.org/10.2337/dc18-0243
18. Hampl SE, Hassink SG, Skinner AC, et al. Clinical practice guideline for the evaluation and treatment of children and adolescents with obesity. *Pediatrics*. 2023;151(2):e2022060640. https://doi.org/10.1542/peds.2022-060640
19. Khare S, Desimone M, Kasim N, Chan CL. Cystic fibrosis-related diabetes: prevalence, screening and diagnosis. *J Clin Transl Endocrinol*. 2021;27:100290. https://doi.org/10.1016/j.jcte.2021.100290
20. Moran A, Brunzell C, Cohen RC, et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. *Diabetes Care*. 2010;33(12):2697–2708. https://doi.org/10.2337/dc10-1768
21. O'Riordan SM, Robinson PD, Donaghue KC, Moran A. Management of cystic fibrosis-related diabetes in children and adolescents. *Pediatr Diabetes*. 2009;10(suppl 12):43–50. https://doi.org/10.1111/j.1399-5448.2009.00587.x
22. Schwarzenberg SJ, Hempstead SE, McDonald CM, et al. Enteral tube feeding for individuals with cystic fibrosis: Cystic Fibrosis Foundation evidence-informed guidelines. *J Cyst Fibros*. 2016;15(6):724–735. https://doi.org/10.1016/j.jcf.2016.08.004
23. Schwarzenberg SJ, Thomas W, Olsen TW, et al. Microvascular complications in cystic fibrosis-related diabetes. *Diabetes Care*. 2007;30(5):1056–1061. https://doi.org/10.2337/dc06-1576
24. Tosur M, Viau-Colindres J, Astudillo M, Redondo MJ, Lyons SK. Medication-induced hyperglycemia: pediatric perspective. *BMJ Open Diabetes Res Care*. 2020;8(1):e000801. https://doi.org/10.1136/bmjdrc-2019-000801

25. Siegel DA, Henley SJ, Li J, Pollack LA, Van Dyne EA, White A. Rates and trends of pediatric acute lymphoblastic leukemia—United States, 2001–2014. *MMWR Morb Mortal Wkly Rep*. 2017;66(36):950–954. https://doi.org/10.15585/mmwr.mm6636a3
26. Raja RA, Schmiegelow K, Frandsen TL (2012), Asparaginase-associated pancreatitis in children. *Br J Haematol*, 159:18–27. https://doi.org/10.1111/bjh.12016
27. National data: transplants in the US by recipient age. Organ Procurement and Transplantation Network. Accessed July 31, 2023. https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/
28. Grundman JB, Wolfsdorf JI, Marks BE. Post-transplantation diabetes mellitus in pediatric patients. *Horm Res Paediatr*. 2020;93(9–10):510–518. https://doi.org/10.1159/000514988
29. de Bock M, Codner E, Craig ME, et al. ISPAD clinical practice consensus guidelines 2022: glycemic targets and glucose monitoring for children, adolescents, and young people with diabetes. *Pediatr Diabetes*. 2022;23(8):1270–1276. https://doi.org/10.1111/pedi.13455
30. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:977–986. https://doi.org/10.1056/nejm199309303291401
31. Bjorgaas M, Gimse R, Vik T, Sand T. Cognitive function in type 1 diabetic children with and without episodes of severe hypoglycaemia. *Acta Paediatr*. 1997;86:148–153. https://doi.org/10.1111/j.1651-2227.1997.tb08856.x
32. Rovet J, Alvarez M. Attentional functioning in children and adolescents with IDDM. *Diabetes Care*. 1997;20:803–810. https://doi.org/10.2337/diacare.20.5.803
33. Nathan DM, DCCT/EDIC Research Group. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. *Diabetes Care*. 2014;37(1):9–16. https://doi.org/10.2337/dc13-2112
34. Demeterco-Berggren C, Ebekozien O, Noor N, et al. Factors associated with achieving target A1C in children and adolescents with type 1 diabetes: findings from the T1D exchange quality improvement

collaborative. *Clin Diabetes*. 2022;41(1):68–75. https://doi.org/10.2337/cd22-0073
35. Tauschmann M, Forlenza G, Hood K, et al. ISPAD clinical practice consensus guidelines 2022: diabetes technologies: glucose monitoring. *Pediatr Diabetes*. 2022;23(8):1390–1405. https://doi.org/10.1111/pedi.13451
36. ElSayed NA, Aleppo G, Aroda VR, et al. 6. Glycemic targets: standards of care in diabetes—2023. *Diabetes Care*. 2023;46(suppl 1):S97–S110. https://doi.org/10.2337/dc23-S006
37. Sherr JL, Schoelwer M, Dos Santos TJ, et al. ISPAD clinical practice consensus guidelines 2022: diabetes technologies: insulin delivery. *Pediatr Diabetes*. 2022;1–26. https://doi.org/10.1111/pedi.13421
38. Nallicheri A, Mahoney KM, Gutow HA, Bellini N, Isaacs D. Review of automated insulin delivery systems for type 1 diabetes and associated time in range outcomes. *touchREV Endocrinol*. 2022;18(1):27–34. https://doi.org/10.17925/ee.2022.18.1.27
39. von dem Berge T, Remus K, Biester S, et al. In-home use of a hybrid closed loop achieves time-in-range targets in preschoolers and school children: results from a randomized, controlled, crossover trial. *Diabetes Obes Metab*. 2022;24(7):1319–1327. https://doi.org/10.1111/dom.14706
40. Sherr JL, Bode BW, Forlenza GP, et al. Safety and glycemic outcomes with a tubeless automated insulin delivery system in very young children with type 1 diabetes: a single-arm multicenter clinical trial. *Diabetes Care*. 2022;45(8):1907–1910. https://doi.org/10.2337/dc21-2359
41. Toro-Polo LM, Ortiz-Lozada RY, Chang-Grozo SL, Hernandez AV, Escalante-Kanashiro R, Solari-Zerpa L. Glycemia upon admission and mortality in a pediatric intensive care unit. *Rev Bras Ter Intersiva*. 2018;30(4):471–478.
42. Bhutia TD, Lodha R, Kabra SK. Abnormalities in glucose homeostasis in critically ill children. *Pediatr Crit Care Med*. 2013;14(1):e16–e25. https://doi.org/10.1097/pcc.0b013e3182604998
43. Dong M, Liu W, Luo Y, et al. Glycemic variability is independently associated with poor prognosis in five pediatric ICU centers in

southwest China. *Front Nutr*. 2022;9:757982. https://doi.org/10.3389/fnut.2022.757982
44. Naranje KM, Poddar B, Bhriguvanshi A, et al. Blood glucose variability and outcomes in critically ill children. *Indian J Crit Care Med*. 2017;21(3):122–126. https://doi.org/10.4103/ijccm.IJCCM_364_16
45. Khan SA, Ibrahim MN, Anwar-ul-Haq. Frequency and mortality associated with hyperglycemic in critically ill children. *J Coll Physicians Surg Pak*. 2015;25(12):878–881. https://jcpsp.pk/archive/2015/Dec2015/09.pdf
46. El-Sherbini SA, Marzouk H, El-Sayed R, Hosam-ElDin S. Etiology of hyperglycemia in critically ill children and the impact of organ dysfunction. *Rev Bras Ter Intensiva*. 2018;30(3):286–293. https://www.scielo.br/j/rbti/a/cwHJ8Yd7g8SVSRXBG6xck4n/abstract/?lang=en#
47. Hacıhamdioğlu B, Kendirli T, Oçal G, et al. Pathophysiology of critical illness hyperglycemia in children. *J Pediatr Endocrinol Metab*. 2013;26(7–8):715–720. https://doi.org/10.1515/jpem-2012-0313
48. Preissig CM, Rigby MR. Hyperglycaemia results from beta-cell dysfunction in critically ill children with respiratory and cardiovascular failure: a prospective observational study. *Crit Care*. 2009;13(1):R27. https://doi.org/10.1186/cc7732
49. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycinemia. *Lancet*. 2009;373(9677):1798–1807. https://doi.org/10.1016/s0140-6736(09)60553–5
50. Vlasselaers D, Milants I, Desmet L, et al. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. *Lancet*. 2009;373:547–556. https://doi.org/10.1016/s0140-6736(09)60044-1
51. Macrae D, Grieve R, Allen E, et al. A randomized trial of hyperglycemic control in pediatric intensive care. *N Engl J Med*. 2014;370:107–118. https://doi.org/10.1056/nejmoa1302564
52. Agus MS, Wypij D, Hirshberg EL, et al. Tight glycemic control in critically ill children. *N Engl J Med*. 2017;376(8):729–741. https://doi.org/10.1056/NEJMoa1612348

53. Agus MS, Steil GM, Wypij D, et al. Tight glycemic control versus standard care after pediatric cardiac surgery. *N Engl J Med*. 2012;367(13):1208–1219. https://doi.org/10.1056/NEJMoa1206044
54. Biagas KV, Hinton VJ, Hasbani NR, et al. Long-term neurobehavioral and quality of life outcomes of critically ill children after glycemic control. *J Pediatr*. 2020;218:57–63.e5. https://doi.org/10.1016/j.jpeds.2019.10.055
55. Gunst J, De Bruyn A, Jacobs A, et al. The association of hypoglycemia with outcome of critically ill children in relation to nutritional and blood glucose control strategies. *Crit Care*. 2023;27(1):251. https://doi.org/10.1186/s13054-023-04514-6
56. Eckert I, Kumbier MCC, Silva FM, Franzosi OS, de Almeida JC. Association of specialized enteral nutrition with glycemic control and clinical outcomes in critically ill patients: a meta-analysis of randomized controlled trials. *Clin Nutr*. 2021;40(6):3940–3949. https://doi.org/10.1016/j.clnu.2021.04.030
57. McMahon MM, Nystrom E, Braunschweig C, et al. A.S.P.E.N. clinical guidelines: nutrition support of adult patients with hyperglycemia. *JPEN J Parenter Enteral Nutr*. 2013;37(1):23–36. https://doi.org/10.1177/0148607112452001
58. Wesorick D, O'Malley C, Rushakoff R, Larsen K, Magee M. Management of diabetes and hyperglycemia in the hospital: a practical guide to subcutaneous insulin use in the non-critically ill, adult patient. *J Hosp Med*. 2008;3:17–28. https://doi.org/10.1002/jhm.353
59. ElSayed NA, Aleppo G, Aroda VR, et al. 16. Diabetes care in the hospital: standards of care in diabetes—2023. *Diabetes Care*. 2023;46(suppl 1):S267–S278. https://doi.org/10.2337/dc23-s016
60. Hsia E, Seggelke SA, Gibbs J, Rasouli N, Draznin B. Comparison of 70/30 biphasic insulin with glargine/lispro regimen in non-critically ill diabetic patients on continuous enteral nutrition therapy. *Nutr Clin Pract*. 2011;26(6):714–717. https://doi.org/10.1177/0884533611420727
61. Hijaze D, Szalat A. Retrospective evaluation of glycemic control with basal-bolus or neutral protamine hagedorn insulin regimens in patients receiving continuous enteral nutrition therapy in medical wards. *Nutr Clin Pract*. 2017;32(4):557–562. https://doi.org/10.1177/0884533617692765

62. Gosmanov AR, Umpierrez GE. Medical nutrition therapy in hospitalized patients with diabetes. *Curr Diab Rep*. 2012;12:93–100. https://doi.org/10.1007/s11892-011-0236-5
63. Henry H, Goossens JF, Kouach M, et al. Behavior of regular insulin in a parenteral nutrition admixture: validation of an LC/MS-MS assay and the in vitro evaluation of insulin glycation. *Pharmaceutics*. 2022;14(5):1081. https://doi.org/10.3390/pharmaceutics14051081
64. Forchielli ML, Bongiovanni F, Platé L, et al. Insulin instability in parenteral nutrition admixtures. *JPEN J Parenter Enteral Nutr*. 2018;42(5):907–912. https://doi.org/10.1002/jpen.1024
65. Olveira G, Abuín J, López R, et al. Regular insulin added to total parenteral nutrition vs subcutaneous glargine in non-critically ill diabetic inpatients, a multicenter randomized clinical trial: INSUPAR trial. *Clin Nutr*. 2020;39(2):388–394. https://doi.org/10.1016/j.clnu.2019.02.036
66. Truong S, Park A, Kamalay S, et al. Glycemic control in adult surgical patients receiving regular insulin added to parenteral nutrition vs insulin glargine: a retrospective chart review. *Nutr Clin Pract*. 2019;34(5):775–782. https://doi.org/10.1002/ncp.10252
67. Kaminski BA, Goldsweig BK, Sidhaye A, Blackman SM, Schindler T, Moran A. Cystic fibrosis related diabetes: nutrition and growth considerations. *J Cyst Fibros*. 2019;18 Suppl 2:S32–S37. https://doi.org/10.1016/j.jcf.2019.08.011
68. Ode KL, Chan CL, Granados A, Moheet A, Moran A, Brennan AL. Cystic fibrosis related diabetes: medical management. *J Cyst Fibros*. 2019;18(suppl 2):S10–S18. https://doi.org/10.1016/j.jcf.2019.08.003
69. Scheuing N, Badenhoop K, Borkenstein M, et al. Why is insulin pump treatment rarely used in adolescents and young adults with cystic fibrosis-related diabetes? *Pediatr Diabetes*. 2015;16(1):10–15. https://doi.org/10.1111/pedi.12158
70. Perano SJ, Couper JJ, Horowitz M, et al. Pancreatic enzyme supplementation improves the incretin hormone response and attenuates postprandial glycemia in adolescents with cystic fibrosis: a randomized crossover trial. *J Clin Endocrinol Metab*. 2014;99(7):2486–2493. https://doi.org/10.1210/jc.2013-4417

71. Kuo P, Stevens JE, Russo A, et al. Gastric emptying, incretin hormone secretion, and postprandial glycemia in cystic fibrosis—effects of pancreatic enzyme supplementation. *J Clin Endocrinol Metab*. 2011;96(5):E851–E855. https://doi.org/10.1210/jc.2010-2460
72. Ghirardello S, Garre ML, Rossi A, Maghnie M. The diagnosis of children with central diabetes insipidus. *J Pediatr Endocr Metab*. 2007;20:359–375. https://doi.org/10.1515/jpem.2007.20.3.359
73. Rivkees SA, Dunbar N, Wilson TA. The management of central diabetes insipidus in infancy: desmopressin, low renal solute load formula, thiazide diuretics. *J Pediatr Endocrinol Metab*. 2007;20:459–469. https://doi.org/10.1515/jpem.2007.20.4.459
74. Bryant WP, Omarcaigh AS, Ledger GA, Zimmerman D. Aqueous vasopressin infusion during chemotherapy in patients with diabetes insipidus. *Cancer*. 1994;74:2589–2592. https://doi.org/10.1002/1097-0142(19941101)74:9<2589::AID-CNCR2820740929>3.0.CO;2-6
75. Bolli GB, Fanelli CG. Physiology of glucose counterregulation to hypoglycemia. *Endocrin Metab Clin*. 1999;28:467–493. https://doi.org/10.1016/s0889-8529(05)70083-9

Test Your Knowledge Answers

1. The correct answer is **D**. The concentration of dextrose used in the PN should be chosen based on the optimal formulation of the PN, rather than on the fact that the child has diabetes mellitus.
2. The correct answer is **C**. Acceptable blood glucose control in children with diabetes mellitus on EN can usually be obtained by using subcutaneous insulin. Insulin is usually not administered enterally.
3. The correct answer is **D**. Acceptable serum sodium concentrations in a child with diabetes insipidus on nutrition support can usually be obtained by using an intravenous drip of aqueous vasopressin.

The author of this chapter would like to thank Diane Olson, RD, CNSD, CSP, LD; Alaa Al Nofal, MD; and W. Frederick Schwenk II, MD, for their contributions to the previous editions of this text.

20

Inborn Errors of Metabolism

Sandy van Calcar, PhD, RD, LD

Learning Objectives

1. Recognize the principles of diagnosis, clinical pathology, and treatment of various inherited metabolic disorders.
2. Acquire knowledge about the biochemistry and medical nutrition therapy for disorders of protein metabolism (eg, phenylketonuria, methylmalonic acidemia, and the urea cycle disorder ornithine transcarbamylase deficiency), lipid metabolism (eg, very long-chain acyl-Coenzyme A [acyl-CoA] dehydrogenase deficiency) and carbohydrate metabolism (eg, classical galactosemia).
3. Explain the biochemistry of and medical nutrition therapy for mitochondrial metabolism disorders and cellular storage.

Introduction

Inborn errors of metabolism (IEM) are inherited disorders caused by variants in the nuclear and mitochondrial genes. These genes are responsible for the synthesis and storage of proteins that function as enzymes, coenzymes, and transporters. These proteins are necessary for the metabolism of amino acids, carbohydrates, lipids, or various micronutrients.[1] The presentation of a disease varies greatly depending on the specific IEM and the degree of deficiency; thus, many IEMs can present

at any age with a wide range of signs and symptoms. Severe forms of some disorders can present with overwhelming illness in the newborn period, including poor feeding, hypotonia, and seizures. Without prompt and aggressive treatment, they may eventually lead to coma and death. Some disorders do not present with overt illness but rather with complications such as intellectual disability that develop more gradually over time.[1]

Newborn Screening

Many IEMs can be detected in the neonate by newborn screening, which facilitates early diagnosis and initiation of treatment.[2,3] Newborn screening was initiated in the 1960s with elevated phenylalanine (Phe) as a marker of phenylketonuria (PKU). PKU is often referred to as the model for newborn screening for 2 reasons: (1) the methodology is reliable and cost-effective, (2), early intervention with medical nutrition therapy yields clear clinical benefits. In the 1990s, screening by tandem mass spectrometry (MS/MS) was introduced. Now, more than 30 IEMs can be detected from dried blood spots collected from newborns 24 to 48 hours after birth. However, the number of IEMs available on newborn screening panels in the United States varies by state and among countries in other parts of the world.[2–4]

Since the initiation of MS/MS screening, the overall prevalence of some IEMs is greater than originally believed. This is because the range of phenotypes that can be detected has increased to include not only those with classical forms of these disorders but milder variants as well.[2] Recent additions to newborn screening include lysosomal storage diseases, among others. Current research efforts to improve the detection of IEMs include development of secondary screening tools, including population-level molecular testing techniques.

Overview of Medical Nutrition Therapy for Inborn Errors of Metabolism

The overall goal of treatment for IEMs is to achieve and maintain improved metabolic homeostasis, while allowing appropriate growth and development. Medical nutrition therapy plays a large role in accomplishing this goal. The basic principles of nutrition management of IEMs include prevention of catabolism with adequate energy intake, restriction of the

offending substrate(s), supplementation of deficient products, and/or supplementation with the enzyme's cofactor(s).[5,6]

To meet nutrient needs but prevent excessive intake of substrates, specialized formulas, termed "medical foods," have been developed for the treatment of numerous IEMs. Medical foods do not contain substrates that cannot be metabolized. For instance, a medical food designed for an aminoacidopathy will be devoid of the amino acid(s) that cannot be completely metabolized, but will provide all other amino acids, with sources of carbohydrate and fat, and micronutrients.[5,6] If the blocked substrate is an essential amino acid, a limited but sufficient quantity of substrate must be provided to allow for protein anabolism. In infants, this is accomplished by providing a source of intact protein from a limited amount of regular infant formula or, for some disorders, human milk. As the patient ages, the intact protein will be provided by limited quantities of lower-protein foods. Careful laboratory, clinical, and developmental monitoring, and ongoing nutrition education are essential for managing individuals with IEMs.[5,6]

Emergency Management

Many IEMs are at high risk for acute metabolic crises and symptoms may be present before newborn screening results become available.[3] These events can also occur during subsequent catabolic events such as illness, surgery, injury, and the postpartum period. Increased energy needs and rapid accumulation of toxic metabolites can lead to life-threatening emergencies that require rapid medical attention. Presentations of neonates in metabolic crisis vary with the disorder, but some common signs and symptoms can include:

- poor feeding
- vomiting
- lethargy
- fluctuating muscle tone
- respiratory failure
- hepatic dysfunction
- cardiac abnormalities
- seizures

- coma[2,6]

Presenting laboratory abnormalities can include:

- hypoglycemia
- metabolic acidosis (high anion gap)
- ketonemia/ketonuria
- lactic acidosis
- hyperammonemia
- abnormal liver function labs
- thrombocytopenia

Metabolic crises need to be managed by physicians trained in treating IEMs with support from a dietitian specializing in nutrition support for these disorders. Caregivers must be educated about the signs and symptoms of an impending crisis and should be provided with an emergency letter that includes paging directions for on-call providers. Often, caregivers are given a "sick day protocol" with diet or other treatment modifications that may allow for home management of milder illness events.

To illustrate the diversity of IEMs and their nutrition management, this chapter provides a basic overview of disorders of protein, lipid, and carbohydrate metabolism; and mitochondrial myopathies. For each group, 1 or more specific disorders are highlighted with details of clinical pathology and treatment. These specific IEMs were selected because each has a relatively high incidence in North American populations and an established medical nutrition therapy is available. Various references can provide further detail about IEM biochemistry, heterogeneity, and treatment.[5–7]

Inborn Errors of Protein and Amino Acid Metabolism

Inherited disorders of protein metabolism that require medical nutrition therapy as part of treatment include aminoacidopathies and organic acidemias which involve the metabolism of essential amino acid(s) and disorders of the urea cycle required for nitrogen excretion from protein catabolism. Medical nutrition therapy (MNT) for these disorders typically

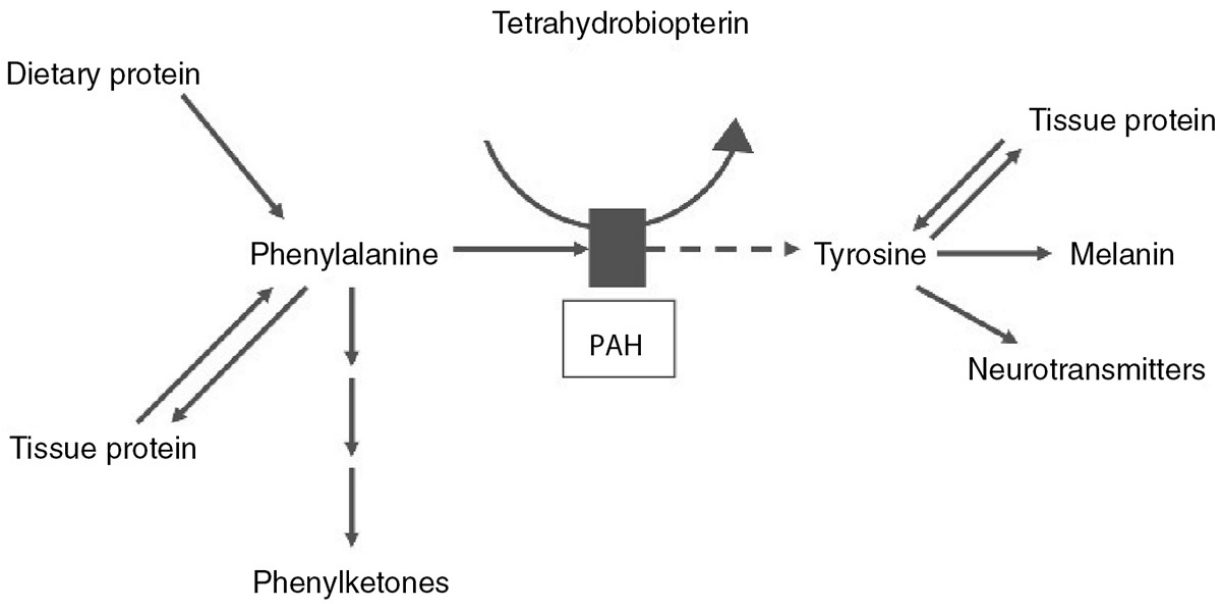
includes the use of medical food. The medical foods used in these disorders are the ones outlined in the example given in this overview.

Examples of protein metabolism disorders, including aminoacidopathy phenylketonuria, organic acidemia methylmalonic acidemia, and the urea cycle disorder ornithine transcarbamylase deficiency are presented in the next sections.

Phenylketonuria

Phenylketonuria (PKU) is an inborn error of phenylalanine (Phe) metabolism caused by a deficiency of the hepatic enzyme phenylalanine hydroxylase (PAH), which catalyzes the hydroxylation of Phe to tyrosine (Tyr; see Figure 20-1). PKU is an autosomal recessive disorder with an incidence of approximately 1 in 10,000–15,000 births with a carrier frequency of approximately 1 in 50 in those of European ancestry.[8] Over 1200 mutations have been identified in the PAH gene, but genotype–phenotype correlations have not proven to always predict outcome.[8,9]

FIGURE 20-1. Phenylketonuria Results From Phenylalanine Hydroxylase Deficiency With Elevated Phenylalanine Concentrations and Tyrosine Deficiency.



Abbreviation: PAH, phenylalanine hydroxylase. PAH requires the cofactor tetrahydrobiopterin. Food products made with glycomacropeptide, a low-phenylalanine whey protein, provide a new alternative to amino acid-based medical foods for nutrition management of phenylketonuria. Adapted with permission from the Academy of Nutrition and Dietetics from van Calcar SC, Ney DM. Food products made with glycomacropeptide, a low-phenylalanine whey protein, provide a new alternative to amino acid–based medical foods for nutrition management of phenylketonuria. *J. Acad. Nutr. Diet.* 2012;112(8):1201–1210.

PKU is often classified based on the degree to which blood Phe concentrations are elevated prior to treatment initiation. Individuals with classical (severe) PKU show blood Phe elevations >1200 μmol/L (20 mg/dL) compared to Phe concentrations <120 μmol/L (2 mg/dL) in individuals without PKU.[10] Individuals with untreated classical PKU are at risk for profound intellectual disability, seizures, and autistic-like behavior. Adequate treatment with a Phe-restricted diet ameliorates this outcome, and individuals with classical PKU can have similar IQ and developmental potential as their unaffected siblings, although adverse effects on executive function skills (ie, attention, memory, processing speed) can develop, even with good metabolic control.[11,12] On the other end of the spectrum, Phe

elevations in those with mild hyperphenylalaninemia remain <360 μmol/L (6 mg/dL) and may not require any diet modification.[13,14]

Treatment recommendations for PKU have evolved since diet therapy was first described in the 1950s.[15] Initially, metabolic specialists discontinued the Phe-restricted diet in early childhood because of the belief that brain development was complete and continuation of the diet could cause nutritional deficiencies.[16] This practice was formally evaluated in the National PKU Collaborative Study (1968–1984) in which 211 participants with classical PKU were randomized at age 6 years to continue or discontinue the PKU diet.[17] Results from this study demonstrated that individuals with PKU who discontinued the diet developed significant reductions in IQ and academic performance by the age of 12 years.[17,18] A follow-up study of 70 adults who participated in the PKU Collaborative Study found significantly fewer adverse medical, cognitive, and psychological outcomes in those who were randomized to remain on the PKU diet compared with those who stopped diet treatment.[19] Conclusions from these and other studies led to the recommendation of lifelong treatment for PKU.[10,12,18,20,21]

Initial Presentation

When an infant with PKU is identified by newborn screening, treatment should be initiated as soon as possible. Depending on the degree of elevation in blood concentrations, dietary Phe is eliminated or greatly reduced in the diet until blood Phe decreases below 360 μmol/L (6 mg/dL).[13,14] This can be accomplished by exclusively feeding a Phe-free medical food. Once plasma Phe concentrations are reduced, a limited quantity of an intact protein provided by a standard infant formula or human milk is added to the medical food to meet minimum Phe needs for growth and protein anabolism (see Table 20-1).[10,13,14]

TABLE 20-1. Recommended Daily Nutrient Intakes for Phenylketonuria[a]

Age	Nutrient			
	Phe	Tyr	Protein[b]	Energy (kcal/kg)
Infants[c] 0 to <3 mo[d] 3 to <6 mo 6to<9mo 9 to <12 mo	25–70 mg/kg 20–45 mg/kg 15–35 mg/kg 10–35 mg/kg	300–350 mg/kg 300–350 mg/kg 250–300 mg/kg 250–300 mg/kg	2.50–3.00 g/kg 2.00–3.00 g/kg 2.00–2.50 g/kg 2.00–2.50 g/kg	120 (145–95) 120 (145–95) 110 (135–80) 105 (135–80)
Early childhood 1 to <4 y[c]	200–320 mg/d	2800–3500 mg/d	≥30 g/d	EER
After early childhood >4 y to adult[e]	200–1100 mg/d	4000–6000 mg/d	120%–140% RDA for age	EER

Abbreviations: EER, estimated energy requirement; Phe, phenylalanine; RDA, recommended dietary allowance; Tyr, tyrosine.

[a] Data from Van Calcar[13] Singh et al.[14]

[b] Protein recommendations are greater than dietary reference intake estimates because of faster absorption and utilization of amino acids compared to intact protein.

[c] Recommended intakes for individuals <4 years old apply to those with classical phenylketonuria treated with diet only.

[d] Requirements for preterm infants may be higher.

[e] Recommended intakes for individuals >4 years old apply to the entire spectrum of phenotypes (mild to classical).

Chronic Management

The primary goal of chronic PKU management is dietary Phe restriction to maintain blood Phe within the recommended treatment range of 120 to 360 µmol/L (2–6 mg/dL) for all ages.[10,20,21] Adjustments in dietary Phe are based on frequent monitoring of blood Phe concentrations. If blood Phe is

elevated above the treatment range, the amount of intact protein is incrementally decreased.[10,13,14] Additional treatment goals include supporting normal growth and development, preventing protein deficiency, and achieving adequate macronutrient and micronutrient status.[13,14]

Energy requirements for individuals with PKU are no different from those for the general population; thus, standard dietary reference intake estimates can be utilized.[14,22] However, total protein needs for those with PKU may be greater than those for the general population because amino acids are more rapidly absorbed and utilized when free amino acids are given as the protein source rather than an intact protein.[23] Medical food continues to provide the primary source of protein for all ages.

Phe needs vary between individuals and change with age, weight, and growth velocity (see Table 20-1). In infancy, the Phe requirement is met by a standard infant formula or human milk (see Figure 20-2). Breastfeeding or chest feeding is possible during PKU treatment because metabolic control in infants consuming human milk is similar to those consuming regular infant formula as their Phe source.[24] The average Phe concentration of mature human milk is approximately 47 mg/100 mL; it is somewhat higher in colostrum.[13,25]

FIGURE 20-2. Calculating a Low Phenylalanine (Phe) Formula

An infant weighing 3.6 kg is diagnosed with phenylketonuria (PKU) with an initial blood Phe concentration of 15 mg/dL. Determine an appropriate formula for this infant.

Answer

Provide a Phe-free medical food until Phe concentrations are less than 6 mg/dL. Then add an intact protein source to meet nutrition needs.

DETERMINE NEEDS

1) ***Determine Phe Requirement using Table 22-2***
   3.6 kg × 45 mg of Phe*/kg = 162 mg of Phe per day
   *Phe requirements range from 25 to 70 mg/kg. Given the moderate elevation in blood Phe of 15 mg/dL, Phe requirements are estimated at 45 mg/kg.
2) ***Determine Tyrosine (Tyr) Requirement***
   3.6 kg × 325 mg of Tyr/kg = 1170 mg
3) ***Determine Protein Requirement***
   3.6 kg × 3.0 g of pro/kg ≈ 11–12 g of protein
4) ***Determine Calorie (kcal) Requirement***
   3.6 kg × ~120 kcal/kg ≈ 430–450 kcal

CALCULATE FORMULA

1) ***Determine the Amount of Infant Formula (the Source of Intact Protein) Needed to Meet Phe Needs***
   Infant formula A contains 330 mg of Phe in 100 g

$\frac{\text{162 mg of Phe needed per day} \times \text{100 g of infant formula}}{\text{330 mg of Phe}}$	= 49 g of infant formula A needed

2) ***Determine Amount of Calories and Protein in Infant Formula***
   Infant formula A contains 10.8 g of protein and 518 kcal in 100 g

$\frac{\text{49 g infant formula A} \times \text{10.8 g protein}}{\text{100 g of infant formula}}$	= 5.3 g of protein
$\frac{\text{49 g of infant formula A} \times \text{518 kcal}}{\text{100 g of infant formula}}$	= 254 kcal

3) ***Determine Amount of Phe-Free Medical Food B Needed to Meet Protein Needs***
   Phe-free medical food B contains 15 g of protein in 100 g
   11.5 g total protein needs − 5.3 g of protein from Infant formula A = 6.2 or ~6 g of protein needed

$\frac{\text{6 g of protein needed} \times \text{100 g of medical food B}}{\text{15 g of protein}}$	= 40 g of Phe-free medical food

4) ***Determine Calories from Phe-Free Medical Food B***

$\frac{\text{40 g of medical food B} \times \text{480 kcal}}{\text{100 g of Phe-free medical food}}$	= 192 kcal

FINAL RECIPE

PRODUCT	AMOUNT (g)	PHE (mg)	PROTEIN (g)	CALORIES (kcal)
Infant formula A	49	162	5	254
Phe-free medical food B	40	0	6	192
Total	—	162	11	446

Volume required at 20 kcal/oz = 22 fluid ounces (625 mL)

An individual's Phe requirement is the same regardless of the source of intact protein consumed (formula, human milk, or solid food). When an infant transitions to solids, the infant formula or human milk is decreased and replaced by an equivalent amount of Phe from foods.[13,14] Meat, legumes, nuts, and dairy products are too high in Phe and are not allowed in the Phe-restricted diet. All grains and most vegetables are weighed or measured, and the Phe content is calculated to ensure optimal blood Phe control (see Table 20-2). Low-protein modified foods, made primarily from wheat starch instead of wheat flour, are available to increase variety and meet the energy needs of individuals with PKU.[26]

TABLE 20-2. Example of a Daily Meal Plan for Classical Phenylketonuria

Age: 3 y, 9 mos
Weight: 15.2 kg
Height: 101 cm
Sex: Female
Medical food prescription: 125 g of Phenex-2 unflavored + 18 fluid ounces of water = 20 fluid ounces total volume
Daily phenylalanine (Phe) prescription from foods: 200 mg
Estimated needs: Protein: >30 g/d; kilocalories: 900–1800 kcal/d

Meal	Food/Liquid	Amount Eaten	Phe	Protein	Calories
Breakfast	Medical food Rice-based cereal Low protein cereal Blueberries[a], fresh	6 oz 32 g 30 g 32 g	0 mg 17 mg 7 mg 8 mg	11 g 0.6 g 0.2 g 0.2 g	154 kcal 145 kcal 120 kcal 18 kcal
Lunch	Medical food French fries Broccoli[a], cooked Thousand island dressing Peaches[a], canned	7 oz 56 g 28 g 16 g 57 g	0 mg 50 mg 14 mg 6 mg 8 mg	13 g 1.4 g 0.6 g 0.1 g 0.3 g	179 kcal 80 kcal 6.0 kcal 59 kcal 42 kcal
Snack	Cantaloupe, fresh	27 g	8 mg	0.2 g	9 kcal
Dinner	Medical food Sweet potato, fresh, with skin, cooked Green beans[a], canned Pears[a], canned	7 oz 22 g 28 g 90 g	0 mg 25 mg 14 mg 8 mg	13 g 0.4 g 0.4 g 0.2 g	179 kcal 23 kcal 6 kcal 66 kcal
Snack	Zoo animal crackers Sorbet, strawberry	22 g 122 g	20 mg 15 mg	1.6 g 0.4 g	94 kcal 119 kcal
Total			200 mg	43.4 g	1179 kcal
% from medical food			0%	85.3%	43.4%

[a] Using the simplified diet, the phe content of these foods would not need to be counted. See Van Calcar[13] and Hansen et al[33] for details about the simplified diet.

Traditionally, caregivers were instructed to "count" milligrams of Phe or use an exchange system (1 exchange = 15 mg Phe), but now the Simplified PKU Diet is typically utilized. The simplified diet allows ad lib intake of all fruit, vegetables containing <75 mg Phe/100 g food, and modified low-protein foods containing <20 mg Phe/serving.[26,27] Web-based programs are available that list the Phe and protein content of various foods and beverages, and various food preparation resources are available for caregivers.[28,29] All foods and medications containing aspartame, a dipeptide derived from aspartic acid and Phe, need to be avoided.[30]

In PKU, decreased PAH activity reduces the production of Tyr. Thus, Tyr becomes a conditionally essential amino acid for this population, and all medical foods for PKU are supplemented with this amino acid. Additional Tyr supplementation is indicated only if the combination of intact protein and medical food does not meet Tyr requirements. Plasma Tyr concentrations should be routinely monitored in individuals with PKU.[13,14,20]

Some micronutrients may be insufficient in the low Phe diet, particularly for individuals consuming a suboptimal amount of medical food. Inadequate intake of iron, folate, vitamin B12, calcium, vitamin D, and essential fatty acids has been reported.[31–33] Dietary intake should be analyzed for micronutrient content and additional supplementation prescribed, as needed. Additionally, reduced bone mineral content and density have been found in some individuals with PKU[34,35] and it is unclear whether this is related to various nutritional factors or is an effect of PAH deficiency.

Medical Food Options

Traditionally, single L-amino acids is the source of protein equivalents in medical foods for PKU. Optional protein source equivalents include glycomacropeptide or large neutral amino acids.

GLYCOMACROPEPTIDE The whey protein glycomacropeptide (GMP) is a by-product of cheese production and purified GMP contains no aromatic amino acids, including Phe, which makes this intact protein suitable for medical foods designed for PKU.[36] However, commercial GMP contains some Phe from contamination of other whey proteins; thus GMP-based medical foods are not Phe-free like amino acid-based medical foods.[36,37] Subjective markers of acceptability (ie, taste, texture) and satiety have been noted in those consuming GMP-based medical foods compared with their usual amino acid-based medical food.[38,39] Inpatient and outpatient clinical trials have noted benefits of GMP compared to L-amino acid medical foods, including improved lab markers of phenylalanine utilization and satiety.[38,39,40]

A meta-analysis of studies primarily with adolescents and adults found no significant difference in blood Phe control with GMP compared to L-amino acid-based medical foods, despite the additional Phe intake from the GMP.[41] However, trials in a younger population (ages 5–16 years) found significantly higher blood Phe when participants consumed GMP versus amino acid-based medical foods.[42] This may suggest that younger patients tend to maintain better control of blood Phe than older patients, and the additional Phe in GMP may have a greater impact on metabolic control when added to the diets of patients who are maintaining strict Phe intake or who have a lower phenylalanine tolerance. Thus, the need to "count" the Phe in GMP as part of the overall Phe prescription must be evaluated on an individual basis.

LARGE NEUTRAL AMINO ACIDS Phe and other large neutral amino acids (LNAA; eg, leucine, valine, isoleucine, methionine, tyrosine, tryptophan, and threonine) share common transporters at the blood-brain barrier and intestinal mucosa. In PKU, competitive inhibition from high concentrations of Phe reduces the transport of other LNAA into cerebral cells, thus reducing the synthesis of various neurotransmitters.[43] Supplementation with high doses of LNAA can reduce both blood and brain concentrations of Phe and may improve executive function skills in individuals who have not been successful in maintaining good dietary control.[43–45] Several LNAA medical foods are commercially available.

Adjunct Medical Therapies

COFACTOR SUPPLEMENTATION Supplementation with sapropterin dihydrochloride, a synthetic form of tetrahydrobiopterin, the cofactor for the PAH enzyme, can increase an individual's Phe tolerance, allow for diet liberalization, and improve neurocognition for some patients with PKU.[46–49] Response to sapropterin needs to be individually assessed because not all individuals with PKU will respond to supplementation, and the degree of response to the drug varies. Individuals with milder forms of PKU are most likely to respond to sapropterin[49]; however, supplementation rarely allows for complete liberalization of the low Phe diet or eliminates the need for medical food.[14,50] The reduced need for medical food may adversely affect the sapropterin-responsive patient's overall nutritional status if other sources of essential nutrients such as fats, vitamins, and minerals are not provided.[51,52]

PHENYLALANINE AMMONIA LYASE Phenylalanine ammonia lyase (PAL) converts Phe to ammonia and trans-cinnamic acid and an injectable medication with a pegylated form of PAL (pegvaliase, Palynziq, Biomarin Pharmaceuticals) was approved by the Food and Drug Administration (FDA) in 2018 for treatment of adults with PKU. Reduced blood Phe was measured in most participants in pegvaliase clinical trials[53,54] with improved long-term measures of executive function.[54,55] Pegvaliase is initiated at a low dose to reduce adverse events including injection-site reactions, arthralgia, dizziness, and skin reactions.[54–57] There is a risk of anaphylaxis with pegvaliase, thus patients are required to carry injectable epinephrine.[58] Nutrition management of patients treated with pegvaliase focuses on reducing medical food intake and increasing intact protein once blood Phe is in the treatment range.[57,59] This diet transition can be challenging for some patients.

Maternal Phenylketonuria

Phe is a known teratogen, and in-utero exposure to elevated blood Phe interferes with embryonic development.[60] Infants born to women with elevated Phe throughout pregnancy are at risk for low birth weight,

microcephaly, intellectual disability, cardiac defects, and other congenital abnormalities. The National Maternal PKU Collaborative Study (1984–2000) found that these detrimental effects on the fetus could be prevented if maternal plasma Phe concentrations remained in the range of 120 to 360 μmol/L (2–6 mg/dL) before conception and throughout pregnancy.[61,62] Other factors influencing the outcome of children born to women with PKU include stability of blood Phe throughout pregnancy[63] and total protein intake from medical food and intact protein sources.[64]

Education about the risks of elevated Phe concentrations during pregnancy should begin early in adolescence for all females with PKU to emphasize the need for good metabolic control prior to conception. During pregnancy, weekly measurements of Phe and tyrosine are required to allow for frequent diet adjustments. An increase in Phe tolerance can be expected, especially in the second and third trimesters as Phe needs for fetal growth and development increase as pregnancy progresses. Over-restriction of dietary Phe also needs to be avoided during pregnancy because poor fetal growth has been noted in infants born to women with excessively low blood Phe.[65]

Table 20-3 provides a summary of PKU.

TABLE 20-3. Phenylketonuria Summary

Enzyme Affected	Phe Hydroxylase
Newborn screening	Yes
Biochemical findings	Increased blood Phe before initiating diet Severe: >1200 µmol/L Moderate: 360–1200 µmol/L Mild: 120–360 µmol/L
Clinical features, if untreated	Severe intellectual disability, seizures, hyperactivity, and eczema
Nutritional modifications	Medical food devoid of Phe, dietary Phe restriction, ± Tyr supplementation Phe goal range: 120–360 µmol/L for all ages
Adjunct therapies	Sapropterin; pegvaliase (adults only)
Monitoring	Phe and Tyr weekly or monthly, depending on age; plasma amino acids
Risk for acute decompensation	None

Abbreviations: Phe, phenylalanine; Tyr, tyrosine.

Organic Acidemias

Organic acidemias (OA) are a group of inherited genetic disorders involved in the degradation of branched-chain amino acids (leucine, isoleucine, valine), methionine, lysine, tryptophan, and/or threonine with production of non-amino acid organic acids that disrupt normal metabolism, including the citric acid cycle and other pathways associated with energy metabolism.[2] Chronic medical nutrition therapy (MNT) for organic acids includes a protein-restricted diet and amino acid-based medical foods devoid of the offending amino acids. Organic acids bind to carnitine (as acylcarnitine) and are detected in the blood and urine. Thus, supplemental L-carnitine is included in OA treatment to avoid depletion of free carnitine stores. OA can present in a severe neonatal form; milder forms present during the first year or later. Several organic acidemias are included in newborn screening panels.

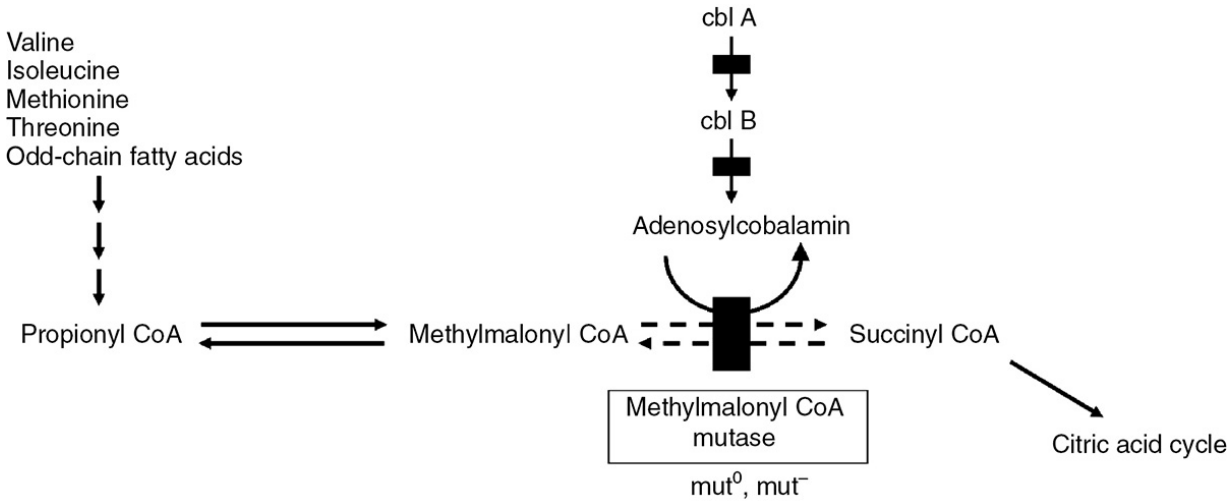
Because of catabolism of protein stores and increased production of associated organic acids, individuals with OA are at risk for metabolic

decompensation with any illness, surgery, or injury. MNT for these episodes varies depending on the disorder but typically requires protein reduction or discontinuation and provision of sufficient energy to stop catabolism and promote anabolism by infusion of dextrose and intralipid with appropriate electrolytes to reduce acidosis.

Methylmalonic Acidemia

Methylmalonic acidemia (MMA) is an inborn error of the metabolism of the propiogenic amino acids isoleucine, methionine, threonine and valine, and odd-chain fatty acids. MMA is caused by a deficiency of the enzyme methylmalonyl-CoA mutase responsible for converting methylmalonyl CoA to succinyl-CoA, which is eventually oxidized in the citric acid cycle (see Figure 20.3).[66–68] In MMA, methylmalonyl-CoA is not metabolized, leading to accumulation of various methylmalonate intermediates. The degree of deficiency in the mutase enzyme affects the clinical outcome of this disorder.[69,70] Those classified with MMA can have a deficiency (mut−) or absence (mut0) of the methylmalonyl-CoA mutase enzyme. Those with a mut– genotype of MMA have some residual enzyme activity and often a less severe clinical course than those with a mut0 genotype who have <2% residual enzyme activity.[69,70] Methylmalonyl-CoA mutase requires the cofactor 5-dehydroxyadenosylcobalamin, which is derived from vitamin B12. Synthesis or utilization defects of the cobalamin (cbl) cofactor, such as cbl A or cbl B deficiency, can also cause MMA. The estimated prevalence of all forms of MMA is 1 in 80,000 births.[71]

FIGURE 20-3. Methylmalonic Acidemia Caused by a Defect in Methylmalonyl Coenzyme A Mutase



cbl A and B are 2 of 6 known cbl cofactor synthesis defects, which also cause methylmalonic acidemia. cbl, cobalamin; CoA, coenzyme A. Adapted with permission from Oxford University Press from Nyhan WL, Barshop BA, Ozand PT. *Atlas of Metabolic Diseases.* 2nd ed. Oxford University Press Inc; 2005:14.

Infants with classical MMA caused by a severe deficiency of the mutase enzyme often present in the first week of life with overwhelming illness. Symptoms include poor feeding, hypotonia, vomiting, and dehydration with ketosis, acidosis, hyperammonemia, and hypoglycemia.[69,70] Acute episodes are often fatal without aggressive medical and nutrition management. Despite treatment, individuals with severe mutase deficiency often develop intellectual and physical disabilities, progressive renal failure, and other medical complications. Screening for MMA is included in the MS/MS screening panel, leading to earlier diagnosis and improved clinical outcomes of this disorder, although infants with severe forms of this disorder may have significant illness before screening results become available.[72]

For patients with MMA caused by a mild late-onset mut− deficiency or a defect in cofactor production, high doses of vitamin B12 supplementation may be sufficient to achieve metabolic control. This is particularly true for patients with cbl A defects.[69] Other cofactor deficiencies, such as cbl B and

cbl C, can have a more complicated clinical course and require both medical nutrition therapy and vitamin B12 supplementation.[69,73]

Liver and/or renal transplantation is now a treatment option for MMA, particularly for individuals with severe mutase deficiency.[74,75] Although transplantation can greatly reduce the incidence of metabolic episodes and improve the clinical outcome, it is not curative, and continued medical nutrition therapy is typically required.[76,77]

Acute Management

INITIAL PRESENTATION Infants with MMA presenting in an acute episode require immediate medical attention to control acidosis, hyperammonemia, and hypoglycemia.[70,78,79] Nutrition management during the acute phase of illness concentrates on the delivery of nonprotein energy sources to help slow catabolism. Typically, intravenous (IV) dextrose at the maximum glucose infusion rate (GIR) with additional lipid is provided to achieve maximal energy intake.[77,78,79] Insulin may be required to maintain normoglycemia when delivery of a high GIR is required. Intravenous L-carnitine may also be indicated.[70,78,79]

A protein source must be added within 24 to 48 hours of presentation to prevent further catabolism.[80] Enteral feedings of medical food containing all amino acids except propiogenic amino acids can be initiated; if it is poorly tolerated, specialized parenteral solutions without the offending amino acids are available.[81] As metabolic control improves, standard infant formula or parenteral amino acid solution is incrementally added to provide a protein source to meet the infant's methionine, valine, isoleucine and threonine needs.[79,80] Frequent monitoring of ammonia, bicarbonate, and plasma amino acids is necessary to adjust the dietary prescription to achieve optimal metabolic control.[80]

ILLNESS Any illness, significant injury, or surgery can lead to catabolism of protein stores. In MMA, the offending amino acids cannot be utilized, and a metabolic episode with similar symptoms to those observed during the initial episode in infancy can develop. A metabolic crisis can occur at any age and can be life-threatening if not managed aggressively.[70,79,80]

To manage a nonacute illness at home, a "sick day" diet can be prescribed to increase energy intake and reduce intact protein by 50% to 100%, depending on the severity of the illness.[80] If tolerated, medical food is continued to provide adequate amino acids and energy to promote protein anabolism. Fasting times need to be reduced to prevent hypoglycemia and reduce protein catabolism. For any illness causing oral intake intolerance, aggressive medical intervention is required.[70,79]

Chronic Management

Long-term medical nutrition therapy for individuals with mutase deficiency includes restricting propiogenic amino acids with adequate energy intake to prevent catabolism. Often 30% to 50% of total protein needs are provided by medical food and the remainder comes from intact protein sources; however, the tolerance for the offending amino acids can vary greatly among patients.[82] Maximizing intact protein sources to normalize plasma concentrations of the propiogenic amino acids and preventing excessive medical food prescription is recommended.[67,83] Total protein (intact protein and medical food) should be limited to 120% of the protein daily recommended intake (DRI) for age.[82]

In infants, standard infant formula or expressed human milk provides the source of isoleucine, valine, threonine, and methionine. When the child is developmentally ready for solid foods, low-protein foods replace the intact protein from these sources. However, for infants with intellectual disability and poor feeding skills, enteral feedings may be required.[70,81]

Individuals with MMA may have significant deviations in growth and body composition, resulting in lower energy expenditure than that predicted by standard equations.[84,85] Adjusting predicted resting energy expenditure by a patient's fat-free mass may provide a more accurate assessment of energy requirements.[84] Protein-free energy modules containing sources of

carbohydrate and fat are utilized to ensure adequate energy if a patient is unable to meet energy needs from other diet sources.[80,82]

For individuals responding to vitamin B12 supplementation, the initial dose is 1000 μg/d given via intramuscular injection; further dose adjustments are based on monitoring serum MMA and other metabolite concentrations.[86] For some patients, high doses of oral vitamin B12 may be sufficient to maintain adequate metabolic control.[70,86] The preferred source of vitamin B12 for individuals with MMA is hydroxocobalamin rather than the standard cyanocobalamin formulation.[87]

L-carnitine is often deficient in individuals with MMA. Carnitine binds to the intermediate metabolites that accumulate in this disorder; thus, individuals with MMA can have a higher requirement for this nutrient.[88] Supplementation with prescription-strength L-carnitine is common, especially if low levels of free carnitine are measured. Doses for carnitine supplementation range from 50 to 300 mg/kg/d depending on serum carnitine concentrations.[70,82] Side effects from excessive carnitine intake include diarrhea, gastrointestinal upset, and a fishy odor.

Frequent laboratory, clinical, and developmental monitoring is required to assess metabolic status and determine dietary prescription changes. Biochemical testing typically includes plasma amino acids, carnitine, acylcarnitine profile, and methylmalonic acid in plasma or serum and organic acids in urine.[70] In addition, labs should be routinely measured to assess general nutrition status, including iron indices, vitamin D, and essential fatty acids.[80]

Table 20-4 provides a summary of MMA.

TABLE 20-4. Methylmalonic Acidemia Summary

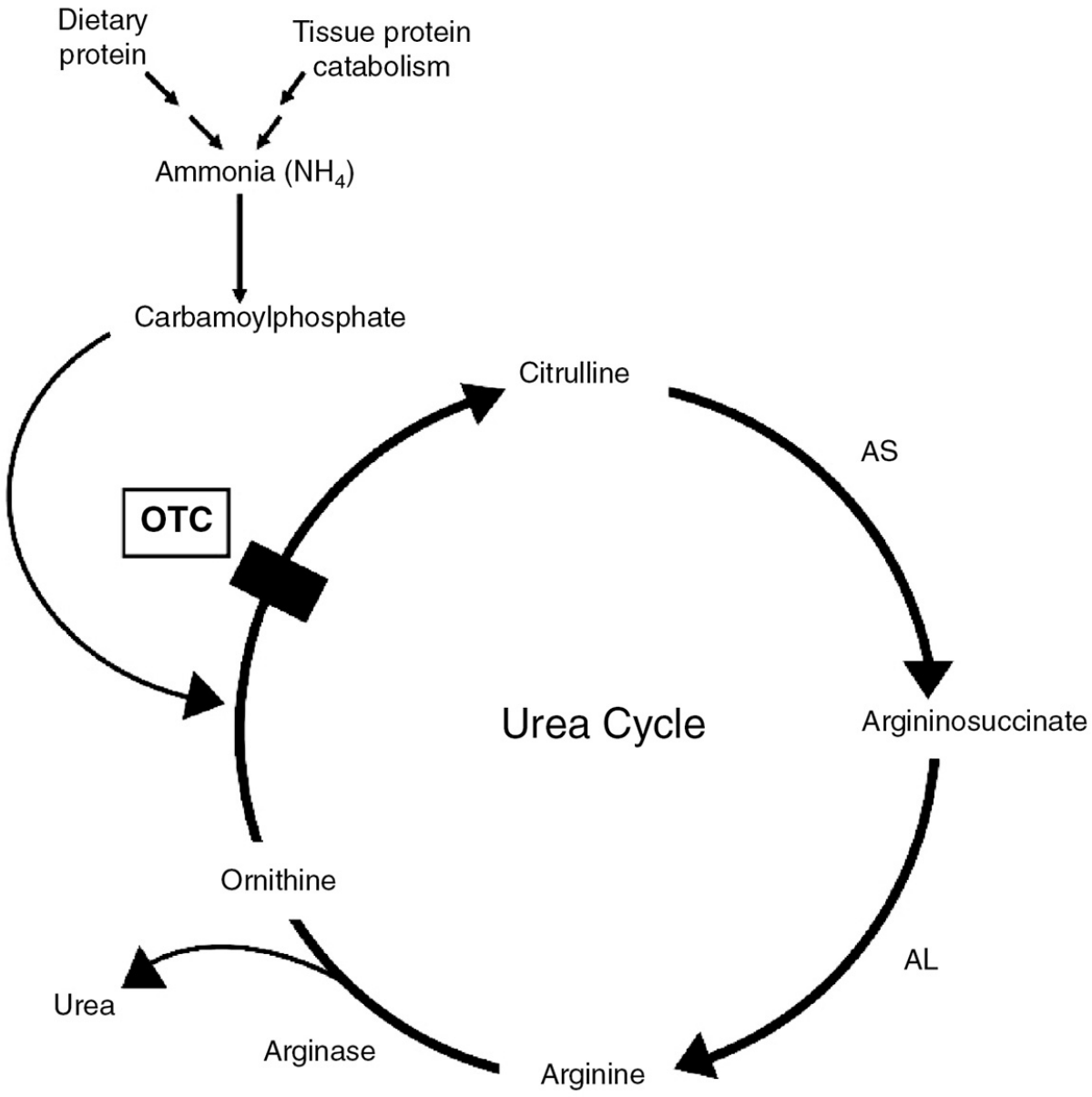
Enzyme affected	Methylmalonyl-CoA mutase (mut0 or mut– forms) cbl processing defect (cbl A, cbl B)
Newborn screening	Yes
Biochemical findings	Metabolic acidosis, ketonuria, hypoglycemia, hyperammonemia, hyperglycinemia; elevated methylmalonic acid
Clinical features, if untreated	Lethargy, poor feeding, vomiting, hepatomegaly, hypotonia, coma, death; intellectual disability long-term
Nutritional modifications	Medical food devoid of isoleucine, methionine, valine, and threonine; diet protein restriction
Adjunct therapies	IM hydroxocobalamin daily to weekly for cbl defects; L-carnitine supplementation; liver transplant for severe forms
Monitoring	Plasma amino acids, serum carnitine panel, serum methylmalonic acid
Risk for acute decompensation	Yes. Highest risk for those with mut0 form of mutase deficiency

Abbreviations: cbl, cobalamin; CoA, coenzyme A.

Urea Cycle Disorders

Inborn errors of the urea cycle, called urea cycle disorders (UCDs), are a group of 8 disorders affecting the enzymes or transporters associated with the urea cycle with an overall incidence of 1 in 35,000 births (see Figure 20-4).[89,90] Except in arginase deficiency, the hallmark of UCDs is hyperammonemia, which can be rapidly lethal in those with severe neonatal forms of these disorders. However, milder forms of these disorders can present at any age.[91,92] Later-onset symptoms include cognitive delay, neurological/psychiatric symptoms, and chronic liver disease. Currently, only argininosuccinic acid synthetase, argininosuccinic acid lyase, and arginase deficiencies can be detected by newborn screening (NBS); thus, it is essential to include ammonia in the initial laboratory evaluations of critically ill infants.[89,93]

FIGURE 20-4. Nitrogen Metabolism in the Urea Cycle.



OTC deficiency results in hyperammonemia, elevated glutamine concentrations, and deficiency of arginine. Other enzymes in the urea cycle include AS, AL, and arginase. AL, argininosuccinate lyase; AS, argininosuccinate synthetase; OTC, ornithine transcarbamylase

Adapted with permission from Springer from Wijburg FA, Nassogne MC. Disorders of the urea cycle and related enzymes. In: Saudubray JM, van den Berghe G, Walter JH, eds. *Inborn Metabolic Diseases: Diagnosis and Treatment.* Springer Medizin; 2012:297–310.

Except in milder forms of these disorders, diet treatment is typically paired with medications, including nitrogen scavengers or enzyme cofactors (eg, carglumic acid for *N*-acetylglutamate synthase [NAGS] deficiency).[89] Treatment outcome varies depending on the enzyme defect severity and prevention of hyperammonemia with aggressive illness management. For those with severe forms of these disorders, early liver transplant is often indicated.[89]

Ornithine Transcarbamylase Deficiency

The most common inborn error of the urea cycle is ornithine transcarbamylase (OTC) deficiency, which results in hyperammonemia because ammonia to nontoxic urea conversion is impaired. Production of arginine is decreased, and arginine becomes a conditionally essential amino acid in this disorder (see Figure 22-4).[89–91] OTC deficiency is an X-linked disorder; therefore, males are often more severely affected than females. However, various clinical presentations exist, including childhood or adult-onset OTC deficiency, especially in females who are carriers of this disorder.[92]

The severe form of the disease is characterized by overwhelming hyperammonemia in the newborn period causing recurrent vomiting, lethargy, irritability, and seizures, which can quickly lead to coma and death if not treated aggressively to rapidly decrease ammonia concentrations.[91,93] Intellectual and developmental disabilities are common in those surviving the initial episode.[89,91] Milder forms of the disorder may not present until later in life, often precipitated by a severe illness or other catabolic stress. Histories of vomiting episodes, aversion to dietary protein, and psychiatric complications have been reported in late-onset OTC deficiency.[92] At this time, OTC deficiency is not included in the newborn screening panel, so diagnosis relies on recognition of clinical presentations. Long-term outcomes vary greatly and often depend on preventing further episodes of hyperammonemia. Liver transplantation is a treatment option for this disorder, especially for those with recurring episodes, despite medication and diet treatment.[94,95]

ACUTE MANAGEMENT Acute management may be necessary at the time of initial presentation or with any intercurrent illness or injury. The goal of acute management of OTC deficiency is to slow protein catabolism and thus reduce ammonia production by providing a protein-free, high-calorie nutrition source via enteral and/or parenteral nutrition.[86,89,90] Ideally, a minimal source of protein should be initiated within 24 hours of admission to reduce catabolism of lean muscle mass. If the patient requires dialysis, a limited amount of an IV amino acid solution is given, since dialysis will remove amino acids as well as ammonia.[93,96,97]

A medical food comprising only essential amino acids as the protein source is incrementally added as ammonia concentrations decrease. If the patient is unable to tolerate enteral feedings, a standard parenteral amino acid solution can be added. Providing essential amino acids promotes protein anabolism, yet restricts intake of the nonessential amino acids that can contribute to the nitrogen load.[96–98] As clinical status continues to improve, an intact protein source is initiated to provide approximately 50% of total protein needs.[96]

Since arginine is a conditionally essential amino acid in OTC deficiency, supplementation with IV L-arginine is often indicated during illness. Arginine bypasses the enzymatic block to allow for urea production rather than further ammonia production.[93,96–98] Acute medical management often includes the use of nitrogen-scavenger drugs, which are available in both oral (Buphenyl or Ravicti) and IV forms (Ammunol).[99,100]

CHRONIC MANAGEMENT Given the wide range of clinical phenotypes in OTC deficiency, chronic management needs to be individualized but typically includes dietary restriction of total protein with approximately 50% to 70% from intact sources and the remainder from a medical food providing essential amino acids.[96,101,102] The total protein prescription for OTC deficiency may be lower than the protein requirements outlined in the dietary reference intakes, but over-restriction can adversely affect ammonia control and growth.[101,103,104] Sufficient total energy with additional fat and/or carbohydrate-based medical foods or dietary sources is needed to promote anabolism.

In infancy, the intact protein source can be provided by a standard infant formula or expressed human milk transitioning to lower-protein foods when the patient is developmentally ready for oral feeding. The use of specialty low-protein foods may be necessary to meet energy needs, increase satiety, and provide variety in the diet.[96] For individuals with more severe forms of this disorder, medical food via gastrostomy feeding is often necessary to provide adequate energy and appropriate protein sources.[96,105] In addition, L-citrulline is routinely supplemented at an initial dose of 100 to 200 mg/kg since it is the precursor for arginine and utilizes additional nitrogen via aspartate in the urea cycle.[93]

To assess metabolic control, frequent monitoring of ammonia and plasma amino acids is necessary. Of particular interest are concentrations of citrulline and arginine to evaluate L-citrulline supplementation and glutamine, which increases with excessive protein intake and/or inadequate energy intake.[93,96] Additionally, monitoring concentrations of the branched-chain amino acids Leu, Val, and Ile is necessary given that chronic use of a nitrogen-scavenging medication can increase their oxidation. This can lead to deficient concentrations of these amino acids despite adequate total protein intake, and additional essential amino acid supplementation may be indicated.[106] Routine monitoring of indicators of nutrition status is also recommended.[96]

Table 20-5 provides a summary of OTC.

TABLE 20-5. Ornithine Transcarbamylase Deficiency Summary

Enzyme affected	OTC in urea cycle
Newborn screening	Rare to include in panels
Biochemical findings	Hyperammonemia; respiratory alkalosis; elevated glutamine +; others in plasma amino acids
Clinical features, if untreated	Lethargy, vomiting, apnea, coma, and death if untreated; intellectual disability long-term
Nutritional modifications	Total protein restriction to ~DRI for age: 50% from medical food with essential amino acids and 50% protein-restricted diet; L-citrulline supplementation
Adjunct therapies	Nitrogen scavenging medications; liver transplant for severe forms
Monitoring	Plasma amino acids; ammonia especially with concern for decompensation
Risk for acute decompensation	Yes

Abbreviations: DRI, daily recommended intake; OTC, ornithine transcarbamylase.

Lipid Metabolism Disorders

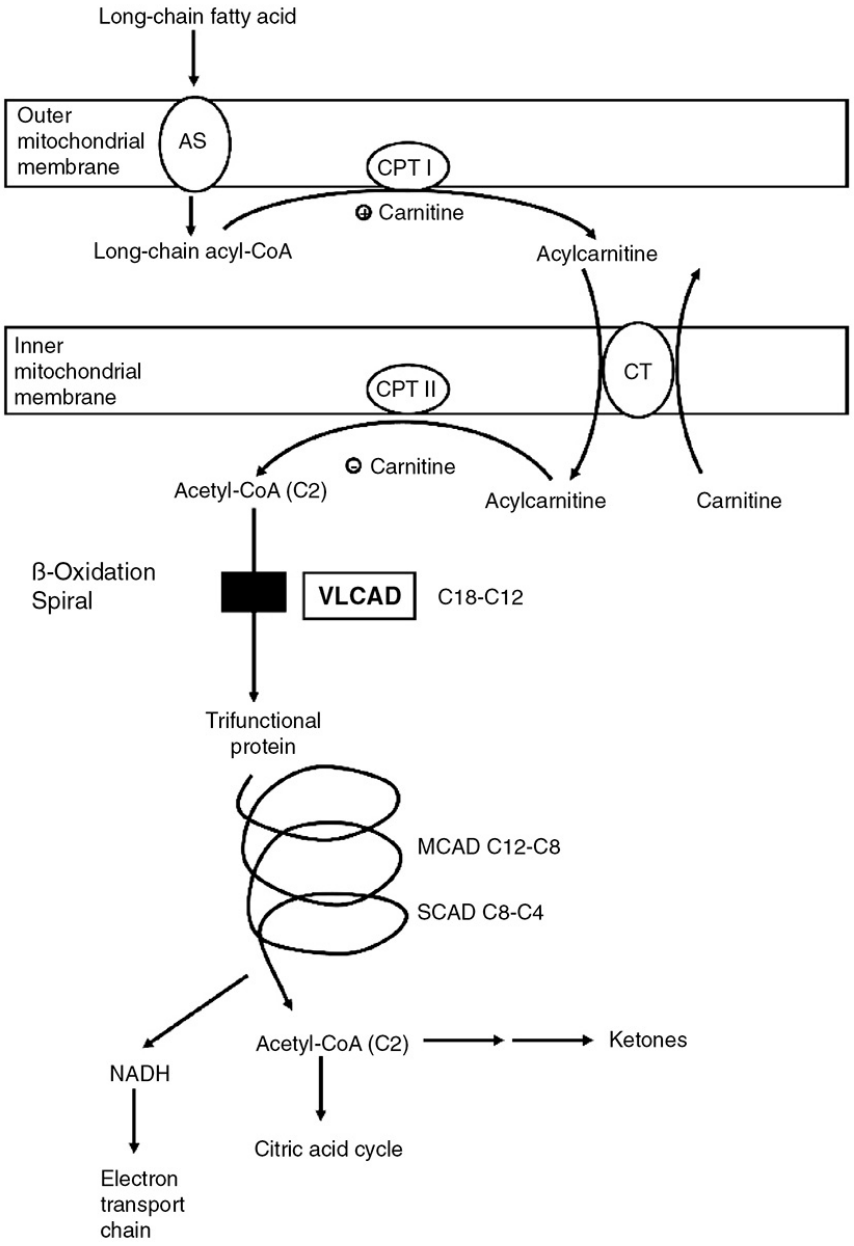
Fatty acid oxidation disorders (FAODs) are a group of inherited genetic disorders involved in the carnitine cycle for the transport of fatty acids across the mitochondrial membrane, β-oxidation, or ketone utilization.[1,2] Prevention of extended fasting and attention during intercurrent illnesses or other catabolic events is essential for all FAODs. Medium-chain acyl-CoA dehydrogenase (MCAD) is one of the most common metabolic disorders with an estimated prevalence of 1 in 13,000–19,000 in the United States.[107] MCAD does not require a specific diet intervention. However, the long-chain FAODs (LC-FAODs) typically require restriction of long-chain fat (LCF) sources and supplementation of medium-chain triglycerides (MCTs).

Very Long-Chain Acyl-CoA Dehydrogenase Deficiency

Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD) is an inborn error in the first step of mitochondrial β-oxidation of long-chain fatty acids (12–20 carbons in length), resulting in disturbed energy production with

hypoglycemia, reduced ketone production, and accumulation of fatty acid intermediates (see Figure 20-5).[107,108] Severe forms of this disorder can present in a neonate with hypoglycemia, liver dysfunction, cardiomyopathy, and myopathy, and can be fatal without medical intervention. Moderate forms of this disorder may present later in infancy or during early childhood with episodes of hypoglycemic encephalopathy associated with illness or other catabolic processes. Mild VLCAD can present in adolescents and adults with episodes of muscle pain and rhabdomyolysis, especially after intense or prolonged exercise.[108,109] Even for individuals with more severe forms of VLCAD, long-term development and outcomes can be favorable with early treatment and diagnosis.[110,111]

FIGURE 20-5. Fatty Acid Oxidation and Very Long-Chain Acyl-CoA Dehydrogenase Deficiency



Fatty acid oxidation requires entry of LCFAs into the mitochondria. This process requires carnitine. Carnitine cycle enzymes include AS, CPT I and II, and acylcarnitine/CT. Once in the mitochondria, the β-oxidation spiral sequentially oxidizes the fatty acyl-CoA to the 2-carbon unit acetyl-CoA. Oxidation of LCFAs requires VLCAD and a trifunctional protein, which includes 3 enzyme activities. In the treatment of VLCAD deficiency, supplementation with MCTs bypasses the LCFA enzymes and utilizes enzymes that oxidize medium-chain and short-chain fatty acids, including MCAD and SCAD enzymes. AS, acyl-CoA synthetase;

CoA, coenzyme A; CPT, carnitine palmitoyltransferase; CT, carnitine translocase; LCFAs, long-chain fatty acids; MCAD, medium-chain acyl-CoA dehydrogenase; MCTs, medium-chain triglycerides; SCAD, short-chain acyl-CoA dehydrogenase; VLCAD, very long chain acyl-CoA dehydrogenase. Adapted with permission from Oxford University Press from Nyhan WL, Barshop BA, Ozand PT. *Atlas of Metabolic Diseases.* 2nd ed. Oxford University Press Inc; 2005:167.

With MS/MS screening, VLCADD appears to be more prevalent than earlier estimates since screening identifies milder forms of this disorder that may not have presented clinically in the past.[112,113] Consensus is lacking about the necessity and degree of treatment required during infancy for individuals with phenotypes that may not present until later in life.[114] Research continues to establish evidence to predict the long-term phenotype based on newborn screening values and genotype.[110]

Acute Management

The primary goal of acute management of VLCAD is to provide sufficient energy to prevent hypoglycemia and slow catabolism of fat stores. Typically, IV dextrose with a minimum 10% concentration is infused at the upper threshold of the GIR for the patient's age and weight.[114,115] Intravenous lipid sources are contraindicated in VLCAD deficiency but should be considered if a patient has been without a sufficient source of essential fatty acids for longer than 7 days.[114] As enteral feeding becomes possible, sources of glucose and MCTs are provided to meet energy demands. Medical foods that provide the majority of total fat as MCT but contain sufficient LCF sources to meet essential fatty acid needs are available.

Even for those with mild VLCAD who remain asymptomatic during infancy, any illness or other catabolic event can trigger an acute metabolic crisis.[116] Glucose polymer solutions can be used for home treatment[117] but caregivers need to understand the signs of decompensation and have an emergency protocol in place.

Chronic Management

Long-term nutrition management of VLCAD includes prevention of fasting, restriction of long-chain fatty acid intake, and supplementation with MCT.[114,115,118] Prevention of fasting, especially in infancy when energy stores are limited, is imperative to prevent acute decompensation. Fasting guidelines need to be individualized, but fasting is typically limited to a maximum of 4 hours for infants up to 4 months of age with an additional 1 hour for each additional month of age.[114,118,119] A feeding during the night is often recommended for the first year, and in severe VLCAD, continuous overnight feedings may be needed.[114]

The total amount of fat in the diet is not restricted, only the source of the fat. Recommended LCF intakes range from 10% of energy in infants with severe forms of VLCAD to 45% of energy in infants with mild forms of the disease.[114,115] The remaining energy provided by fat is supplied by MCT, which includes fatty acids of 6 to 12 carbons in length and thus can bypass the enzymatic block in long-chain fatty acid oxidation (see Figure 20-5).

In asymptomatic infants with mild forms of VLCAD, a standard infant formula or feeding human milk can be continued, as long as milk production remains adequate and fasting guidelines are followed. For those with more severe forms of the disorder, MCT-based medical foods are prescribed.[114]

In older children, restriction of dietary fat and supplementation of low-fat or nonfat foods and beverages with MCT from an oil, powder, or emulsified liquid source is necessary to maintain metabolic control. Additionally, a high protein intake (25% of total energy) is associated with the preservation of lean body mass and lower concentrations of abnormal fatty acid metabolites when compared to lower protein intakes.[120]

Triheptanoin is a source of MCTs that contains an odd number of carbons (n = 7) in a fatty acid side chain rather than an even number of carbons (n = 8) in fatty acids from MCT. Compared to MCT, triheptanoin improves the delivery of intermediates to the citric acid cycle to improve gluconeogenesis and ketone production in those with VLCAD and other long-chain fatty acid oxidation disorders (LC-FAOD).[121,122] Replacing standard sources of MCT with triheptanoin (Doljolvi, Ultragenyx Pharmaceutical) has been shown to improve cardiac function and reduce the

number of metabolic crises, especially in those with severe forms of LC-FAOD.[121,122]

Individuals with VLCAD are at risk for muscle pain and episodes of rhabdomyolysis during prolonged exercise. To improve exercise tolerance, recommendations include providing a source of complex carbohydrates and supplemental MCT (0.3 g/kg) within 20 to 45 minutes prior to activity.[114,123] With the restriction in long-chain fat, it is important to assess the intake of the essential fatty acids, linoleic acid and α-linolenic acid. An essential fatty acid profile, measured in red blood cells or plasma, needs to be routinely monitored.[114,118] Supplementation with walnut, flax, or safflower oil may be necessary to meet linoleic acid and α-linolenic acid needs unless the child is prescribed a medical food supplemented with arachidonic acid and docosahexaenoic acid. Other parameters to monitor typically include creatine kinase, plasma carnitine, and acylcarnitine profile.[114]

Table 20-6 provides a summary of VLCAD.

TABLE 20-6. Very Long-Chain Acyl-CoA Dehydrogenase Deficiency Summary

Enzyme affected	VLCAD in fatty acid β-oxidation
Newborn screening	Yes
Biochemical findings	Hypoketotic hypoglycemia, ± hyperammonemia
Clinical features, if untreated	Poor feeding, hypotonia, lethargy, hepatomegaly, cardiomyopathy, coma, and death in severe forms Late onset: exercise intolerance, rhabdomyolysis
Nutritional modifications	Fasting avoidance; ± long-chain fat restriction (10%–25% of energy); MCT-based medical food or MCT oil after infancy (10%–25% of energy); ± essential fatty acid supplementation
Adjunct therapies	L-carnitine supplementation only if low free carnitine level; Triheptanoin (Doljolvi) may replace MCT in diet
Monitoring	Plasma acylcarnitine profile, carnitine profile, creatine kinase essential fatty acid profile, fat-soluble vitamins
Risk for acute decompensation	Yes, especially for those with severe forms of the disorder

Abbreviations: CoA, coenzyme A; MCT, medium-chain triglyceride; VLCAD, very long-chain acyl-CoA dehydrogenase.

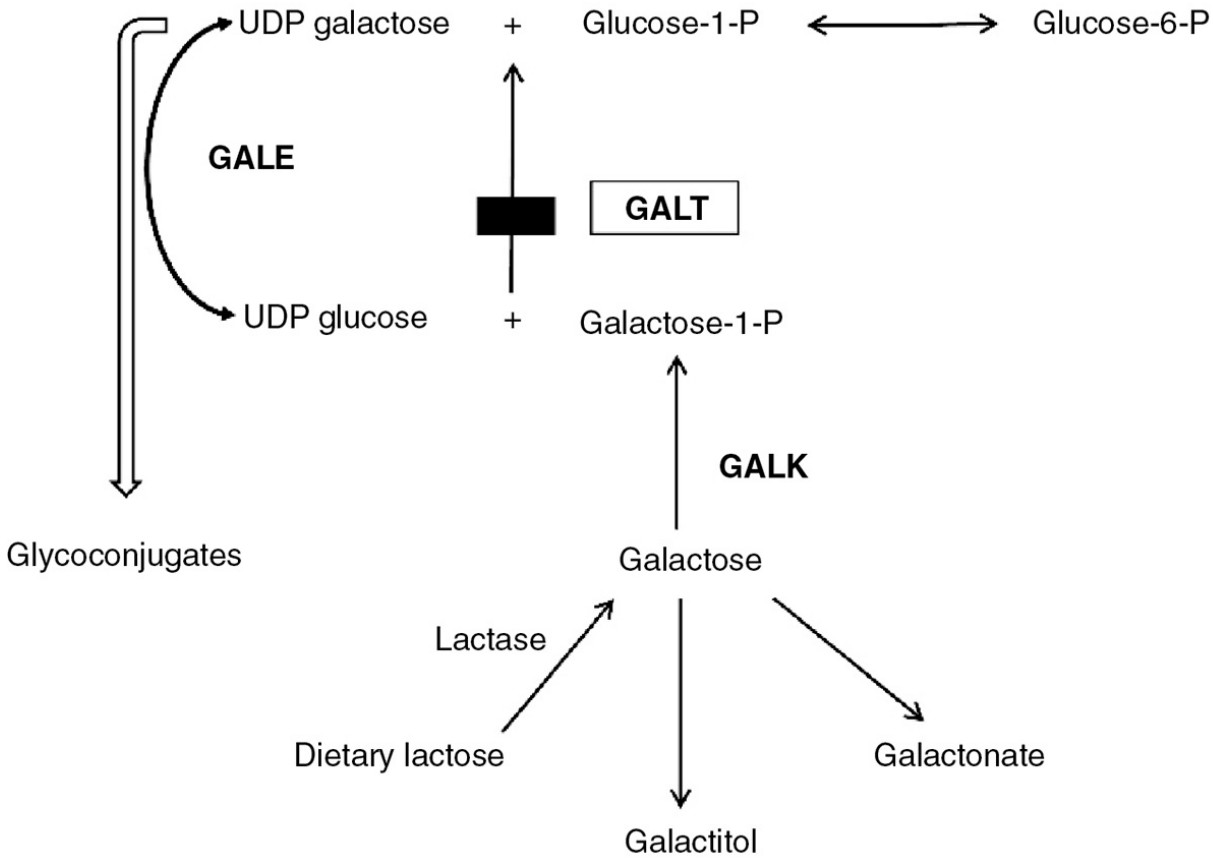
Carbohydrate Metabolism Disorders

Disorders of enzyme deficiencies in the metabolism of glucose, fructose, and galactose include hereditary fructose intolerance, galactosemia,[1,2] and glycogen storage diseases (GSDs). GSDs result from a deficiency of enzymes involved in the synthesis or use of glycogen primarily in hepatic and/or muscle tissue, although other tissues such as cardiac or cerebral tissue can be involved.[124] GSDs involving the liver often present with hypoglycemia, hepatomegaly, hyperlipidemia, and lactic acidosis (see discussion in Chapter 24, "Hepatic Disease").[124] Those involving muscle present with muscle wasting, hypotonia, and/or rhabdomyolysis.[???,124] Treatment of these disorders varies greatly with the disease but typically includes modification of the source and quantity of dietary carbohydrate and/or protein prescribed in the diet. GSDs often require strict avoidance of fasting.

Galactosemia

Classical galactosemia, with an incidence of 1 in 60,000 births, is an autosomal recessive disorder caused by the enzymatic deficiency of galactose-1-phosphate uridyltransferase (GALT).[125,126] Abnormal elevations of galactose-1-phosphate (gal-1-P), galactitol, and galactonate are present (see Figure 20-6). Over 300 mutations have been identified in the GALT gene.[126] There is a common genetic variant, c.Q188R on chromosome 9p13, in those of Northern European descent; homozygosity of this variant results in a severe phenotype, often with no residual enzyme activity. The c.S135L mutation, prevalent in the African American population, results in a milder clinical course. Another prevalent form of galactosemia is the Duarte variant, which results in a mild phenotype that does not require dietary intervention.[126]

FIGURE 20-6. Classical Galactosemia is Caused by Galactose-1-phosphate Uridyltransferase Deficiency



Elevations in galactose1-phosphate, galactose, galactitol, and galactonate are present in this disorder. Other enzymes involved in this pathway include GALK and UDP GALE. UDP galactose is used as a substrate to produce various glycoconjugates, such as glycoproteins and galactolipids. GALE, galactose-4-epimerase; GALK, galactokinase; GALT, galactose-1-phosphate uridyltransferase; UDP, uridyl diphosphate

Adapted with permission from Springer from Berry GT, Walter JH. Disorders of galactose metabolism. In: Saudubray JM, van den Berghe G, Walter JH, eds. *Inborn Metabolic Diseases: Diagnosis and Treatment.* Springer Medizen; 2012:141–150.

Infants with classical galactosemia can present within the first few days of life with jaundice, poor feeding, and vomiting. If not treated, symptoms can progress to liver failure and risk of *Escherichia coli* sepsis, which can be fatal. Galactosemia is detected by newborn screening, which has reduced the incidence of severe illness during the neonatal period.[125]

Treatment of classical galactosemia requires a lifelong galactose-restricted diet.[127] Despite early nutrition management for neonates, long-term complications can include intellectual disability, neurological abnormalities, speech delay, and premature ovarian failure in females.[126,128,129] The etiology of these complications remains unknown, although endogenous production of galactose, abnormal glycosylation of glycoproteins, and/or excessive galactitol exposure have been implicated.[126,130]

Acute Management

Infants identified with classical galactosemia should be immediately placed on a soy-based medical food containing soy protein isolate as the protein source. These formulas contain minimal galactose compared to cow's milk-based formulas or human milk.[127,131] Since soy-based formulas are not recommended for premature infants, an amino acid-based formula needs to be considered for premature infants with classical galactosemia.[132] If an infant does not tolerate enteral feeds, standard parenteral nutrition (PN) may be used. Efforts should be made to choose medications that are free of lactose fillers. Unlike some disorders of carbohydrate metabolism, those with galactosemia do not develop further episodes of metabolic decompensation associated with illness or other catabolic processes.[126]

Chronic Management

Long-term management of classical galactosemia requires dietary restriction of galactose. Lactose is the primary source of galactose and most dairy-based products are eliminated. Throughout infancy, a soy-based formula is provided, and feeding human milk or milk-based infant formulas is contraindicated.[127,132] Amino acid-based formulas devoid of galactose have been used to treat some infants with classical galactosemia who have erythrocyte gal-1-P concentrations that are slow to decrease into the treatment range.[133,134] Whether routine use of elemental formulas could lead to a more rapid reduction in gal-1-P concentrations or whether this reduction could reduce or prevent long-term complications remains unknown.[132]

When starting infants on solids, caregivers are instructed to check food labels for foods and ingredients that contain lactose or galactose (see Exhibit 20-1).[127,132] Restricted foods and ingredients are primarily dairy-based; however, negligible galactose has been found in some aged cheeses, and the additives calcium and sodium caseinate. These products are allowed in the diet for classical galactosemia.[124] Many fruits, vegetables, and legumes contain small amounts of free galactose, but guidelines are no longer recommending elimination of these minor sources of galactose.[127,132]

EXHIBIT 20-1. Foods and Ingredients Containing Lactose and/or Galactose That Are Eliminated in the Diet for Classical Galactosemia

Foods

- Butter
- Buttermilk, buttermilk solids
- Cheese[a]
- Cream
- Dry milk, dry milk solids
- Ice cream
- Meat byproducts
- Milk chocolate
- Milk, milk solids
- Nonfat dry milk, nonfat dry milk solids
- Organ meats
- Sherbet
- Sour cream
- Yoghurt

Ingredients

- Fermented soy products[b]
- Fermented soy sauce[c]
- Hydrolyzed casein protein
- Hydrolyzed whey protein
- Lactalbumin
- Lactoglobulin
- Lactose
- Whey, whey solids

[a] Allowed aged cheeses include Jarlsberg, Emmentaler, Swiss, Gruyere, Tilsiter, Parmesan (aged >10 months), 100% Parmesan cheese powder, and sharp Cheddar cheese.

[b] Includes miso, tempeh, natto, sufu, and similar products.

[c] Unfermented soy sauce is made from hydrolyzed soy protein and is allowed.

Adapted with permission from Elsevier from van Calcar SC, Bernstein LE, Rohr FJ, Scaman CH, Yannicelli S, Berry GT. A re-evaluation of life-long severe galactose restriction for the nutrition management of classic galactosemia. Mol. Genet. Metab. 2014;3(7):191–197.

Erythrocyte gal-1-P is the primary metabolite monitored in galactosemia and concentrations below 4 mg/dL are considered optimal, although some individuals maintain higher gal-1-P concentrations even with strict dietary management. Gal-1-P is not a sensitive measure of treatment compliance; however, a significant increase above a patient's typical gal-1-P concentrations should be investigated for possible dietary indiscretions.[127]

Osteopenia and abnormal concentrations of various measures of bone metabolism have been described in this population.[135,136] International guidelines recommend yearly monitoring of serum total 25-hydroxy vitamin D and completing an initial dual-energy X-ray absorptiometry (DXA) scan at ages 8 to 10 years. If the *z*-score is ≤ 2 SD, follow-up is advised. If there is no evidence of reduced bone density at this age, a repeat DXA is not recommended until the completion of puberty.[127,135] While the mechanism of decreased bone density in patients with galactosemia is not well understood, ensuring adequate intake of calcium, vitamin D, and other nutrients associated with bone metabolism can prevent deficiencies that could exacerbate the development of bone complications.[127,135]

Table 20-7 provides a summary of galactosemia.

TABLE 20-7. Classical Galactosemia Summary

Enzyme affected	Galactose-1-phosphate uridyltransferase
Newborn screening	Yes
Biochemical findings	Galactose in blood and urine; elevated RBC galactose-1-phosphate
Clinical features, if untreated	Cataracts, diarrhea, failure to thrive, hepatomegaly, jaundice, vomiting; *E. coli* sepsis, and death Long term: intellectual disability, speech abnormality, osteopenia; ovarian dysfunction in females
Nutritional modifications	Soy or amino acid-based formula for infants; restrict lactose and galactose in diet; calcium and vitamin D supplementation
Adjunct therapies	Not applicable
Monitoring	RBC galactose-1-phosphate; 25-hydroxyvitamin D; DXA scans
Risk for acute decompensation	Yes, as a neonate only

Abbreviations: DXA, dual-energy X-ray absorptiometry; RBC, red blood cells.

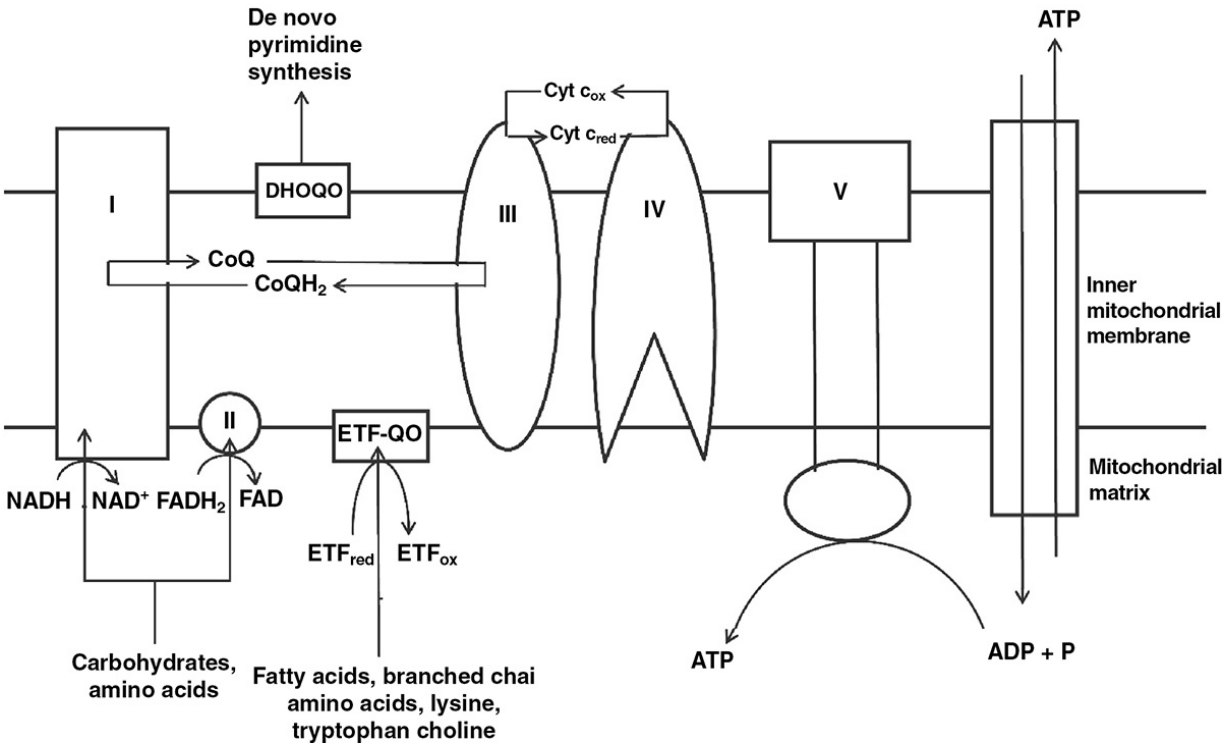
Mitochondrial Disorders

The first mitochondrial disorder was initially described over 35 years ago, but the number of known disorders has increased greatly since that time; the estimated incidence is now 1 in 4300 births as molecular analysis techniques, such as mitochondrial DNA sequencing or whole genome sequencing, are improving diagnosis.[137] Disorders have been described in the synthesis, transport, assembly, or maintenance of mitochondrial proteins.[137,138]

These disorders can be inherited by defects in encoded genes in either mitochondrial DNA or nuclear DNA. The inheritance pattern is typically autosomal recessive or autosomal dominant for disorders stemming from nuclear DNA and maternal inheritance for disorders stemming from mitochondrial DNA.[137,138] Mitochondrial disorders ultimately affect the functioning of the electron transport chain (ETC), which is composed of 5 complexes with 70 protein subunits (see Figure 20-7). Disorders can either directly affect the production of one or more of the complexes or cause

secondary reductions in their activity, thus preventing adequate adenosine triphosphate (ATP) production for cellular function.[137,138]

FIGURE 20-7. The Electron Transport Chain Produces Adenosine Triphosphate From ADP by Oxidative Phosphorylation



The ETC is composed of 5 multiprotein enzyme complexes: complex 1 = NADH:ubiquinone oxidoreductase; complex II = succinate:ubiquinone; complex III = cytochrome bc; complex IV = cytochrome c oxidase; and complex V = ATP synthetase. There are 2 electron carriers, coenzyme Q-10 and cytochrome C. The figure indicates the entry point of electrons from various macronutrients. Electrons from carbohydrate and amino acid sources enter via complexes I and II. Fatty acids, choline, branched-chain amino acids, lysine, and tryptophan enter via the ETF. Nutritional supplements such as coenzyme Q-10 or various B vitamins are prescribed as precursors to ETC substrates or cofactors. ADP, adenosine diphosphate; ATP, adenosine triphosphate; ETF, electron transfer flavoprotein; FAD, flavin adenine dinucleotide; NAD, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide + hydrogen.

Adapted with permission from Oxford University Press from Nyhan WL, Barshop BA, Ozand PT. *Atlas of Metabolic Diseases.* 2nd ed. Oxford University Press Inc; 2005:262.

Mitochondrial disorders can present at any point in the lifespan and the same disorder can have a wide range of phenotypes, even in members of the same family (see Exhibit 20-2). Typically, the earlier the onset, the more severe the disorder; neonatal and infant presentations are often eventually fatal.[138] Once the diagnosis is clinically suspected, molecular testing is used to confirm the disorder.[139]

EXHIBIT 20-2. Common Mitochondrial Myopathies

MELAS = Mitochondrial enchephalomyopathy, lactic acidosis, and stroke-like episodes
MERFF = Myoclonic epilepsy and ragged red fiber disease
NARP = Neurodegeneration, ataxia, and retinitis pigmentosa
Kearns-Sayre syndrome
Pearson Syndrome
Mitochondrial DNA depletion syndrome
MNGIE = mitochondrial neurogastrointestinal encephalopathy
Electron transport chain enzyme deficiencies (complex I deficiency, others)

Acute and Chronic Management

Few mitochondrial disorders present as an acute event; most progress slowly over time. A specific treatment does not exist for any mitochondrial disorder, and care is primarily supportive. Infants and children with mitochondrial disorders are often clinically fragile and have a difficult time recovering from illness or other stress.[138] To prevent catabolism, nutrition support should be initiated at an early stage of disease. Infants and children may have severe intellectual and physical delays and are often unable to consume adequate nutrition by mouth. Many require enteral feeding methods on a chronic basis. Gastrointestinal dysfunction and dysmotility are common symptoms of mitochondrial disorders and can be severe enough to make enteral feeding impossible.[140] In these cases, PN may be required on a chronic basis.

High doses of various vitamins and nutritional supplements that serve as antioxidants, ETC substrates, and/or ETC cofactors have been prescribed to augment the production and utilization of ATP. Few of these therapies have been evaluated in randomized clinical trials, and most reported success is from single cases or case series. These therapies are used in various

combinations, and dosing recommendations are typically not standardized (see Table 20-8).[141,142] Fasting avoidance and progressive exercise training have also been useful for some.[142] Research continues to find more effective nutritional and pharmaceutical options.[141]

TABLE 20-8. Common Nutritional Supplements Prescribed for Various Mitochondrial Disorders

Supplement	Example Pediatric Daily Dose[a]
Co-enzyme Q-10 (ubiquinone)	5–15 mg/kg
B vitamins Riboflavin Thiamin Combination therapy	 50–200 mg 10 mg/kg Vitamin B-50 or B-100 complex
α-Lipoic acid	5–25 mg/kg
Vitamin E	5–15 IU/kg
Creatine monohydrate	100 mg/kg
L-arginine	For MELAS only: Acute: IV Initial 500 mg/kg dose; continuous infusion of 500 mg/kg/d for 3–5 days Chronic: Oral 150–300 mg/kg, 3 doses/d
Taurine	For MELAS only: Oral 250 mg/kg

Abbreviations: IV, intravenous; MELAS, mitochondrial enchephalomyopathy, lactic acidosis, and stroke-like episodes.

Data from El-Hattab, Adesina, Jones, Scaglia[132], El-Hattab, Zarante, Almannai, Scaglia[134], Tarnopolsky[135], and Ohsawa[140].

[a] Total daily doses are listed; doses are divided throughout the day.

Mitochondrial Encephalomyopathy, Lactic Acidosis

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is one of the most common mitochondrial disorders and is caused by a variant in mitochondrial genes encoding for transfer RNA resulting in a severe reduction in activity of complex I and IV of the ETC, thus impairing ATP synthesis.[139] Presentations in infancy include motor and

cognitive delay, hypotonia, and respiratory distress. Symptoms in later-onset MELAS often do not develop until ages 4 to 15 years when increasing number and severity of episodes with vomiting, headache, convulsions, and visual abnormalities are reported. These events are called "stroke-like" episodes because the vascular changes or inflammation typically associated with stroke are not present.[139]

Over time, MELAS develops into a multisystem disorder with seizures, dementia, migraines, sensorineural deafness, ophthalmoplegia, and/or intestinal dysfunction, often with renal and cardiac involvement. The development of type 2 diabetes mellitus has also been associated with the syndrome. MELAS carries a high morbidity and mortality rate with a reported mean survival time of approximately 6.5 years from disease onset.[143]

After the initial presentation, individuals with MELAS are at risk for developing further stroke-like episodes. As a vasodilator, L-arginine has been shown to reduce the frequency and severity of these episodes if administered soon after the development of symptoms. The initial recommended dose is 500 mg L-arginine/kg in 5% to 10% dextrose at 1.25 to 1.5 times the patient's maintenance fluid rate.[143] Repeated doses are administered every 6 hours for 1 to 3 days until symptoms resolve. Hydration status and acid-base balance need frequent monitoring. This treatment is specific for MELAS and is not advocated for other mitochondrial disorders. Following an episode, oral L-arginine at a dose of 150 to 300 mg/kg/d, given 3 times per day, has been shown to reduce the chronic symptoms associated with MELAS, as well as reduce the frequency and severity of symptoms during future episodes.[136,144,] Providing oral L-arginine in doses to maintain plasma arginine concentrations above 168 μmol/L has been suggested.[145]

Additionally, taurine supplementation at 250 mg/kg/d eliminated or reduced the frequency of episodes by increasing taurine modification in post-translational tRNA.[146,147] Some of the therapies listed in Table 20-8 are also recommended; coenzyme Q-10, α-lipoic acid, vitamin E, and creatine monohydrate have been specifically mentioned as beneficial in this disorder.[142]

Conclusion

Management of those with an IEM is complex and often requires lifelong medical and nutrition therapy. For any IEM, medical nutrition therapy can vary greatly depending on the severity of the disorder and the patient's age, growth parameters, development, and other clinical factors. Practitioners need to remain aware of the significant burden of disease and its impact on health, social, and financial quality of life for both caregivers and patients dealing with a lifelong IEM. Thus, care by a team specializing in IEM treatment, including a medical geneticist and pediatric dietitian who are trained to manage these disorders, is imperative for successful outcomes.

Test Your Knowledge Questions

1. PKU is often referred to as the model for newborn screening because of which of the following?
   A. Screening is economically feasible, and results are reliable.
   B. Early medical nutrition therapy is available.
   C. Nutrition therapy prevents intellectual disability associated with untreated PKU.
   D. All of the above.
2. Which statement accurately reflects nutrition management of OTC deficiency?
   A. During illness, a protein source should not be added to a patient's enteral or parenteral feedings until the ammonia level decreases into the normal range.
   B. In routine monitoring of a patient with OTC deficiency, an elevated glutamine level in plasma amino acids can suggest that a patient is getting too many calories.
   C. In OTC deficiency, a medical formula that provides only essential amino acids is included in a patient's diet to allow for restriction of total protein intake at, or below, the DRI for age.
   D. Both A and C are correct.
3. In VLCAD deficiency, which of the following is/are contraindicated and why?
   A. Medium-chain triglyceride because it cannot be metabolized.

B. Intralipid because of its long-chain fat content.
C. Carbohydrates because they interfere with fatty acid oxidation.
D. Prolonged fasting because it helps prevent excessive weight gain.

4. Which of the following statements is FALSE?
   A. IV dextrose infusions are often used during acute episodes of metabolic decompensation in several types of IEM.
   B. During acute episodes, parenteral solutions should never contain more than a 5% dextrose concentration because of the high risk of hyperglycemia in these disorders.
   C. Often, dextrose solutions are infused at the high end of the recommended GIR for the patient's age and weight to help promote anabolism.
   D. Both statements B and C are false.
5. Which of the following statements best describes the mitochondrial disorder MELAS?
   A. It typically presents as an acute episode with hypoglycemia and reduced ketone production in early infancy.
   B. Vitamin C in doses of 4–10 g/d is often prescribed because of its documented benefits as an antioxidant.
   C. High doses of the IV form of L-alanine given at the first sign of a stroke-like episode can reduce the severity of symptoms.
   D. Daily oral intake of L-arginine at 150–300 mg/kg/d may reduce the incidence or severity of stroke-like episodes.

References

1. Saudubray JM, Garcia-Cazorla A. Inborn errors of metabolism overview: pathophysiology, manifestations, evaluation, and management. *Pediatr Clin North Am*. 2018;65(2):179–208. https://doi.org/10.1016/j.pcl.2017.11.002
2. Fabie NAV, Pappas KB, Feldman GL. The current state of newborn screening in the United States. *Pediatr Clin North Am*. 2019;66(2):369–386. https://doi.org/10.1016/j.pcl.2018.12.007
3. American College of Medical Genetics Newborn Screening Expert Group. Newborn screening: toward a uniform screening panel and

system—executive summary. *Pediatrics*. 2006;117(5 Pt 2):S296–307. https://doi.org/10.1542/peds.2005-2633I

4. Chace DH, Kalas TA, Naylor EW. The application of tandem mass spectrometry to neonatal screening for inherited disorders of intermediary metabolism. *Annu Rev Genomics Hum Genet*. 2002;3:17–45. https://doi.org/10.1146/annurev.genom.3.022502.103213
5. Ogata B, Trahms C. Medical nutrition therapy for genetic metabolic disorders. *Krause's Food & the Nutrition Care Process*. Elsevier; 2017:890–909.
6. Bernstein L, Rohr F, Van Calcar S, eds. *Nutrition Management of Inherited Metabolic Diseases*. 2nd ed. Springer Nature; 2022.
7. Valle D, Antonarakis S, Ballabio A, Beaudet A, Mitchell G. *The Online Metabolic & Molecular Bases of Inherited Disease*. McGraw-Hill Education. Accessed October 30, 2022. https://ommbid.mhmedical.com/book.aspx?bookID=2709
8. Hillert A, Anikster Y, Belanger-Quintana A, et al. The genetic landscape and epidemiology of phenylketonuria. *Am J Hum Genet*. 2020;107(2):234–250. https://doi.org/10.1016/j.ajhg.2020.06.006
9. biopku.org. Updated 2022. Accessed November 2, 2022. http://www.biopku.org/home/home.asp
10. Camp KM, Parisi MA, Acosta PB, et al. Phenylketonuria Scientific Review Conference: state of the science and future research needs. *Mol Genet Metab*. 2014;112(2):87–122. https://doi.org/10.1016/j.ymgme.2014.02.013
11. Ashe K, Kelso W, Farrand S, et al. Psychiatric and cognitive aspects of phenylketonuria: the limitations of diet and promise of new treatments. *Front Psychiatry*. 2019;10:561. https://doi.org/10.3389/fpsyt.2019.00561
12. Waisbren SE, Noel K, Fahrbach K, et al. Phenylalanine blood levels and clinical outcomes in phenylketonuria: a systematic literature review and meta-analysis. *Mol Genet Metab*. 2007;92(1–2):63–70. https://doi.org/10.1016/j.ymgme.2007.05.006
13. Van Calcar S. Nutrition management of phenylketonuria. In: Bernstein LE Rohr F, Van Calcar S, eds. *Nutrition Management of Inherited Metabolic Diseases*. 2nd ed. Springer Nature; 2022:127–152.

14. Singh RH, Cunningham AC, Mofidi S, et al. Updated, web-based nutrition management guideline for PKU: An evidence and consensus based approach. *Mol Genet Metab*. 2016;118(2):72–83. https://doi.org/10.1016/j.ymgme.2016.04.008
15. Bickel H, Gerrard J, Hickmans EM. Influence of phenylalanine intake on phenylketonuria. *Lancet*. 1953;265(6790):812–813. https://doi.org/10.1016/s0140-6736(53)90473-5
16. Berry HK, Wright S. Conference on treatment of phenylketonuria. *J Pediatr*. 1967;70(1):142–147. https://doi.org/10.1016/s0022-3476(67)80181-1
17. Koch R, Azen C, Friedman EG, Williamson ML. Paired comparisons between early treated PKU children and their matched sibling controls on intelligence and school achievement test results at eight years of age. *J Inherit Metab Dis*. 1984;7(2):86–90. https://doi.org/10.1007/BF01805813
18. Azen CG, Koch R, Friedman EG, et al. Intellectual development in 12-year-old children treated for phenylketonuria. *Am J Dis Child*. 1991;145(1):35–39. https://doi.org/10.1001/archpedi.1991.02160010037012
19. Koch R, Burton B, Hoganson G, et al. Phenylketonuria in adulthood: a collaborative study. *J Inherit Metab Dis*. 2002;25(5):333–346. https://doi.org/10.1023/a:1020158631102
20. Vockley J, Andersson HC, Antshel KM, et al. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. *Genet Med*. 2014;16(2):188–200. https://doi.org/10.1038/gim.2013.157
21. Singh RH, Rohr F, Frazier D, et al. Recommendations for the nutrition management of phenylalanine hydroxylase deficiency. *Genet Med*. 2014;16(2):121–131. https://doi.org/10.1038/gim.2013.179
22. Otten J, Helwig J, Meyers L. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. National Academies Press; 2006.
23. Dangin M, Boirie Y, Garcia-Rodenas C, et al. The digestion rate of protein is an independent regulating factor of postprandial protein retention. *Am J Physiol Endocrinol Metab*. 2001;280(2):E340–348. https://doi.org/10.1152/ajpendo.2001.280.2.E340
24. van Rijn M, Bekhof J, Dijkstra T, Smit PG, Moddermam P, van Spronsen FJ. A different approach to breast-feeding of the infant with

phenylketonuria. *Eur J Pediatr*. 2003;162(5):323–326. https://doi.org/10.1007/s00431-003-1182-2
25. Lemons JA, Reyman D, Moye L. Amino acid composition of preterm and term breast milk during early lactation. *Early Hum Dev*. 1983;8(3–4):323–329. https://doi.org/10.1016/0378-3782(83)90015-4
26. Rohde C, Mutze U, Weigel JF, et al. Unrestricted consumption of fruits and vegetables in phenylketonuria: no major impact on metabolic control. *Eur J Clin Nutr*. 2012;66(5):633–638. https://doi.org/10.1038/ejcn.2011.205
27. Hansen J, Hollander S, Drilias N, Van Calcar S, Rohr F, Bernstein L. Simplified diet for nutrition management of phenylketonuria: A survey of U.S. metabolic dietitians. *JIMD Rep*. 2020;53(1):83–89. https://doi.org/10.1002/jmd2.12106
28. Daly A, Evans S, Pinto A, Ashmore C, Rocha JC, MacDonald A. A 3 year longitudinal prospective review examining the dietary profile and contribution made by special low protein foods to energy and macronutrient intake in children with phenylketonuria. *Nutrients*. 2020;12(10). https://doi.org/10.3390/nu12103153
29. Cook for Love—Low Protein Recipes. Accessed November 2, 2022. https://cookforlove.org/
30. Yagasaki M, Hashimoto S. Synthesis and application of dipeptides; current status and perspectives. *Appl Microbiol Biotechnol*. 2008;81(1):13–22. https://doi.org/10.1007/s00253-008-1590-3
31. Montoya Parra GA, Singh RH, Cetinyurek-Yavuz A, Kuhn M, MacDonald A. Status of nutrients important in brain function in phenylketonuria: a systematic review and meta-analysis. *Orphanet J Rare Dis*. 2018;13(1):101. https://doi.org/10.1186/s13023-018-0839-x
32. Hochuli M, Bollhalder S, Thierer C, Refardt J, Gerber P, Baumgartner MR. Effects of inadequate amino acid mixture intake on nutrient supply of adult patients with phenylketonuria. *Ann Nutr Metab*. 2017;71(3–4):129–135. https://doi.org/10.1159/000479746
33. Rohde C, von Teeffelen-Heithoff A, Thiele AG, et al. PKU patients on a relaxed diet may be at risk for micronutrient deficiencies. *Eur J Clin Nutr*. 2014;68(1):119–124. https://doi.org/10.1038/ejcn.2013.218
34. Mendes AB, Martins FF, Cruz WM, da Silva LE, Abadesso CB, Boaventura GT. Bone development in children and adolescents with

PKU. *J Inherit Metab Dis*. 2012;35(3):425–430. https://doi.org/10.1007/s10545-011-9412-7
35. Hansen KE, Ney D. A systematic review of bone mineral density and fractures in phenylketonuria. *J Inherit Metab Dis*. 2014;37(6):875–880. https://doi.org/10.1007/s10545-014-9735-2
36. van Calcar SC, Ney DM. Food products made with glycomacropeptide, a low-phenylalanine whey protein, provide a new alternative to amino Acid-based medical foods for nutrition management of phenylketonuria. *J Acad Nutr Diet*. Aug 2012;112(8):1201–10. https://doi:10.1016/j.jand.2012.05.004
37. Pena MJ, Pinto A, Daly A, et al. The Use of Glycomacropeptide in Patients with Phenylketonuria: A Systematic Review and Meta-Analysis. *Nutrients*. Nov 18 2018;10(11). https://doi:10.3390/nu10111794
38. van Calcar SC, MacLeod EL, Gleason ST, et al. Improved nutritional management of phenylketonuria by using a diet containing glycomacropeptide compared with amino acids. *Am J Clin Nutr*. Apr 2009;89(4):1068–77. https://doi:10.3945/ajcn.2008.27280
39. MacLeod EL, Clayton MK, van Calcar SC, Ney DM. Breakfast with glycomacropeptide compared with amino acids suppresses plasma ghrelin levels in individuals with phenylketonuria. *Mol Genet Metab*. Aug 2010;100(4):303–8. https://doi:10.1016/j.ymgme.2010.04.003
40. Ney DM, Stroup BM, Clayton MK, et al. Glycomacropeptide for nutritional management of phenylketonuria: a randomized, controlled, crossover trial. *Am J Clin Nutr*. Aug 2016;104(2):334–345. https://doi:10.3945/ajcn.116.135293
41. Daly A, Evans S, Chahal S, et al. Glycomacropeptide: long-term use and impact on blood phenylalanine, growth and nutritional status in children with PKU. *Orphanet J Rare Dis*. Feb 15 2019;14(1):44. https://doi:10.1186/s13023-019-1011-y
42. Daly A, Evans S, Chahal S, Santra S, MacDonald A. Glycomacropeptide in children with phenylketonuria: does its phenylalanine content affect blood phenylalanine control? *J Hum Nutr Diet*. Aug 2017;30(4):515–523. https://doi:10.1111/jhn.12438
43. Schindler S, Ghosh-Jerath S, Thompson S, et al. The effects of large neutral amino acid supplements in PKU: an MRS and

neuropsychological study. *Mol Genet Metab*. 2007;91(1):48–54. https://doi.org/10.1016/j.ymgme.2007.02.002
44. Scala I, Riccio MP, Marino M, Bravaccio C, Parenti G, Strisciuglio P. Large neutral amino acids (LNAAs) supplementation improves neuropsychological performances in adult patients with phenylketonuria. *Nutrients*. 2020;12(4). https://doi.org/10.3390/nu12041092
45. Matalon R, Michals-Matalon K, Bhatia G, et al. Double blind placebo control trial of large neutral amino acids in treatment of PKU: effect on blood phenylalanine. *J Inherit Metab Dis*. 2007;30(2):153–158. https://doi.org/10.1007/s10545-007-0556-4
46. Levy HL, Milanowski A, Chakrapani A, et al. Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase III randomised placebo-controlled study. *Lancet*. 2007;370(9586):504–510. https://doi.org/10.1016/S0140-6736(07)61234-3
47. Keil S, Anjema K, van Spronsen FJ, et al. Long-term follow-up and outcome of phenylketonuria patients on sapropterin: a retrospective study. *Pediatrics*. 2013;131(6):E1881–1888. https://doi.org/10.1542/peds.2012-3291
48. Burton B, Grant M, Feigenbaum A, et al. A randomized, placebo-controlled, double-blind study of sapropterin to treat ADHD symptoms and executive function impairment in children and adults with sapropterin-responsive phenylketonuria. *Mol Genet Metab*. 2015;114(3):415–424. https://doi.org/10.1016/j.ymgme.2014.11.011
49. Waisbren S, Burton BK, Feigenbaum A, et al. Long-term preservation of intellectual functioning in sapropterin-treated infants and young children with phenylketonuria: a seven-year analysis. *Mol Genet Metab*. 2021;132(2):119–127. https://doi.org/10.1016/j.ymgme.2021.01.001
50. Cunningham A, Bausell H, Brown M, et al. Recommendations for the use of sapropterin in phenylketonuria. *Mol Genet Metab*. 2012;106(3):269–276. https://doi.org/10.1016/j.ymgme.2012.04.004
51. Thiele AG, Rohde C, Mutze U, et al. The challenge of long-term tetrahydrobiopterin (BH4) therapy in phenylketonuria: effects on

metabolic control, nutritional habits and nutrient supply. *Mol Genet Metab Rep*. 2015;4:62–67. https://doi.org/10.1016/j.ymgmr.2015.07.002
52. Ilgaz F, Marsaux C, Pinto A, et al. Protein substitute requirements of patients with phenylketonuria on BH4 treatment: a systematic review and meta-analysis. *Nutrients*. 2021;13(3). https://doi.org/10.3390/nu13031040
53. Harding CO, Amato RS, Stuy M, et al. Pegvaliase for the treatment of phenylketonuria: a pivotal, double-blind randomized discontinuation phase 3 clinical trial. *Mol Genet Metab*. 2018;124(1):20–26. https://doi.org/10.1016/j.ymgme.2018.03.003
54. Thomas J, Levy H, Amato S, et al. Pegvaliase for the treatment of phenylketonuria: results of a long-term phase 3 clinical trial program (PRISM). *Mol Genet Metab*. 2018;124(1):27–38. https://doi.org/10.1016/j.ymgme.2018.03.006
55. Longo N, Zori R, Wasserstein MP, et al. Long-term safety and efficacy of pegvaliase for the treatment of phenylketonuria in adults: combined phase 2 outcomes through PAL-003 extension study. *Orphanet J Rare Dis*. 2018;13(1):108. https://doi.org/10.1186/s13023-018-0858-7
56. Zori R, Thomas JA, Shur N, et al. Induction, titration, and maintenance dosing regimen in a phase 2 study of pegvaliase for control of blood phenylalanine in adults with phenylketonuria. *Mol Genet Metab*. 2018;125(3):217–227. https://doi.org/10.1016/j.ymgme.2018.06.010
57. Longo N, Dimmock D, Levy H, et al. Evidence- and consensus-based recommendations for the use of pegvaliase in adults with phenylketonuria. *Genet Med*. 2019;21(8):1851–1867. https://doi.org/10.1038/s41436-018-0403-z
58. Hausmann O, Daha M, Longo N, et al. Pegvaliase: immunological profile and recommendations for the clinical management of hypersensitivity reactions in patients with phenylketonuria treated with this enzyme substitution therapy. *Mol Genet Metab*. 2019;128(1–2):84–91. https://doi.org/10.1016/j.ymgme.2019.05.006
59. Rohr F, Burton B, Longo N, et al. Evaluating change in diet with Pegvaliase treatment in adults with phenylketonuria: results from

phase 2 and 3 clinical trials. American College of Medical Genetics and Genomics Annual Meeting, 2020.
60. Levy HL, Ghavami M. Maternal phenylketonuria: a metabolic teratogen. *Teratology*. 1996;53(3):176–184. https://doi.org/10.1002/(SICI)1096-9926(199603)53:3<176::AID-TERA5>3.0.CO;2–2
61. Waisbren SE, Hanley W, Levy HL, et al. Outcome at age 4 years in offspring of women with maternal phenylketonuria: the Maternal PKU Collaborative Study. *JAMA*. 2000;283(6):756–762. https://doi.org/10.1001/jama.283.6.756
62. Waisbren SE, Azen C. Cognitive and behavioral development in maternal phenylketonuria offspring. *Pediatrics*. 2003;112(6 Pt 2):1544–1547. https://doi.org/10.1542/peds.112.S4.1544
63. Maillot F, Lilburn M, Baudin J, Morley DW, Lee PJ. Factors influencing outcomes in the offspring of mothers with phenylketonuria during pregnancy: the importance of variation in maternal blood phenylalanine. *Am J Clin Nutr*. 2008;88(3):700–705. https://doi.org/10.1093/ajcn/88.3.700
64. Acosta PB, Matalon K, Castiglioni L, et al. Intake of major nutrients by women in the Maternal Phenylketonuria (MPKU) Study and effects on plasma phenylalanine concentrations. *Am J Clin Nutr*. 2001;73(4):792–796. https://doi.org/10.1093/ajcn/73.4.792
65. Teissier R, Nowak E, Assoun M, et al. Maternal phenylketonuria: low phenylalaninemia might increase the risk of intrauterine growth retardation. *J Inherit Metab Dis*. 2012;35(6):993–999. https://doi.org/10.1007/s10545-012-9491-0
66. Thomas J. Organic acidemias. In: Bernstein L, Rohr F, Van Calcar S, eds. *Nutrition Management of Inherited Metabolic Diseases*. 2nd ed. Springer Nature; 2022:257–275.
67. Manoli I, Myles JG, Sloan JL, Shchelochkov OA, Venditti CP. A critical reappraisal of dietary practices in methylmalonic acidemia raises concerns about the safety of medical foods. Part 1: isolated methylmalonic acidemias. *Genet Med*. 2016;18(4):386–395. https://doi.org/10.1038/gim.2015.102
68. Fraser JL, Venditti CP. Methylmalonic and propionic acidemias: clinical management update. *Curr Opin Pediatr*. 2016;28(6):682–693.

https://doi.org/10.1097/MOP.0000000000000422
69. Merinero B, Perez B, Perez-Cerda C, et al. Methylmalonic acidaemia: examination of genotype and biochemical data in 32 patients belonging to mut, cblA or cblB complementation group. *J Inherit Metab Dis*. 2008;31(1):55–66. https://doi.org/10.1007/s10545-007-0667-y
70. Baumgartner MR, Horster F, Dionisi-Vici C, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. *Orphanet J Rare Dis*. 2014;9:130. https://doi.org/10.1186/s13023-014-0130-8
71. Manoli I, Sloan J, Venditti C. Isolated methylmalonic acidemia. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa GM, eds. *GeneReviews*. University of Washington; 1993–2022. Updated December 1, 2016. Accessed October 30, 2022. https://www.ncbi.nlm.nih.gov/books/NBK1231/
72. Dionisi-Vici C, Deodato F, Roschinger W, Rhead W, Wilcken B. 'Classical' organic acidurias, propionic aciduria, methylmalonic aciduria and isovaleric aciduria: long-term outcome and effects of expanded newborn screening using tandem mass spectrometry. *J Inherit Metab Dis*. 2006;29(2–3):383–389. https://doi.org/10.1007/s10545-006-0278-z
73. Weisfeld-Adams JD, Bender HA, Miley-Akerstedt A, et al. Neurologic and neurodevelopmental phenotypes in young children with early-treated combined methylmalonic acidemia and homocystinuria, cobalamin C type. *Mol Genet Metab*. 2013;110(3):241–247. https://doi.org/10.1016/j.ymgme.2013.07.018
74. Critelli K, McKiernan P, Vockley J, et al. Liver transplantation for propionic acidemia and methylmalonic acidemia: perioperative management and clinical outcomes. *Liver Transpl*. 2018;24(9):1260–1270. https://doi.org/10.1002/lt.25304
75. Niemi AK, Kim IK, Krueger CE, et al. Treatment of methylmalonic acidemia by liver or combined liver-kidney transplantation. *J Pediatr*. 2015;166(6):1455–1461 e1. https://doi.org/10.1016/j.jpeds.2015.01.051
76. Clothier JC, Chakrapani A, Preece MA, et al. Renal transplantation in a boy with methylmalonic acidaemia. *J Inherit Metab Dis*.

2011;34(3):695–700. https://doi.org/10.1007/s10545-011-9303-y
77. Chu TH, Chien YH, Lin HY, et al. Methylmalonic acidemia/propionic acidemia—the biochemical presentation and comparing the outcome between liver transplantation versus non-liver transplantation groups. *Orphanet J Rare Dis*. 2019;14(1):73. https://doi.org/10.1186/s13023-019-1045-1
78. Chapman KA, Gropman A, MacLeod E, et al. Acute management of propionic acidemia. *Mol Genet Metab*. 2012;105(1):16–25. https://doi.org/10.1016/j.ymgme.2011.09.026
79. New England Regional Genetics Consortium. Methylmalonic acidemia. 2022. Accessed November 2, 2022. https://www.newenglandconsortium.org/methyl
80. Sowa M. Nutrition management of propionic acidemia and methylmalonic acidemia. In: Bernstein LE, Rohr F, Van Calcar S, eds. *Nutrition Management of Inherited Metabolic Disorders*. 2nd ed. Springer; 2022:295–308.
81. Integrity. Integrity compounding pharmacy. Accessed October 2022. https://www.mixwithintegrity.com/
82. Jurecki E, Ueda K, Frazier D, et al. Nutrition management guideline for propionic acidemia: An evidence- and consensus-based approach. *Mol Genet Metab*. 2019;126(4):341–354. https://doi.org/10.1016/j.ymgme.2019.02.007
83. Bernstein LE, Burns C, Drumm M, Gaughan S, Sailer M, Baker PR 2nd. Impact on isoleucine and valine supplementation when decreasing use of medical food in the nutritional management of methylmalonic acidemia. *Nutrients*. 2020;12(2). https://doi.org/10.3390/nu12020473
84. Hauser NS, Manoli I, Graf JC, Sloan J, Venditti CP. Variable dietary management of methylmalonic acidemia: metabolic and energetic correlations. *Am J Clin Nutr*. 2011;93(1):47–56. https://doi.org/10.3945/ajcn.110.004341
85. Feillet F, Bodamer OA, Dixon MA, Sequeira S, Leonard JV. Resting energy expenditure in disorders of propionate metabolism. *J Pediatr*. 2000;136(5):659–663. https://doi.org/10.1067/mpd.2000.104290
86. Fowler B, Leonard JV, Baumgartner MR. Causes of and diagnostic approach to methylmalonic acidurias. *J Inherit Metab Dis*.

2008;31(3):350–360. https://doi.org/10.1007/s10545-008-0839-4
87. Andersson HC, Shapira E. Biochemical and clinical response to hydroxocobalamin versus cyanocobalamin treatment in patients with methylmalonic acidemia and homocystinuria (cblC). *J Pediatr*. 1998;132(1):121–124. https://doi.org/10.1016/s0022-3476(98)70496-2
88. Chalmers RA, Roe CR, Stacey TE, Hoppel CL. Urinary excretion of l-carnitine and acylcarnitines by patients with disorders of organic acid metabolism: evidence for secondary insufficiency of l-carnitine. *Pediatr Res*. 1984;18(12):1325–1328. https://doi.org/10.1203/00006450-198412000-00021
89. Ah Mew N, Simpson KL, Gropman AL, Chapman KA, Summar ML. Urea cycle disorders overview. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa GM, eds. *GeneReviews*. University of Washington; 1993–2022. Updated June 22, 2017. Accessed November 2022. https://www.ncbi.nlm.nih.gov/books/NBK1217/
90. Summar ML, Koelker S, Freedenberg D, et al. The incidence of urea cycle disorders. *Mol Genet Metab*. 2013;110(1–2):179–180. https://doi.org/10.1016/j.ymgme.2013.07.008
91. Batshaw ML, Tuchman M, Summar M, et al. A longitudinal study of urea cycle disorders. *Mol Genet Metab*. 2014;113(1–2):127–30. https://doi.org/10.1016/j.ymgme.2014.08.001
92. Ruegger CM, Lindner M, Ballhausen D, et al. Cross-sectional observational study of 208 patients with non-classical urea cycle disorders. *J Inherit Metab Dis*. 2014;37(1):21–30. https://doi.org/10.1007/s10545-013-9624-0
93. Haberle J, Burlina A, Chakrapani A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders: first revision. *J Inherit Metab Dis*. 2019;42(6):1192–1230. https://doi.org/10.1002/jimd.12100
94. Gerstein MT, Markus AR, Gianattasio KZ, et al. Choosing between medical management and liver transplant in urea cycle disorders: a conceptual framework for parental treatment decision-making in rare disease. *J Inherit Metab Dis*. 2020;43(3):438–458. https://doi.org/10.1002/jimd.12209

95. Perito ER, Rhee S, Roberts JP, Rosenthal P. Pediatric liver transplantation for urea cycle disorders and organic acidemias: United Network for Organ Sharing data for 2002–2012. *Liver Transpl*. 2014;20(1):89–99. https://doi.org/10.1002/lt.23765
96. MacLeod EL. Nutrition management of urea cycle disorders. In: Bernstein LE, Rohr F, Van Calcar S, eds. *Nutrition Management of Inherited Metabolic Disorders*. 2nd ed. Springer; 2022:225–240.
97. New England Regional Genetics Consortium. Ornithine Transcarbamylase Deficiency (OTC Deficiency). 2022. Accessed November 2, 2022. https://www.newenglandconsortium.org/ornithine-transcarbamylase-deficiency-otc-deficiency
98. MacLeod EL, Hall KD, McGuire PJ. Computational modeling to predict nitrogen balance during acute metabolic decompensation in patients with urea cycle disorders. *J Inherit Metab Dis*. 2016;39(1):17–24. https://doi.org/10.1007/s10545-015-9882-0
99. Batshaw ML, MacArthur RB, Tuchman M. Alternative pathway therapy for urea cycle disorders: twenty years later. *J Pediatr*. 2001;138(suppl 1):S46–S54. https://doi.org/10.1067/mpd.2001.111836
100. Diaz GA, Krivitzky LS, Mokhtarani M, et al. Ammonia control and neurocognitive outcome among urea cycle disorder patients treated with glycerol phenylbutyrate. *Hepatology*. 2013;57(6):2171–2179. https://doi.org/10.1002/hep.26058
101. Boneh A. Dietary protein in urea cycle defects: How much? Which? How? *Mol Genet Metab*. 2014;113(1–2):109–112. https://doi.org/10.1016/j.ymgme.2014.04.009
102. Singh RH. Nutritional management of patients with urea cycle disorders. *J Inherit Metab Dis*. 2007;30(6):880–887. https://doi.org/10.1007/s10545-007-0718-4
103. Molema F, Gleich F, Burgard P, et al. Evaluation of dietary treatment and amino acid supplementation in organic acidurias and urea-cycle disorders: on the basis of information from a European multicenter registry. *J Inherit Metab Dis*. 2019;42(6):1162–1175. https://doi.org/10.1002/jimd.12066
104. Evans M, Truby H, Boneh A. The relationship between dietary intake, growth, and body composition in inborn errors of intermediary protein

metabolism. *J Pediatr*. 2017;188:163–172. https://doi.org/10.1016/j.jpeds.2017.05.048
105. Gardeitchik T, Humphrey M, Nation J, Boneh A. Early clinical manifestations and eating patterns in patients with urea cycle disorders. *J Pediatr*. 2012;161(2):328–332. https://doi.org/10.1016/j.jpeds.2012.02.006
106. Holecek M. Branched-chain amino acids and branched-chain keto acids in hyperammonemic states: metabolism and as supplements. *Metabolites*. 2020;10(8). https://doi.org/10.3390/metabo10080324
107. Knottnerus SJG, Bleeker JC, Wust RCI, et al. Disorders of mitochondrial long-chain fatty acid oxidation and the carnitine shuttle. *Rev Endocr Metab Disord*. 2018;19(1):93–106. https://doi.org/10.1007/s11154-018-9448-1
108. Leslie ND, Saenz-Ayala S. Very long-chain acyl-Coenzyme A dehydrogenase deficiency. In: Adam MP, Everman DB, Mirzaa GM, et al. eds. *GeneReviews(R)*. 1993–2022. Updated 2020. Accessed November 2, 2022. https://pubmed.ncbi.nlm.nih.gov/20301763/
109. Fatehi F, Okhovat AA, Nilipour Y, et al. Adult-onset very-long-chain acyl-CoA dehydrogenase deficiency (VLCADD). *Eur J Neurol*. 2020;27(11):2257–2266. https://doi.org/10.1111/ene.14402
110. Rovelli V, Manzoni F, Viau K, Pasquali M, Longo N. Clinical and biochemical outcome of patients with very long-chain acyl-CoA dehydrogenase deficiency. *Mol Genet Metab*. 2019;127(1):64–73. https://doi.org/10.1016/j.ymgme.2019.04.001
111. Takizaki N, Hanakawa J, Iwano R, Hirano Y, Muroya K. Very long-chain acyl-CoA dehydrogenase deficiency: No developmental delay after cardiopulmonary arrest. *Pediatr Int*. 2021;63(8):992–994. https://doi.org/10.1111/ped.14666
112. Hesse J, Braun C, Behringer S, Matysiak U, Spiekerkoetter U, Tucci S. The diagnostic challenge in very-long chain acyl-CoA dehydrogenase deficiency (VLCADD). *J Inherit Metab Dis*. 2018;41(6):1169–1178. https://doi.org/10.1007/s10545-018-0245-5
113. Liebig M, Schymik I, Mueller M, et al. Neonatal screening for very long-chain acyl-coA dehydrogenase deficiency: enzymatic and molecular evaluation of neonates with elevated C14:1-carnitine levels.

Pediatrics. 2006;118(3):1065–1069. https://doi.org/10.1542/peds.2006-0666
114. Van Calcar SC, Sowa M, Rohr F, et al. Nutrition management guideline for very-long chain acyl-CoA dehydrogenase deficiency (VLCADD): an evidence- and consensus-based approach. *Mol Genet Metab*. 2020;131(1–2):23–37. https://doi.org/10.1016/j.ymgme.2020.10.001
115. Bleeker JC, Kok IL, Ferdinandusse S, et al. Proposal for an individualized dietary strategy in patients with very long-chain acyl-CoA dehydrogenase deficiency. *J Inherit Metab Dis*. 2019;42(1):159–168. https://doi.org/10.1002/jimd.12037
116. Coughlin CR, Ficicioglu C. Genotype-phenotype correlations: sudden death in an infant with very-long-chain acyl-CoA dehydrogenase deficiency. *J Inherit Metab Dis*. 2010;33(suppl 3):S129–S131. https://doi.org/10.1007/s10545-009-9041-6
117. Kripps KA, Baker PR, Thomas JA, et al. REVIEW: Practical strategies to maintain anabolism by intravenous nutritional management in children with inborn metabolic diseases. *Mol Genet Metab*. 2021;133(3):231–241. https://doi.org/10.1016/j.ymgme.2021.04.007
118. Rohr F. Nutrition management of fatty acid oxidation disorders. In: Bernstein LE, Rohr F, Van Calcar S, eds. *Nutrition Management of Inherited Metabolic Disorders*. 2nd ed. Springer; 2022:309–324.
119. Walter JH. Tolerance to fast: rational and practical evaluation in children with hypoketonaemia. *J Inherit Metab Dis*. 2009;32(2):214–217. https://doi.org/10.1007/s10545-009-1087-y
120. Gillingham MB, Elizondo G, Behrend A, et al. Higher dietary protein intake preserves lean body mass, lowers liver lipid deposition, and maintains metabolic control in participants with long-chain fatty acid oxidation disorders. *J Inherit Metab Dis*. 2019;42(5):857–869. https://doi.org/10.1002/jimd.12155
121. Gillingham MB, Heitner SB, Martin J, et al. Triheptanoin versus trioctanoin for long-chain fatty acid oxidation disorders: a double blinded, randomized controlled trial. *J Inherit Metab Dis*. 2017;40(6):831–843. https://doi.org/10.1007/s10545-017-0085-8

122. Vockley J, Burton B, Berry G, et al. Effects of triheptanoin (UX007) in patients with long-chain fatty acid oxidation disorders: results from an open-label, long-term extension study. *J Inherit Metab Dis*. 2021;44(1):253–263. https://doi.org/10.1002/jimd.12313
123. Gillingham MB, Scott B, Elliott D, Harding CO. Metabolic control during exercise with and without medium-chain triglycerides (MCT) in children with long-chain 3-hydroxy acyl-CoA dehydrogenase (LCHAD) or trifunctional protein (TFP) deficiency. *Mol Genet Metab*. 2006;89(1–2):58–63. https://doi.org/10.1016/j.ymgme.2006.06.004
124. Korlimala A, Gibson R, Kishnani P. Glycogen Storage Diseases, Nutrition management of fatty acid oxidation disorders. In: Bernstein LE, Rohr F, Van Calcar S, eds. *Nutrition Management of Inherited Metabolic Disorders*. 2nd ed. Springer; 2022:349–362.
125. Lak R, Yazdizadeh B, Davari M, Nouhi M, Kelishadi R. Newborn screening for galactosaemia. *Cochrane Database Syst Rev*. 2017;12:CD012272. https://doi.org/10.1002/14651858.CD012272.pub2
126. Berry GT. Classic galactosemia and clinical variant galactosemia. In: Adam MP, Everman DB, Mirzaa GM, et al. eds. *GeneReviews(R)*; 1993–2021. Accessed November 2022. https://www.ncbi.nlm.nih.gov/books/NBK1518/
127. Welling L, Bernstein LE, Berry GT, et al. International clinical guideline for the management of classical galactosemia: diagnosis, treatment, and follow-up. *J Inherit Metab Dis*. 2017;40(2):171–176. https://doi.org/10.1007/s10545-016-9990-5
128. Waggoner DD, Buist NR, Donnell GN. Long-term prognosis in galactosaemia: results of a survey of 350 cases. *J Inherit Metab Dis*. 1990;13(6):802–818. https://doi.org/10.1007/BF01800204
129. Waisbren SE, Potter NL, Gordon CM, et al. The adult galactosemic phenotype. *J Inherit Metab Dis*. 2012;35(2):279–286. https://doi.org/10.1007/s10545-011-9372-y
130. Coss KP, Hawkes CP, Adamczyk B, et al. N-glycan abnormalities in children with galactosemia. *J Proteome Res*. 2014;13(2):385–394. https://doi.org/10.1021/pr4008305
131. Van Calcar SC, Bernstein LE, Rohr FJ, Yannicelli S, Berry GT, Scaman CH. Galactose content of legumes, caseinates, and some hard

cheeses: implications for diet treatment of classic galactosemia. *J Agric Food Chem*. 2014;62(6):1397–1402. https://doi.org/10.1021/jf404995a

132. Van Calcar SC, Bernstein LE, Rohr FJ, Scaman CH, Yannicelli S, Berry GT. A re-evaluation of life-long severe galactose restriction for the nutrition management of classic galactosemia. *Mol Genet Metab*. 2014;112(3):191–197. https://doi.org/10.1016/j.ymgme.2014.04.004
133. Ficicioglu C, Hussa C, Yager C, Segal S. Effect of galactose free formula on galactose-1-phosphate in two infants with classical galactosemia. *Eur J Pediatr*. 2008;167(5):595–596. https://doi.org/10.1007/s00431-007-0520-1
134. Zlatunich CO, Packman S. Galactosaemia: early treatment with an elemental formula. *J Inherit Metab Dis*. 2005;28(2):163–168. https://doi.org/10.1007/s10545-005-5516-2
135. van Erven B, Welling L, van Calcar SC, et al. Bone health in classic galactosemia: systematic review and meta-analysis. *JIMD Rep*. 2017;35:87–96. https://doi.org/10.1007/8904_2016_28
136. Batey LA, Welt CK, Rohr F, et al. Skeletal health in adult patients with classic galactosemia. *Osteoporos Int*. 2013;24(2):501–509. https://doi.org/10.1007/s00198-012-1983-0
137. de Barcelos IP, Emmanuele V, Hirano M. Advances in primary mitochondrial myopathies. *Curr Opin Neurol*. 2019;32(5):715–721. https://doi.org/10.1097/WCO.0000000000000743
138. Olimpio C, Tiet MY, Horvath R. Primary mitochondrial myopathies in childhood. *Neuromuscul Disord*. 2021;31(10):978–987. https://doi.org/10.1016/j.nmd.2021.08.005
139. El-Hattab AW, Adesina AM, Jones J, Scaglia F. MELAS syndrome: Clinical manifestations, pathogenesis, and treatment options. *Mol Genet Metab*. 2015;116(1–2):4–12. https://doi.org/10.1016/j.ymgme.2015.06.004
140. Rahman S. Gastrointestinal and hepatic manifestations of mitochondrial disorders. *J Inherit Metab Dis*. 2013;36(4):659–673. https://doi.org/10.1007/s10545-013-9614-2
141. El-Hattab AW, Zarante AM, Almannai M, Scaglia F. Therapies for mitochondrial diseases and current clinical trials. *Mol Genet Metab*. 2017;122(3):1–9. https://doi.org/10.1016/j.ymgme.2017.09.009

142. Tarnopolsky MA. Metabolic myopathies. *Continuum (Minneap Minn)*. 2016;22(6):1829–1851. https://doi.org/10.1212/CON.0000000000000403
143. Santa KM. Treatment options for mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome. *Pharmacotherapy*. 2010;30(11):1179–1196. https://doi.org/10.1592/phco.30.11.1179
144. Koga Y, Povalko N, Inoue E, et al. Therapeutic regimen of L-arginine for MELAS: 9-year, prospective, multicenter, clinical research. *J Neurol*. 2018;265(12):2861–2874. https://doi.org/10.1007/s00415-018-9057-7
145. Ikawa M, Povalko N, Koga Y. Arginine therapy in mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes. *Curr Opin Clin Nutr Metab Care*. 2020;23(1):17–22. https://doi.org/10.1097/MCO.0000000000000610
146. Ng YS, Bindoff LA, Gorman GS, et al. Consensus-based statements for the management of mitochondrial stroke-like episodes. *Wellcome Open Res*. 2019;4:201. https://doi.org/10.12688/wellcomeopenres.15599.1
147. Ohsawa Y, Hagiwara H, Nishimatsu SI, Hirakawa A, Kamimura N, et al.; KN01 Study Group. Taurine supplementation for prevention of stroke-like episodes in MELAS: a multicentre, open-label, 52-week phase III trial. *J Neurol Neurosurg Psychiatry*. 2019;90(5):529–536. https://doi.org/10.1136/jnnp-2018-317964

Test Your Knowledge Answers

1. The correct answer is **D**. Disorders selected for newborn screening programs must be cost-effective and reliably detected by population-based screening methods. Realistic and effective treatment modalities should be available for the disorder to prevent severe sequelae of the disease.
2. The correct answer is **C**. Using a medical formula that contains only essential amino acids maximizes protein synthesis without the release of excessive nitrogen from nonessential amino acids, which can lead to

additional ammonia production. This allows for restriction of total protein to DRI recommendations, or lower, for age.

3. The correct answer is **B**. Individuals with VLCADD cannot metabolize long-chain fats effectively and Intralipid is a long-chain fat source. Answer A is incorrect since MCTs provide a source of fat that can be metabolized to meet calorie needs. Answer C is incorrect since carbohydrates provide an energy source that can be utilized without fatty acid oxidation. Answer D is incorrect since fasting time is limited to reduce reliance on fatty acid oxidation as an energy source.
4. The correct answer is **B**. In IEM, higher concentrations of dextrose (usually 10% by peripheral PN or higher concentrations if central access is available) are used to slow catabolism and prevent hypoglycemia, which is more common in IEM than hyperglycemia.
5. The correct answer is **D**. Oral supplementation with L-arginine may help reduce the incidence or severity of developing stroke-like episodes in MELAS. Intravenous L-arginine is used during these episodes to reduce the severity of symptoms, not L-alanine as given in Answer C.

21

Cardiac Disease

Kavisha Shah, MD

The author would like to acknowledge Janice Antino, RD, MS, CNSC; Mindy Freudenberg, RD, MS, CNSC; and Anupama Chawla, MD, DCH (UK), CNSC, for their contributions to earlier editions of this text.

Learning Objectives

1. Identify factors contributing to growth failure in children with congenital heart disease.
2. Summarize the components of nutrition assessment and the optimal methods of nutrient delivery in children with congenital heart disease.
3. Recognize and manage postoperative complications and prescribe appropriate nutrition therapy.
4. Identify interventions for cardiovascular disease risk reduction through pediatric screening.

Introduction

Congenital heart diseases (CHDs) are abnormalities in the heart structure that are present at birth. Approximately 8 out of every 1000 infants are born with a CHD. CHD can be classified into 2 major categories: cyanotic and acyanotic (see Exhibit 21-1).[1]

EXHIBIT 21-1. Two Major Categories of Congenital Heart Disease

Acyanotic

Atrial septal defect
Ventricular septal defect
Patent ductus arteriosus
Common A-V canal
Pulmonary stenosis[a]
Coarctation of aorta[a]
Aortic stenosis
Tetralogy of Fallot[a]
Transposition of the great vessels[a]
Total anomalous pulmonary venous return[a]
Truncus arteriosus[a]
Tricuspid atresia[a]
Hypoplastic left heart syndrome[a]

Cyanotic

Interrupted aortic arch
Pulmonary atresia
Ebstein's anomaly

[a] These conditions may present as cyanotic congenital heart disease or as acyanotic congenital heart disease that transitions to the cyanotic state.

With acyanotic heart defects, shunting of blood occurs from the left side of the heart to the right side of the heart. The development of congestive heart failure (CHF) is a major concern in acyanotic heart disease. In cyanotic heart defects, oxygen-poor blood mixes with oxygen-rich blood. The main concern with cyanotic heart disease is hypoxia. The tissues do not receive fully oxygenated blood, which is apparent from the bluish tint (cyanosis) of the skin, lips, and nail beds.

This population is presented with unique challenges in meeting energy requirements for optimal growth and development. Depending on the severity of the defect, a child with CHD may face feeding difficulties and malnutrition during a critical developmental period.

Nutrition Assessment and Malnutrition

Malnutrition is well documented in infants and children with CHD. The severity of malnutrition can range from mild to severe, with the potential for both acute and chronic health implications. The degree of impact on an infant's nutrition status varies with the type of cardiac malformation and tends to be the most severe in cardiac conditions associated with increased pulmonary blood flow, severe cyanosis, and pulmonary hypertension.[2]

Acute and chronic malnutrition is of particular concern for infants and children with cyanotic heart disease due to their chronic hypoxic state and the prolonged course until final surgical correction. Cameron et al reported the prevalence of acute and chronic malnutrition to be as high as 33% and 64%, respectively.[3] Although malnutrition is more likely with cyanosis and CHF, it can be encountered with any cardiac defect with or without cyanosis.[4]

CHDs associated with significant rates of morbidity and mortality are hypoplastic left heart syndrome (HLHS) and other single ventricle defect variants. Infants with these conditions typically undergo a series of palliative surgical procedures and have difficulty achieving adequate growth between surgical stages.[5] They are particularly at risk for malnutrition between neonatal surgical palliation (the Norwood procedure) and the second surgical stage, the bidirectional Glenn procedure (BDG), typically performed at 4 to 6 months of age. The time between these 2 procedures, during which weight gain is often suboptimal, is commonly referred to as the interstage period.[6,7] Kelleher et al evaluated the growth of 50 infants with HLHS during the interstage period.[5] From initial discharge and subsequent readmission for BDG shunt surgery, infants experienced a significant drop in weight age *z* score (WAZ), with a median WAZ of −2.0, suggesting that 50% of infants were severely underweight at the time of major cardiac surgery. Anderson and colleagues also identified lower WAZ in a group of infants who underwent BDG.[6] Infants with lower WAZ tended to experience a longer duration of mechanical ventilation, prolonged hospitalization, additional days in the intensive care unit, and more frequent postoperative complications.[5,6]

The interstage period is a critical time for infants with CHD and presents unique challenges to the practitioner providing nutrition care. To address the challenges these infants face, the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC) was formed with the mission of improving outcomes of children with cardiovascular disease (CVD). The NPC-QIC is the first multicenter quality improvement collaborative within pediatric cardiology. Nutrition is a major focus of this group, which aims to improve survival and quality of life during the interstage period.

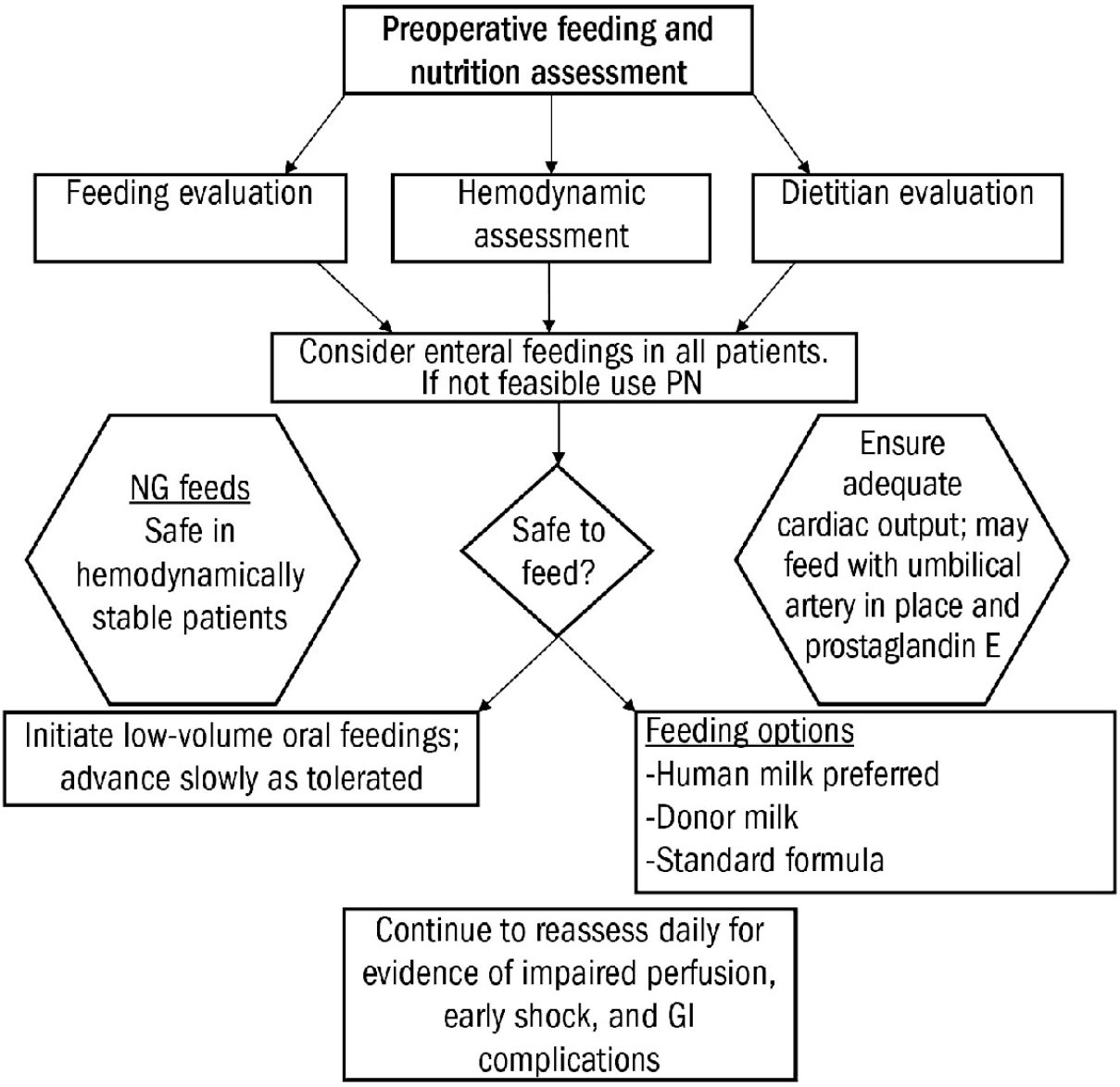
Significant variations in nutrition practices exist between different surgical cardiac centers; however, the NPC-QIC demonstrated that if energy goals are met and children are closely monitored during the interstage phase, adequate growth can be achieved.[6–8] Early identification of children with growth and feeding difficulties leading to early intervention results in improved growth outcomes and reduced mortality. Considering these facts, the Feeding Work Group (FWG) of the NPC-QIC was formed to develop consensus recommendations for feeding and nutrition for infants with single ventricle heart disease. The algorithms are presented in Figures 21-1 through 21-4. Recommendations for feeding preoperatively, postoperatively, and after hospital discharge are summarized as follows:[9]

1. Preoperative feeding guidelines (see also Figure 21-1)
    a. Because of the high risk for malnutrition, parenteral nutrition (PN) should be initiated early and advanced to full calorie and protein goals until enteral feeding goals can be achieved.
    b. Enteral nutrition (EN) should be provided if the infant is hemodynamically stable. With appropriate monitoring, EN can be achieved safely.
    c. Preoperative oral feeding should be encouraged but may become a challenge. Nasogastric (NG) tube feeds have been a widely accepted practice and are used as an adjunct to oral feeds. Therefore, NG tube feeding support should be considered preoperatively.
    d. Patients with umbilical arterial catheters may be fed enterally without increased adverse outcomes, based on several case studies and observational studies.

e. Prostaglandin infusions increase concern for gastrointestinal complications, systemic vasodilation, respiratory depression, edema, and increased secretions. Despite these concerns, enteral feedings have been used safely in these cases, and the infusions are not a contraindication to enteral feeding.
f. Human milk is the preferred option for initiating enteral feeds because of its immunologic benefits and protein, which have high biological value. When it is unavailable, standard infant formula can be used.

2. Postoperative enteral feeding (see Figures 21-2 and 21-3)
    a. Postoperative PN should be used to achieve energy goals initially. When the infant is hemodynamically stable, and gut function returns, enteral feeding should be initiated.
    b. Due to the high incidence of vocal cord injury and oral motor dysfunction, a feeding evaluation should be conducted to evaluate aspiration risk and safety of providing oral feeds.
    c. During the feeding advancement, close monitoring for gastrointestinal and cardiac complications is required.
3. Interstage feeding guidelines (see Figure 21-4)
    a. During the interstage period, close weight monitoring is critical to modify the feeding regimen to promote growth.
    b. Oral aversions must be addressed in this stage, and referral to speech and occupational therapy should be considered to improve oral–motor skills.
    c. For symptoms of vomiting and feeding intolerance, medications should be reviewed, accounting for their side effects and toxicity.

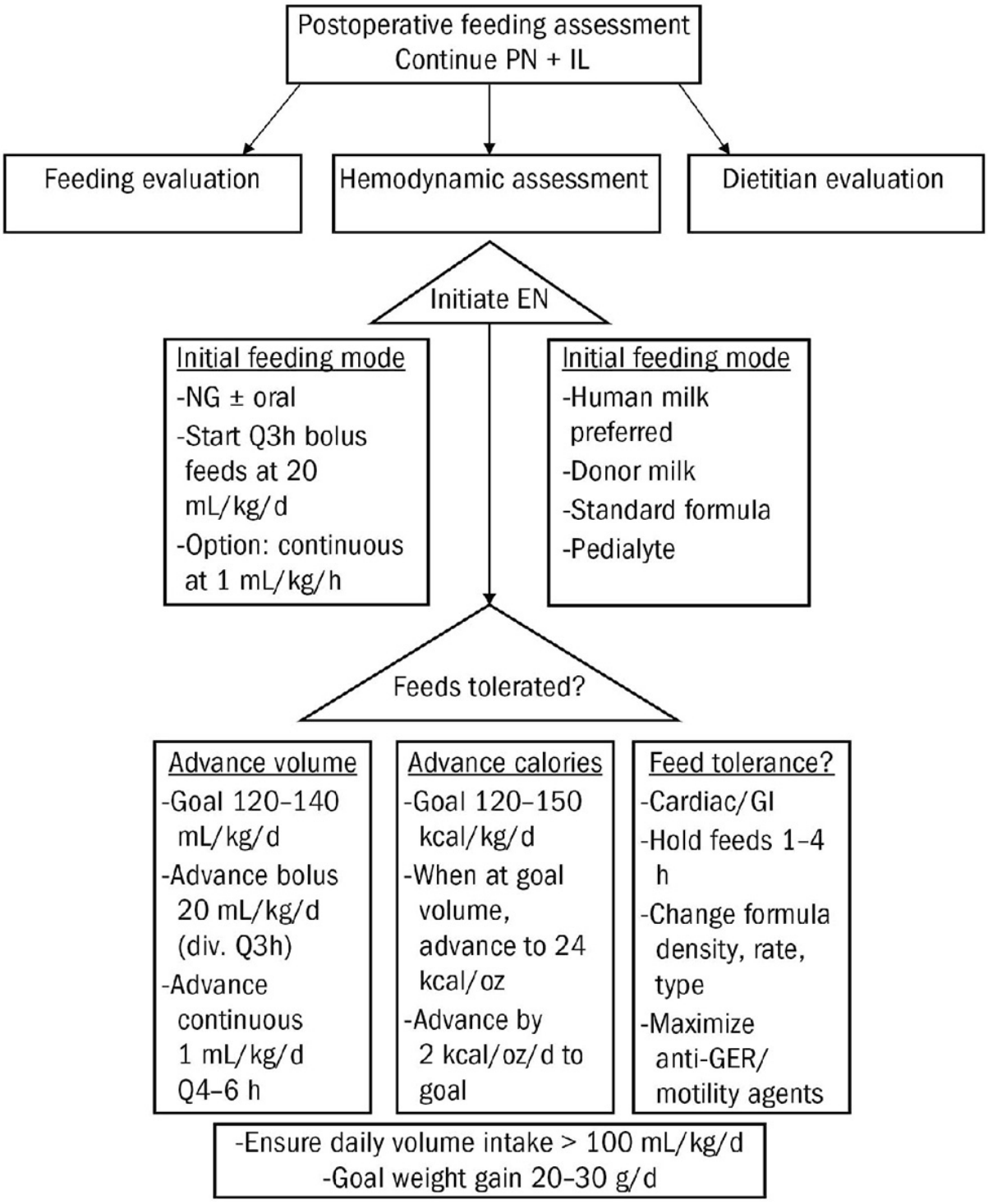
FIGURE 21-1. Recommendations for Preoperative Feeding



Abbreviations: GI, gastrointestinal; IL, Intralipids; NG, nasogastric; PN, parenteral nutrition.

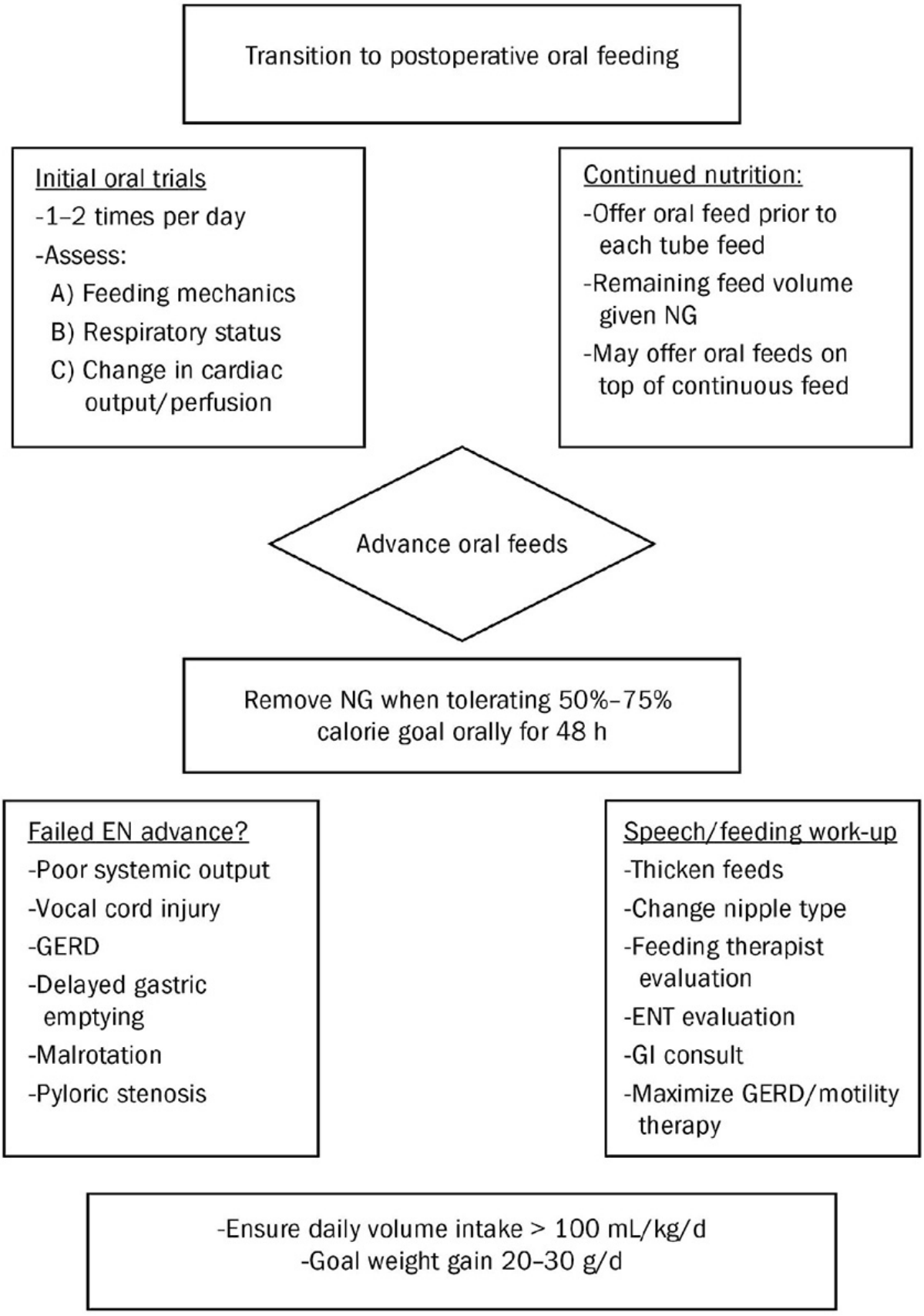
Adapted with permission from Blackwell Publishing from Slicker et al.[9]

FIGURE 21-2. Recommendations for Postoperative Enteral Feeding



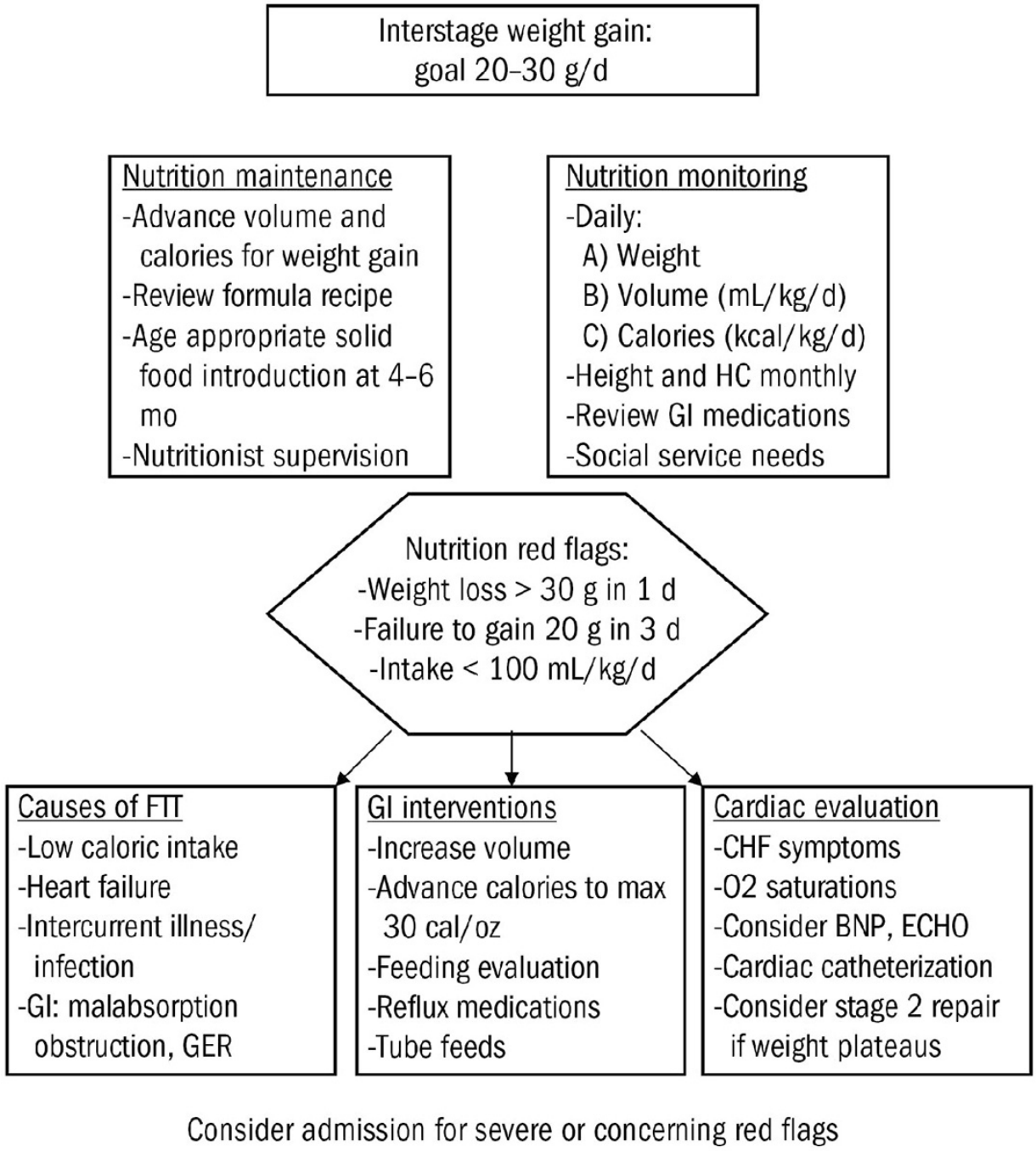
Abbreviations: EN, enteral nutrition; GER, gastroesophageal reflux; GI, gastrointestinal; IL, Intralipids; NG, nasogastric; Q3; Q4–6; PN, parenteral nutrition. Adapted with permission from Blackwell Publishing from Slicker et al.[9]

FIGURE 21-3. Transition to Postoperative Oral Feeding


Transition to postoperative oral feeding
Initial oral trials
-1–2 times per day
-Assess:
A) Feeding mechanics
B) Respiratory status
C) Change in cardiac output/perfusion
Continued nutrition:
-Offer oral feed prior to each tube feed
-Remaining feed volume given NG
-May offer oral feeds on top of continuous feed
Advance oral feeds
Remove NG when tolerating 50%–75% calorie goal orally for 48 h
Failed EN advance?
-Poor systemic output
-Vocal cord injury
-GERD
-Delayed gastric emptying
-Malrotation
-Pyloric stenosis
Speech/feeding work-up
-Thicken feeds
-Change nipple type
-Feeding therapist evaluation
-ENT evaluation
-GI consult
-Maximize GERD/motility therapy
-Ensure daily volume intake > 100 mL/kg/d
-Goal weight gain 20–30 g/d

EN, enteral nutrition; ENT, ear, nose, and throat specialist; GERD, gastroesophageal reflux disease; GI, gastrointestinal; NG, nasogastric. Adapted with permission from Blackwell Publishing from Slicker et al.[9]

FIGURE 21-4. Interstage Feeding Guidelines



Abbreviations: BNP, B-type natriuretic peptide; CHF, congestive heart failure; ECHO, echocardiogram; FTT, failure to thrive; GER, gastroesophageal reflux; GI, gastrointestinal; HC, head circumference. Adapted with permission from Blackwell Publishing from Slicker et al.[9]

Etiology of Growth Impairment

Many published reports support the high prevalence of malnutrition among infants with CHD; however, whether malnutrition is a result of high metabolic demands, poor feeding, hypoxia, or all 3 factors remains unclear. All factors are interdependent; for example, hypoxia leads to an increased respiratory effort, resulting in increased metabolic demands. Hypoxia and increased respiratory rate also result in infant fatigue, which leads to poor feeding effort. The exact etiology of documented energy deficit, whether it arises from decreased intake or increased energy expenditure, is difficult to determine and is often multifactorial, compounded by the complexity of congenital anomalies, comorbidities, age, and aggressiveness of nutrition support.[10]

The factors that have been identified as contributing to growth failure in this population are listed in Table 21-1.

TABLE 21-1. Factors Contributing to Growth Failure in Congenital Heart Disease

Etiology	Signs and Symptoms
Increased energy requirements	Tachypnea and tachycardia can increase metabolic demands
Decreased energy intake	Anorexia, dysphagia, reflux, fatigue during feeding
Increased nutrient losses	Protein-losing enteropathy, renal electrolyte losses
Insufficient utilization of nutrients	Acidosis, hypoxia
Malabsorption	Gut edema

Energy Expenditure

Increased metabolic demands contribute to malnutrition in infants with CHD, and cyanosis is an important factor in determining basal metabolic rate. Cyanosis is associated with increased myocardial lactate levels, suggesting that infants with CHD may have increased metabolic demands because they have a greater dependence on anaerobic metabolism for ATP production with reduced oxygen .[11] An increased reliance on anaerobic

metabolism in these patients may be less energy-efficient and thereby increase energy demands.[10]

Several studies have evaluated the energy needs of infants with CHD to identify factors contributing to alterations in the metabolic rate.[10–14] Avitzur et al measured the metabolic rate using indirect calorimetry of 29 children with cyanotic or noncyanotic heart disease to determine if cyanosis contributes to increased metabolic rate.[12] No differences between resting energy expenditure (REE) were found before or 5 days after open heart surgery using indirect calorimetry. In contrast, Nydegger et al observed an increased REE in 108 infants with CHD by using indirect calorimetry and found that it normalized within 1 week after corrective surgery.[13] Both studies cautioned against the use of predictive equations because their results showed a high rate of variability and did not correlate to measurements obtained by indirect calorimetry.

Leitch et al failed to identify a difference in REE but did detect increased total energy expenditure (TEE).[10] The authors measured REE by using indirect calorimetry and TEE by using the double-labeled water technique in 12 infants with uncorrected cyanotic CHD and compared them to a group of age-matched controls at 2 weeks and again at 3 months of age. No significant differences in REE were identified at either time. However, a significant increase in TEE was identified at 3 months of age.[10] Therefore, an increased TEE but not an increased REE may be the primary factor in the reduced growth of infants with cyanotic CHD. This finding suggests that TEE should not be extrapolated from REE and that caloric recommendations determined by indirect calorimetry may significantly underestimate the actual energy needs of patients.

Nutrition Assessment

A thorough and accurate nutrition assessment is the primary step for the early recognition of feeding difficulties and growth delay in children with CHD. Identifying infants at nutrition risk early allows intervention by a dietitian or feeding specialist to address inadequate intake and feeding difficulties. Known risk factors for infants with CHD have been identified and are outlined in the infant malnutrition and feeding checklist for CHD (see Table 21-2). The early identification of infants with known risk factors

can facilitate a nutrition care plan that promotes better outcomes for infants with CHD.[15]

TABLE 21-2. Infant Feeding and Nutrition Checklist for Congenital Heart Disease[a]

		Yes	Not Sure	No
Fast track: If *yes* or *not sure* for any item, initiate a referral to the dietitian and OT	The following cardiac diagnoses: interrupted aortic arch, hypoplastic left heart, coarctation of the aorta, truncus arteriosus			
	The following known/suspected chromosomal or other abnormalities:			
	• DiGeorge (22q11 del), trisomy 18/13, CHARGE, VACTERL			
	• Brain injury			
	• Vocal cord paresis			
Nutrition: If *yes* or *not sure* to any item, initiate a referral to the dietitian	Weight (any of the following): • < 3rd percentile • Dropped 2 major percentile groups			
	Diet • Fortified breast milk or hypercaloric formula			
	Feeding tube			
	GI tolerance: • Vomiting			
Feeding: If *yes* or *not sure* for any item, initiate a referral to the OT	Physiological status: • RR > 65 bpm • Increased WOB • Tachycardia • Desaturations			
	Vocal cords: • Stridor, hoarse voice, or wheezy cry			
	During feeds: • Coughing, choking, or gagging • Congestion/upper airway sounds • Poor sucking • Not taking full feeds orally			

Abbreviations: CHARGE, coloboma, heart defects, atresia of the choanae, retardation of growth and development, genital and urinary abnormalities, ear abnormalities and/or hearing loss; CHD, congenital heart disease; GI, gastrointestinal; OT, occupational therapist; RR, respiratory rate; VACTERL, vertebral, anal atresia, cardiac, trachea, esophageal, renal, and limb defects; WOB, work of breathing.

[a] Complete checklist for all babies with CHD admitted or transferred into a unit.

Reproduced with permission from Elsevier from St. Pierre et al.[15]

A thorough and accurate nutrition assessment including feeding history, a visual assessment, and an anthropometric evaluation is the primary step in the nutrition care process. Using the checklist outlined in Table 21-2 will help identify children with CHD who are at risk for malnutrition and feeding difficulties. Standard growth charts are used for monitoring children with CHD without any underlying syndrome. However, CHD may be present in conjunction with an underlying chromosomal abnormality or syndrome. In these conditions, anthropometric data can be evaluated using specialized growth charts such as those available for children with trisomy 21, trisomy 18, and Turner syndrome and for infants born preterm (see Chapter 32, "Assessment of Nutrition Status by Age and Determining Nutrient Needs").

Biochemical evaluation should include kidney and liver function, iron panels, measurements of electrolytes (including magnesium, phosphorous, and ionized calcium), total protein, albumin, prealbumin, complete blood count, and thyroid levels.[16] Serum albumin results must be interpreted with caution because these are highly sensitive to the patient's hydration status. Prealbumin is influenced by infection, sepsis, inflammation, and operative course, and it should be evaluated with consideration of non-nutrition factors.[17] Fluid overload secondary to CHF or dehydration secondary to diuretics can alter fluid and electrolyte balance and may affect renal function. If the serum albumin is low, then protein-losing enteropathy (PLE) is a consideration, and stool should be obtained for an α-1-antitrypsin and total lymphocyte count to assess for PLE.[18]

Recent data support the use of B-type natriuretic peptide (BNP) as a useful adjunct prognostic and disease-severity marker in children undergoing cardiac surgery. Both preoperative values and postsurgical

variations in BNP should be interpreted first according to age and disease severity and only secondarily as the consequence of additional factors, including malnutrition and body fat mass. An inverse correlation exists between total body fat mass and BNP levels. Infants and children with heart disease that causes significant pressure or volume overload of the right or the left ventricle have elevated BNP levels. Perioperative BNP levels predict outcomes, specifically longer duration of mechanical ventilation and longer intensive care unit stay after surgery for CHD.[19]

Nutrition Management

Growth failure is a common, multifactorial systemic consequence of CHD. Early detection and appropriate intervention with frequent evaluation are crucial to reduce the morbidity and mortality associated with malnutrition.[16] Based on the severity of their lesions, infants may require increased energy intakes to achieve significant growth but are often unable to achieve their nutritional goal due to anorexia and increased fatigue during feeding.

Nutrient Delivery

During the neonatal period, enteral feeding should be initiated as soon as clinically possible with either breastmilk or formula to meet energy and macronutrient goals.[16,20] The preferred route of choice is oral; however, if there is a hemodynamic compromise, fatigue, hypoxia, or respiratory distress, an NG tube may be indicated to provide the increased nutritional requirements without increased energy expenditure for adequate weight gain (see Figures 21-1 to 21-4).[16] A retrospective study indicated that early introduction of enteral feedings and trial of oral feedings showed PN reduction, mechanical ventilation, and infectious complications. Early introduction of trophic feeds helps restore gut microbiome and decreases bacterial translocation.[21] Even though there is strong evidence of the benefits of enteral feeds, there is no prospective, randomized control trial of critically ill children with CHD to determine the superior route of nutrition.[17,21]

Initially, a term newborn infant with CHD needs 40 to 60 kcal/kg/d with a gradual increase to 90 to 120 ml/kg/d. Based on the severity of their lesion

and malnutrition, some infants may require a daily caloric intake that is 50% higher than baseline without exceeding the 150 ml/kg/d liquid volume. Due to fluid restriction, increasing formula concentration from 20 kcal/oz to 24 or 27 kcal/oz with fortified human milk or high-calorie formula to maintain adequate nutritional intake may be required.[20] If the infant shows signs of fatigue, anorexia, or poor sucking or swallowing reflex, an oral or NG tube is indicated.[22]

With tube feeding, infants can be fed either continuous or bolus feeds. Intermittent bolus feeding mimics the feeding schedule of an infant who is fed orally. This pattern can promote more physiological feeding−fasting hormonal levels than continuous feeds. However, if poor somatic growth, compromised motility, or respiratory distress continues with bolus feeds, continuous feeds are recommended because of less energy expenditure.[22,23]

Many infants with CHD are unable to develop the skills to transition to exclusive oral feeds, which leads to the placement of a gastrostomy tube. There is conflicting literature regarding the risk factors that lead to increased rates of gastrostomy-tube placement. Some risk factors include hypoplastic left heart syndrome, lower gestational age, prolonged mechanical ventilation, poor oral feeding preoperatively/post-operatively, and vocal cord dysfunction.

Because of varying practices among institutions regarding nasogastric management, the timing of gastrostomy-tube placement is not well defined.[21,24,25] One of the practice variations is discharge protocol for patients with NG tubes versus gastrostomy tubes, which affects the timing of gastrostomy-tube placement. Many factors are assessed by the medical team to determine the safety of discharging families of patients with NG tubes. With any tube feeding, this adds additional stress and anxiety for families. Families have described feeding their children as an “energy-producing and anxiety-producing procedure.”

A gastrostomy tube is better accepted socially and decreases the risks associated with prolonged NG tube feeds, which include dislodgement of the tube, stenting open the lower esophageal sphincter with resultant increased sinusitis, and nasal skin and cartilage breakdown.[18] Infants and children who are unable to meet their nutrition needs via the enteral route should be considered for PN, which can be initiated preoperatively or

postoperatively, with a therapeutic goal of restoring or maintaining nutrition status and inducing somatic growth.

Given the relatively high prevalence of malnutrition in infants and children with CHD, aggressive nutrition support via PN is an appropriate approach to prevent a further decline in their nutrition status. Significant caloric intake not only considerably impacts the surgical outcomes but also the ultimate growth and development in children with CHD. Almost all children can be nourished enterally after corrective surgery. However, during the preoperative and perioperative periods, PN support may be indicated. PN formulation in children with CHD requires close electrolyte monitoring. Long-term PN has increased risk for bacteremia, venous thrombosis, and PN-associated liver disease.[21,24]

Complications After Congenital Heart Disease Surgery

Feeding Difficulties

The coordination of sucking, swallowing, and breathing is a crucial development for adequate oral feeding. However, many neonates with complex CHD require surgery within the first month of life for survival and do not have the opportunity to meet this important neurodevelopmental milestone that leads to long-term feeding abilities and growth. Over 50% of neonates and infants with complex CHD are discharged home with an enteral feeding tube.[26] Factors that can affect the delay of enteral nutrition include poor cardiac output, necrotizing enterocolitis (NEC), prolonged mechanical ventilation, reflux, open chest, and increased catabolic state requiring higher caloric need. The highest risk group is the single-ventricle group for postoperative growth failure due to many of the above risk factors.[27]

Emesis occurs frequently in infants and children with CHD and has been identified as the most common feeding intolerance.[28–31] Suboptimal intake and loss of nutrients from vomiting can further decrease the amount of energy available for growth. Vomiting after feeding results in a loss of up to approximately 12% of the infant's energy intake.[30] Utilization of nutrients

is compromised in the setting of chronic hypoxia and acidosis and is often seen in infants with CHD. Most of these patients required modified oral feeds and nutrition support.[32] Literature has shown that these patients can have gradual improvement in swallowing function over time; however, full recovery of vocal cord motion is unclear.[33]

Patients who undergo cardiac surgery with the use of transesophageal echocardiography often have symptoms of dysphagia. Transesophageal echocardiography has been identified to cause airway obstruction, common pulmonary vein compression, vascular compression, tracheal extubation, esophageal perforation, gastric perforation, and dental injury. Transesophageal echocardiography probe size in relation to the patient's weight was identified as a risk factor for dysphagia. In infants weighing <3 kg, transesophageal echocardiography should be used cautiously.[33]

Chylothorax

Chylothorax, a known complication of pediatric cardiac surgery, requires special nutrition support considerations. Chylothorax is the accumulation of chyle within the pleural space. The chyle leak can result from injury to the thoracic duct, disruption of accessory lymphatics, or an increased systemic venous pressure exceeding that in the thoracic duct. Most recent studies indicate that the risk of chylothorax ranges between 0.5% and 6.5% after cardiac surgery[22,24,34–38] and the increase in chylothorax prevalence is because of increasing complex congenital heart surgeries (1% for risk adjustment for congenital heart surgery [RACHS] score of 1 and 5.6% for RACHS score of 5 and 6) and the introduction of early postoperative feeding.[31]

Additional risk factors of chylothorax include low weight and height, age (neonates having 7 times increased risk compared to teenagers), the duration of cardiopulmonary bypass and cross-clamping, and the presence of a genetic syndrome (Down, Noonan, and Turner's syndromes). Specific cardiac lesions that increase chylothorax risk include Fontan procedure, heart transplant, and Tetralogy of Fallot repair (right ventricular dysfunction leading to increased right atrial central venous pressures).[34,35] Chylothorax can prolong hospitalization with a median of 22 days versus 8 days if a leak develops, which can significantly increase morbidity and mortality of these

patients.[33,39,40] Associated adverse effects of increased length of stay exposures include:[41]

- Malnutrition.
- Poor wound healing.
- Hydroelectrolytic disorders.
- Prolonged intubation.
- Longer use of invasive devices (including chest tubes).
- Increased risk of infection.
- Prolonged need for inotropic support.

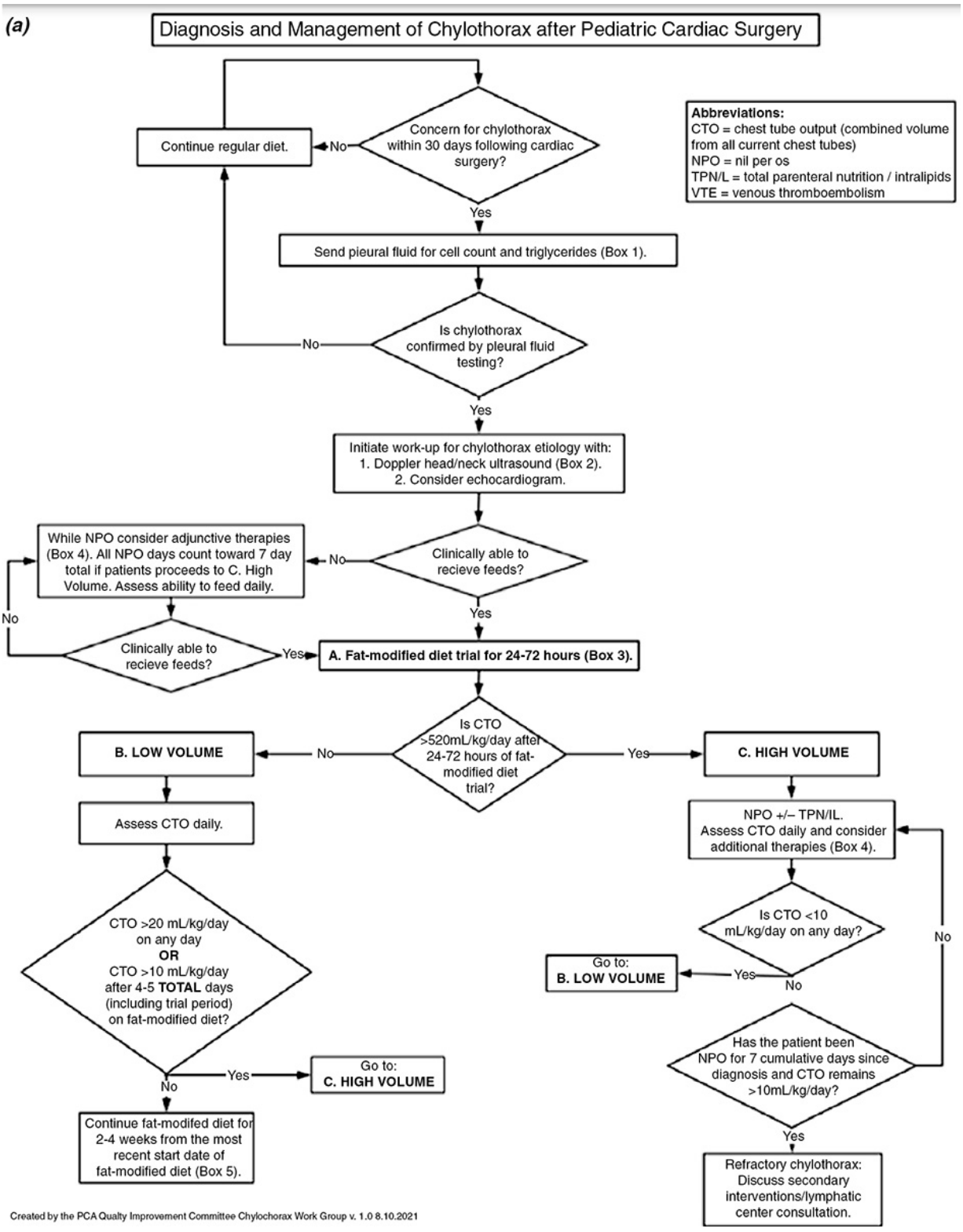
The management of chylothorax is institution-dependent and nutrition, pharmacological support, and surgical intervention can vary. Therapies include chest-tube placement, restrictive feeding with a low-lipid diet containing medium-chain triglycerides (MCT) or fasting with total PN. The goal is to provide adequate calories and nutrients while reducing chylous effusion output. The use of an MCT–enriched diet is based on the understanding that MCTs are readily absorbed by the enterocytes into circulation, providing adequate calories and minimizing lymphatic flow to allow for healing.[35,41] To prevent essential fatty acid deficiency, 2% to 4% of total calories should be in the form of linoleic acid, with 0.25% to 0.5% from linolenic acid. If patients are on oral feedings and adequate calories can be consumed, a low-fat diet may be sufficient. In a study by Chan et al. 34 of 48 patients (71%) had resolution with changes to their enteral diet.[35]

Pharmacologic support includes corticosteroids and octreotide (synthetic somatostatin).[41] Octreotide has been used as a treatment for chylothorax drainage that did not respond to dietary manipulations alone. In a study conducted from 1981 to 2004, 83% of patients receiving octreotide responded with complete resolution of their chylothorax after approximately 15 days of treatment, and no side effects were noted after 2 weeks of treatment.[31] In an extensive analysis of a large multi-institution database, octreotide therapy was found to be as beneficial as adjunctive therapy.[35]

However, if these conservative therapies fail, surgical intervention is indicated, which includes thoracic duct ligation, lymphovenous anastomosis, pleuroperitoneal shunt, pleurodesis, and pleurectomy.[41] With

the variation of chylothorax therapies, a recent consensus recommendation with an algorithm was published by Lion and colleagues in 2022 (see Figure 21-5).[39] The early diagnosis and treatment of chylothorax can reduce the length of the chylous leak. At present, dietary management is the mainstay of treatment when managing these patients conservatively.

FIGURE 21-5. Diagnosis and Management of Chylothorax After Pediatric Cardiac Surgery



Reproduced with permission from Lion et al.[39]

Protein-Losing Enteropathy

Protein-losing enteropathy (PLE) is a severe loss of protein (primarily albumin) from the digestive tract or the inability of the digestive tract to absorb protein. PLE is suspected based on history, physical examination, and hypoalbuminemia and is confirmed with alpha-1 antitrypsin in the stool. Symptoms include edema, diarrhea, and ascites.[42,43] The prevalence of PLE in infants and children with CHD is 3.7% to 24% and is most prominent after the Fontan procedure (anastomosis of the inferior vena cava to the pulmonary artery, which is the preferred surgical correction for tricuspid atresia, HLHS, and other single ventricle physiology) with an incidence rate of 3% to 13%.[42,43] The median onset of PLE after a Fontan procedure is 5 to 10 years.[44] PLE can be a life-threatening complication, with a 5-year survival rate as low as 50%, but with advanced medical therapies, survival rates have increased to 88% and 72% at 5 and 10 years, respectively.[43]

Children with PLE have changes in bowel habits, abdominal discomfort, and diarrhea. With ongoing protein loss in the stool, the concentrations of serum protein can become severely depleted over time, resulting in hypoproteinemia and especially hypogammaglobulinemia. Hypocalcemia and lymphocytopenia are often seen in this condition as well. The loss of serum proteins decreases the vascular oncotic pressure and promotes the development of edema, ascites, and pleural as well as pericardial effusion. Edema of the intestinal wall secondary to chronic hypoalbuminemia may result in poor absorption of nutrients and promote worsening of the diarrhea.[45]

Nutrition management of infants and children with PLE should be tailored to the severity of bowel dysfunction, diarrhea, and malabsorption. Dietary changes should include a high-protein (≥ 2 g/kg/day), low-fat (≤ 25% of caloric intake) diet, transitioning to an MCT-based diet to lessen enteric protein loss and optimize nutritional status.[44] The use of an MCT-enriched diet is based on the understanding that enterocytes absorb MCTs directly into the portal circulation, allowing the delivery of adequate calories while reducing lymphatic flow to allow for healing. MCTs are

rapidly absorbed and reduce the amount of high-protein lymph fluid moving through the vessels within the intestines, thereby reducing the quantity of protein loss. Specialized nutrition support with the use of formulas with very high MCT levels (80%–90% of the total fat content) should be provided to infants and children with intractable diarrhea who are unable to maintain their nutrition status with standard formula.[46] With the long-term use of these formulas, essential fatty acids should be monitored due to the risk of developing deficiency. In severe cases, the use of PN may be implemented to allow complete enteric rest to minimize lymphatic flow and promote healing.[47] With diet change and risk of hypocalcemia, impairment of fat-soluble vitamin absorption, immunoglobulin and iron deficiency, supplementation may be required.[46]

With nutritional changes, medical therapies are available for symptomatic relief and enteric-specific treatment. With fluid overload symptoms, diuretics are used, especially in the setting of intestinal edema, low albumin, or ascites, because it will reduce the absorption of oral medications. With diuretics therapy, albumin infusion is used to increase oncotic pressure. Pulmonary vasodilators are also used to lower hydrostatic pressure on the lymphatic vessels and lower mesenteric vascular resistance.[44]

Several reports exist on the efficacy of heparin therapy and the beneficial effects of an enteric-specific steroid (Budesonide) in patients with PLE.[48–50] Heparin reduces protein loss; however, studies are inconsistent regarding the benefits for PLE. Heparin can also cause further risk of bone demineralization, thus heparin is recommended as a supportive therapy rather than a first-line therapy. Budesonide has shown significant improvement in albumin levels in children and young adults with PLE post-Fontan surgery.[44] Octreotide, a somatostatin analogue, has also been used with some success in patients with PLE following Fontan surgery who have been refractory to other therapies.[29,44] The precise mechanism is unclear; however, it is postulated that reduced lymph formation leads to decreased triglyceride absorption. Adverse effects are common, with limited use in PLE.

If medical therapies have failed, surgical intervention can be considered. Surgical interventions carry a high risk of mortality, but Fontan revisions

with conversion of older-style Fontans to that of an extracardiac or lateral tunnel, surgical relief of obstruction to the pulmonary venous return, and cardiac transplantation have all been reported as potential treatment strategies.[51–52]

For necrotizing enterocolitis management, please refer to Chapter 29, "Surgery."

Cardiomyopathy

Cardiomyopathy is a chronic disease of the heart muscle in which the myocardium is abnormally enlarged, thickened, and/or stiffened. Eventually, the weakened heart loses the ability to pump blood effectively and arrhythmias or dysthymia may occur. According to the National Pediatric Cardiomyopathy Registry, 1 in every 100,000 children in the United States is diagnosed with primary cardiomyopathy. Cardiomyopathy is a common cause of heart failure in children and is the most common cause of heart transplantation in children older than 1 year of age. Nearly 40% of children who present with symptomatic cardiomyopathy receive a heart transplant or die within the first 2 years of diagnosis.[53]

Pediatric cardiomyopathies are generally classified as nonischemic and predominately involve the heart's abnormal structure and function. Because of varying clinical features and therapies, the disease is separated into 4 categories:

1. dilated (or congestive)
2. hypertrophic
3. restrictive
4. arrhythmogenic right ventricular (see Table 21-3)

TABLE 21-3. Types of Pediatric Cardiomyopathies

Type	Description
Dilated cardiomyopathy	The heart muscle fibers stretch, causing a chamber of the heart to enlarge, thus weakening the heart's ability to pump blood.
Hypertrophic cardiomyopathy	A functional type of cardiomyopathy that occurs among older children and adults in which the growth or arrangement of muscle fibers is abnormal, leading to a thickening of the heart walls, a size reduction of the chambers, and possible restriction of blood flow.
Restrictive cardiomyopathy	The walls of the ventricles stiffen and lose their flexibility.
Arrhythmogenic right ventricular cardiomyopathy	Myocytes in the right ventricle are replaced with fatty, fibrous tissue.

Each form is determined by the nature of muscle damage, with dilated cardiomyopathy being the most common.

Children with CHD and/or cardiomyopathy often do not grow according to expected age standards, making it especially important for these children to receive adequate energy intake. Optimal intake of macronutrients promoting an anabolic state can help improve cardiac function. In addition, several specific nutrients have been shown to correct abnormalities that often occur with cardiomyopathy and heart failure. Antioxidants can protect against free radical damage, also common in heart failure. Nutrients that augment myocardial energy production are important therapies that have been explored in adults with cardiomyopathies (see Exhibit 21-2). Generally, food factors that trigger the acute-phase response should be avoided (eg, excess carbohydrates and saturated fats). Foods that counteract inflammatory processes such as foods with ω-3 fatty acids have possible favorable effects on ventricular function and should be recommended.[54]

EXHIBIT 21-2. Nutrients That Augment Myocardial Energy Production in Adults

Antioxidants and Nutrients That May Have an Effect on Cardiac Function in Heart Failure

Vitamin A
Vitamin E
Vitamin C
Taurine
Coenzyme Q10

Nutrients That May Improve Myocardial Energy Production
Thiamine
L-carnitine
Creatine
Zinc
Magnesium
Selenium

Coenzyme Q10 and selenium are 2 nutrients of special interest in cardiomyopathy. Coenzyme Q10, also known as ubiquinone, is an oil-soluble, vitamin-like substance present in most eukaryotic cells, primarily in the mitochondria. A component of the electron transport chain, it participates in aerobic cellular respiration, generating energy in the form of adenosine triphosphate (ATP). The clinical evidence for a potential role of coenzyme Q10 in cardiomyopathy is based mainly on adult patients with heart failure. The primary biochemical basis for the use of coenzyme Q10 in the treatment of various types of cardiomyopathy in adults centers on its critical role in mitochondrial bioenergetics; the underlying pathophysiology involves defective bioenergetics, specifically the availability of ATP, which plays a central role in regulating myocardial contractility. Evidence supports that coenzyme Q10 acts at the mitochondrial level to improve the efficiency of energy production in heart tissue. The antioxidant properties of coenzyme Q10 also have an important role in protecting the mitochondria from free radical damage, thus helping it maintain its integrity and function.[54,55]

Because of endogenous production, coenzyme Q10 is not considered a vitamin, and no recommended dietary allowance has been established. Deficiency may be caused by impaired biosynthesis, insufficient dietary intake, poor gastrointestinal absorption, and/or excessive utilization of coenzyme Q10. Exogenous sources of coenzyme Q10 include animal

products (eg, beef, pork, chicken) and plant products (eg, broccoli, spinach, soy and palm oils).[55]

The referenced data are derived from small heterogeneous trials. However, a 2014 Cochrane Collaboration meta-analysis of 7 studies found "no convincing evidence to support or refute" the use of coenzyme Q10 for the treatment of heart failure. More clinical trials and testing are needed, especially in the pediatric population, before recommendations regarding coenzyme Q10 use in cardiomyopathy can be made responsibly.[56]

Selenium is an essential trace mineral with established recommended dietary allowances. Deficiency has been associated with congestive cardiomyopathy (Keshan disease), skeletal myopathy, osteoarthropathy (Kashin-Beck disease), anemia, and immune-system alterations. Selenium's most significant role is its action as a cofactor for the antioxidant enzyme glutathione peroxidase, which removes hydrogen peroxide and the deleterious lipid hydroperoxides generated by oxygen-derived species. Glutathione peroxidase deficiency contributes to endothelial dysfunction, a major actor in heart failure.[54]

Heart Transplant

Malnutrition is common in patients with CHD with end-stage heart failure leading to heart transplant. These patients have had multiple interventions, poor feeding tolerance and absorption, increased energy needs, and inadequate provision of energy.[57] Heart transplantation is a widely accepted treatment for end-stage heart disease in pediatric patients. Evidence exists for suboptimal outcomes in patients who are underweight post-transplant, such as decreased overall graft survival compared with patients with normal weight.

It is crucial to maximize the child's nutrition status before transplant to improve clinical outcomes post-transplant. Anthropometric measurements are easily obtained, and age-specific standards are available for comparison. Growth measurements such as weight, length, weight for length, and head circumference (if <3 years of age) should be measured over time.[58] Children awaiting heart transplants are at high risk for malnourishment due to organ failure. Pretransplant nutrition is focused on addressing increased

energy needs, decreasing malabsorption, reducing anorexia, and altering metabolism. Nutrition can be provided orally; however, if suboptimal, enteral feeds or even PN is required.[59]

Calorie and protein requirements of children on enteral or oral feedings are based on the dietary reference intakes for age with adjustments to promote growth. The requirements of patients supported with EN or PN are estimated at 5% to 10% less than the estimated amounts for enteral or oral alone.[58] It is important to correct malnutrition before transplant because it increases the patient's risk of infection, impaired wound healing, and extended rehabilitation after transplant.[59]

Hypertension, hyperglycemia, and weight gain are common in post-transplant pediatric heart recipients. The goals for post-transplant patients are to maintain an ideal body weight, limit sweets and foods high in cholesterol and fat, and limit salt intake.[60] Calcineurin inhibitors commonly used in post-transplant patients may cause elevated lipid levels. These inhibitors, along with pretransplant nutrition status, diuretics, and steroids, can result in decreased calcium absorption and bone formation. Thus, osteoporosis is a common problem in heart transplant recipients.[61] Supplemental vitamin D (400–800 IU) and calcium (1200–1500 mg) are recommended.

Survival rates for patients with heart transplants are approximately 85%.[62] Growth and development are important determinants of quality of life. Great strides have been made in nutrition management in recent decades, including the identification, treatment, and prevention of nutrition issues leading up to transplant and continuing afterward, and they have had positive influences on outcomes.

Cardiovascular Disease

Atherosclerosis is the buildup of fat and cholesterol on the arterial walls. Atherosclerosis increases the risk of CVDs, including heart attack and stroke. Although secondary effects of atherosclerosis are not common in children because the narrowing of the arteries takes years to develop, the process begins before birth if there is maternal hypercholesterolemia. Risk factors for developing early atherosclerosis include obesity; high blood

pressure; family history of CVD; cigarette smoke exposure; and underlying medical conditions such as diabetes, chronic kidney disease, and childhood cancer treatment.[63]

Children should be screened for cholesterol initially at ages 9 to 11 years and again at ages 17 to 21 years. Children ages 2 years or older who have a family history, or medical diseases associated with CVD and children who have overweight and high blood pressure should be screened as well (see Table 21-4).[64]

TABLE 21-4. Classification of Total and LDL Cholesterol Levels in Children and Adolescents From Families With Hypercholesterolemia or Premature Cardiovascular Disease[a]

Category (mg/DdL)	Acceptable	Borderline	High
TC (mg/dL)	<170	170–199	>200
LDL-C mg/dl	<110	110–129	>200

Abbreviations: LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

[a] Adapted from U.S. Department of Health and Human Services, National Institutes of Health, National Heart Lung and Blood Institute. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. 2012:38.64.

The developmental origin of health and disease theory states that lifestyle changes should begin at conception and proceed through embryonic development to neonatal stages. It is hypothesized that a positive or negative impact can cause lifelong consequences. Maternal nutrition is responsible for shaping the future child's health.[63] The National Cholesterol Education Program (NCEP) provides education about the effects of early elevated lipid levels on adult atherosclerosis and coronary heart disease risk, focusing on prevention and reducing lipid levels in children and adolescents. Eating behavior and genetics affect cholesterol levels. Behavioral changes require intervention at several levels. An individual approach by itself is less effective. The key to success requires both population and individualized approaches.

One approach for lowering cholesterol levels in children and adolescents is through changing eating behaviors on a population-wide basis. The American Academy of Pediatrics has adopted the NCEP recommendations and the American Heart Association guidelines,[65] which include consuming a variety of foods and adequate calories to support growth and maintain an ideal body weight while keeping fat intake at an acceptable level. The NCEP also provides recommendations for organizations that influence the eating behaviors of children, such as schools, health professionals, government agencies, and the food industry.

The individualized approach aims to identify and treat children and adolescents who are at the greatest risk of CVD by screening children from families with a history of premature CVD or who have at least one parent with high cholesterol. Universal screening is not cost-effective and may impose an unnecessary stigma on a child[???.66] Reis et al looked at risk factors in children and investigated whether families at risk for CVD can be identified. [66] Children were assessed to see if identifying their risk factors would help predict risk factors in their parents. This population was targeted because children are more likely to receive regular primary care than adults. Participants were assessed for the following cardiovascular risk factors: obesity, hypertension, dyslipidemia, and metabolic syndrome. The parent−child association was strong for body mass index, waist circumference, systolic blood pressure, triglycerides, and total cholesterol. Risk factors in children were significant predictors of the same risk factors for their parents. This study suggests that CVD risk factors in children can predict elevated CVD risk factors in parents.

Children identified with an elevated cholesterol level at an early age should be treated. Initial therapy should always be diet modification accompanied by lifestyle changes, such as minimizing sedentary habits and promoting physical activity. The Step I Diet mimics the recommendations of the population approach. It limits saturated fat to <10% of total calories, total fat intake to ≤30% of total calories, and cholesterol to < 300 mg/d. If low-density lipoprotein (LDL) levels remain elevated after 3 months of adhering to the Step I Diet, the Step II Diet should be initiated. The Step II Diet reduces saturated fat to <7% of calories and cholesterol to <200 mg/d. Drug therapy is suggested for children 10 years or older if the diet fails after

6 to 12 months for those with LDL levels >190 mg/dL or >160 mg/dL if other risk factors are also present.[63,67,68]

The American Academy of Pediatrics has released a policy statement on cardiovascular risk reduction in high-risk pediatric populations that outlines CVD risk stratification based on existing comorbidities and assesses cardiovascular risk factors to stratify patients into at-risk, moderate-risk, and high-risk categories. Lifestyle changes including diet, exercise, and cessation of smoking as well as disease-specific management are the basis of its recommendations in all 3 groups.[68] Pharmacologic intervention is recommended only if goals are not met.[64,65]

Obesity, hypertension, insulin resistance, and dyslipidemia, also known as the metabolic syndrome or syndrome X (see Chapter 14, "Childhood Overweight and Obesity: Efficacy and Safety of Popular Diets and Weight Control Programs"), are risk factors for childhood CVD. Metabolic syndrome often requires adjunct pharmacotherapy in addition to an aggressive diet and exercise regimen.

Studies suggest that children with obesity with risk factors for CVD have obesity as adults with an increased risk of morbidity from CVD. Prevention and early intervention should be a primary goal of health professionals and government agencies. The NCEP has reported on these issues and implemented recommendations for dietary changes, screening, and treatment of children and adolescents who are identified as at risk for CVD following into adulthood.[66]

Conclusion

Children with CHD often have difficulty achieving adequate caloric intake to support their growth and development and should be provided with nutrition support to maximize growth and development before corrective surgery. The interstage period has been recognized as a critical time for infants with CHD and presents unique challenges for practitioners providing nutrition care. Suboptimal weight gain often occurs during this interstage period. If energy goals are met and children are closely monitored during the interstage phase, adequate growth can be achieved with significantly improved surgical outcomes.[2–4]

Postsurgical complications may occur depending on the complexity of the defect and surgical intervention. Possible postoperative complications include PLE and chylothorax, which require specialized nutrition modifications.

Pediatric cardiac disease care over the past 2 decades has extended to include CVD. Prevention and early intervention will positively impact CVD and its complications in the adult population.

Test Your Knowledge Questions

1. The potential for growth and nutrition recovery in children with CHD seems to be most affected by which of the following factors?
   A. Degree of growth impairment
   B. Feeding difficulties
   C. Energy intake or expenditure
   D. Age and timing of corrective surgery
2. To assess CVD risk, at what age should children have their blood cholesterol levels screened?
   A. Annually
   B. At birth and every 5 years
   C. At ages 9 to 11 years and again at 17 to 21 years of age
   D. Only if their body mass index suggests obesity
3. Malnutrition in infants with CHD is secondary to which of the following?
   A. Poor caloric intake
   B. Increased energy expenditure
   C. Hypoxia
   D. All of the above
4. When selecting a formula for treatment of infants with a chylous leak, which of the following characteristics should be considered?
   A. Only LCTs
   B. Only MCTs
   C. Fat blend (high MCT and low LCT)
   D. Fat blend (high LCT and low MCT)

References

1. Go AS, Mozaffarian D, Roger VL, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation.* 2013;127:e6–e245. https://doi.org/10.1161/cir.0b013e31828124ad
2. Toole BJ, Toole LE, Kyle UG, Cabrera AG, Orellna RA, Coss-Bu JA. Perioperative nutritional support and malnutrition in infants and children with congenital heart disease. *Congenit Heart Dis*. 2014;9(1):15–25. https://doi.org/10.1111/chd.12064
3. Cameron JW, Rosenthal A, Olsen AD. Malnutrition in hospitalized children with congenital heart disease. *Arch Pediatr Adolesc Med*. 1995;149(10):1098–1102. https://doi.org/10.1001/archpedi.1995.02170230052007
4. Mitchell IM, Logen RW, Pollock JCS, Jamieson MPG. Nutritional status of children with congenital heart disease. *Br Heart J*. 1995;73:277–283. https://doi.org/10.1136/hrt.73.3.277
5. Kelleher KD, Laussen P, Teixeira-Pinto A, Duggan C. Growth and correlates of nutritional status among infants with hypoplastic left heart syndrome (HLHS) after stage I Norwood procedure. *Nutrition*. 2006;22:237–244. https://doi.org/10.1016/j.nut.2005.06.008
6. Anderson BJ, Beekman HR 3rd, Border LW, et al. Lower weight age z-score adversely affects hospital length of stay after the bidirectional Glenn procedures in infants with single ventricle. *J Thorac Cardiovasc Surg*. 2009;138(2):397–404. https://doi.org/10.1016/j.jtcvs.2009.02.033
7. Menon SC, McCandless RT, Mack GK, et al. Clinical outcomes and resource use for infants with hypoplastic left heart syndrome during bidirectional Glenn: summary from the Joint Council for Congenital Heart Disease National Cardiology Quality Improvement Collaborative registry. *Pediatr Cardiol.* 2013;34:143–148. https://doi.org/10.1007/s00246-012-0403-8
8. Hill GD, Hehir AD, Bartz PJ, et al. Effect of feeding modality on interstage growth after stage I palliation: a report from the National Pediatric Cardiology Quality Improvement Collaborative. *J Thorac*

Cardiovasc Surg. 2014;148(4):1534–1539. https://doi.org/10.1016/j.jtcvs.2014.02.025
9. Slicker J, Hehir AD, Horsley M, et al; Feeding Work Group of the National Pediatric Cardiology Quality Improvement Collaborative. Nutrition algorithms for infants with hypoplastic left heart syndrome: birth through the first interstage period. *Congenit Heart Dis.* 2013;8(2):89–102. https://doi.org/10.1111/j.1747-0803.2012.00705.x
10. Leitch C, Karn C, Peppard R, et al. Increased energy expenditure in infants with cyanotic congenital heart disease. *J Pediatr*. 1998;133(6):755–760. https://doi.org/10.1016/s0022-3476(98)70146-5
11. Modi P, Suleiman MS, Reeves BC, et al. Basal metabolic rate of heart patients with cyanosis age, and pathology. *Ann Thorac Surg.* 2004;78:1710–1716. https://doi.org/10.1016/j.athoracsur.2004.05.010
12. Avitzur Y, Singer P, Dagan O, et al. Resting energy expenditure in children with cyanotic and non-cyanotic congenital heart disease before and after open heart surgery. *J Parenter Enter Nutr.* 2003;27(1);47–51. https://doi.org/10.1177/014860710302700147
13. Nydegger A, Bines JE. Energy metabolism in infants with congenital heart disease. *Nutrition*. 2006;22(7–8):697–704. https://doi.org/10.1016/j.nut.2006.03.010
14. Leitch C. Growth, nutrition and energy expenditure in pediatric heart failure. *Prog Pediatr Cardiol*. 2000;11:195–202. https://doi.org/10.1016/s1058-9813(00)00050-3
15. St Pierre A, Khattra P, Johnson M, Cender L, Manzano S, Holsti L. Content validation of the infant malnutrition and feeding checklist for congenital heart disease: a toll to identify risk of malnutrition and feeding difficulties in infants with congenital heart disease. *J Pediatr Nurs.* 2010;25(5):367–374. https://doi.org/10.1016/j.pedn.2009.04.009
16. Centeno-Malfaz, F, Morais-Lopez, A, et al. Nutrition in congenital heart disease: consensus document. *Anales de Pediatria*. 2023;98:373–383. https://doi.org/10.1016/j.anpede.2023.02.022
17. Cabrera, A, Prodhan P, Bhutta, A. Nutritional challenges and outcomes after surgery for congenital heart disease. *Curr Opin Cardiol.* 2010;25(2):88–94. https://doi.org/10.1097/hco.0b013e3283365490
18. Itkin, M, Piccoli D, Nadolski, G, et al. Protein-losing enteropathy in patients with congenital heart disease. *J Am Coll Cardiol.*

2017;69(24):2929–2937. https://doi.org/10.1016/j.jacc.2017.04.023
19. Radman M, Mack R, Barnoya J, et al. The effect of preoperative nutritional status on postoperative outcomes in children undergoing surgery for congenital heart defects in San Francisco (UCSF) and Guatemala City (UNICAR). *J Thorac Cardiovasc Surg.* 2014;147(1):441–450. https://doi.org/10.1016/j.jtcvs.2013.03.023
20. Luca A-C, Miron IC, Mîndru DE, Curpăn, AS, Stan RC, et al. Optimal nutrition parameters for neonates and infants with congenital heart disease. *Nutrients.* 2022;14:1671. https://doi.org/10.3390/nu14081671
21. Miller, KI, Kim JH, Fogg K, et al. Nutritional consideration for the neonate with congenital heart disease. *Pediatrics*. 2022;150:S1–S10. https://doi.org/10.1542/peds.2022-056415g
22. Salvatori G, De Rose DU, Massolo AC, eta al. Current strategies to optimize nutrition and growth in newborns and infants with congenital heart disease: a narrative review. *J Clin Med*. 2022;11(7):1841. https://doi.org/10.3390/jcm11071841
23. Schwartz MS, Gewitz HM, See CC, et al. Enteral nutrition in infants with congenital heart disease and growth failure. *Pediatrics.* 1990;86(3):368–373. https://doi.org/10.1542/peds.86.3.368
24. Miller AN, Naples A. Nutritional strategies to optimize outcomes among infants with congenital heart disease. *NeoReviews*. 2023;24(8):e492–e503. https://doi.org/10.1542/neo.24-8-e492
25. Elgersma, KM, Trebilcock AL, Whipple MO, et al. Risk factors for tube feeding at discharge in infants undergoing neonatal surgery for congenital heart disease: a systematic review. *Pediatr Cardiol.* 2023;44(4):769–794. https://doi.org/10.1007/s00246-022-03049-x
26. Jacobwitz M, Dean Durning J, Moriarty H, et al. Oral feeding dysfunction in post-operative infants with CHDs: a scoping review. *Cardiol Young*. 2023;33(4):570–578. https://doi.org/10.1017/S1047951122001299
27. Kataria-Hale J, Gollins L, Bonagurio K, Blanco C, Hair AB. Nutrition for infants with congenital heart disease. *Clin Perinatol*. 2023;50(3):699–713. https://doi.org/10.1016/j.clp.2023.04.007
28. Durai R, Venkatraman R, Ng P. Nasogastric tubes 2: risks and guidance on avoiding and dealing with complications. *Nurs Times*. 2009;105(17):14–16. https://www.nursingtimes.net/clinical-

archive/gastroenterology/nasogastric-tubes-2-risks-and-guidance-on-avoiding-and-dealing-with-complications-29-04-2009/
29. da Silva VM, de Oliveira Lopes MV, de Araujo TL. Growth and nutritional status of children with congenital heart disease. *J Cardiovasc Nurs*. 2007;22(5):390–396. https://doi.org/10.1097/01.jcn.0000287028.87746.11
30. van der Kuip M, Hoos MB, Forget PP, Westerterp KR, Gemke RJ, de Meer K. Energy expenditure in infants with congenital heart disease, including a meta-analysis. *Acta Paediatr*. 2003;92:921–927. https://doi.org/10.1111/j.1651-2227.2003.tb00625.x
31. Kogon BE, Ramaswamy V, Todd K, et al. Feeding difficulty in newborns following congenital heart surgery. *Congenit Heart Dis*. 2007;2(5):332–337. https://doi.org/10.1111/j.1747-0803.2007.00121.x
32. Sachdeva R, Hussain E, Moss M, et al. Vocal cord dysfunction and feeding difficulties after pediatric cardiovascular surgery. *J Pediatr*. 2007;151:312–315. https://doi.org/10.1016/j.jpeds.2007.03.014
33. Kohr LM, Dargan M, Hague A, et al. The incidence of dysphagia in pediatric patients after open heart procedures with transesophageal echocardiography. *Ann Thorac Surg*. 2003;76:1450–1456. https://doi.org/10.1016/s0003-4975(03)00956-1
34. Ahmed MA, Sr. Post-operative chylothorax in children undergoing congenital heart surgery. *Cureus*. 2021;13(3):e13811. https://doi.org/10.7759/cureus.13811
35. Chan S, Lau W, Wong W, et al. Chylothorax in children after congenital heart surgery. *Ann Thorac Surg*. 2006;82:1650–1656. https://doi.org/10.1016/j.athoracsur.2006.05.116
36. Pelletier GJ. Invited commentary. *Ann Thorac Surg*. 2005;80:1870–1871. https://doi.org/10.1016/j.athoracsur.2005.06.029
37. Chan EH, Russell JL, Williams WG, et al. Postoperative chylothorax after cardiothoracic surgery in children. *Ann Thorac Surg*. 2005;80(5):1864–1879. https://doi.org/10.1016/j.athoracsur.2005.04.048
38. Hise M, Brown C. Lipids. In: Gottschlich MM, DeLegge MH, Mattox T, Mueller C, Worthington P, eds. *The A.S.P.E.N. Nutrition Support Core Curriculum: A Case-Based Approach—The Adult Patient.* American Society for Parenteral and Enteral Nutrition; 2007:48–70.

39. Lion RP, Winder MM, Amirnovin R, et al; PC4 Chylothorax Work Group. Development of consensus recommendations for the management of post-operative chylothorax in paediatric CHD. *Cardiol Young*. 2022;32(8), 1202–1209. https://doi.org/10.1017/S1047951122001871
40. Loomba RS, Wong J, Davis M, et al. Medical interventions for chylothorax and their impacts on need for surgical intervention and admission characteristics: a multicenter, retrospective insight. *Pediatr Cardiol*. 2021;42(3):543–553. https://doi.org/10.1007/s00246-020-02512-x
41. Bauer JK, Hocama N, Traub AC, et al. Chylothorax after heart surgery in children. *Pediatr Cardiol*. 2023;44(8):1847–1855. https://doi.org/10.1007/s00246-023-03250-6
42. Feldt RH, Driscoll DJ, Offord KP, et al. Protein-losing enteropathy after the Fontan procedure. *J Thorac Cardiovasc Surg*. 1996;112:672–680. https://doi.org/10.1016/s0022-5223(96)70051-x
43. Itkin M, Piccoli DA, Nadolski G, et al. Protein-losing enteropathy in patients with congenital heart disease. *J Am Coll Cardiol*. 2017;69(24):2929–2937. https://doi.org/10.1016/j.jacc.2017.04.023
44. Mackie AS, Veldtman GR, Thorup L, Hjortdal VE, Dori Y. Plastic bronchitis and protein-losing enteropathy in the fontan patient: evolving understanding and emerging therapies. *Can J Cardiol*, 2022;38(7):988–1001. https://doi.org/10.1016/j.cjca.2022.03.011
45. Ostrow MA, Hudsen F, Rychik J. Protein-losing enteropathy after Fontan operation: investigations into possible pathophysiologic mechanisms. *Ann Thorac Surg*. 2006;83(2):695–700. https://doi.org/10.1016/j.athoracsur.2006.02.048
46. Parrish RC, Krenitky J, Willcutts K, Radigan A. Gastrointestinal disease. In: Gottschlich MM, DeLegge MH, Mattox T, Mueller C, Worthington P, eds. *The A.S.P.E.N. Nutrition Support Core Curriculum: A Case-Based Approach—The Adult Patient.* American Society for Parenteral and Enteral Nutrition; 2007:524–525.
47. Braamskamp MJ, Dolman KM, Tabbers MM. Clinical practice: protein-losing enteropathy in children. *Eur J Pediatr*, 2010;169(10):1179–1185. https://doi.org/10.1007/s00431-010-1235-2

48. Gursu HA, Erdogan I, Varan B, et al. Oral budesonide as a therapy for protein-losing enteropathy in children after the Fontan operation. *J Card Surg.* 2014;3:712–716. https://doi.org/10.1111/jocs.12355
49. Uzun O, Wong JK, Bhole V, Stumper O. Resolution of protein-losing enteropathy and normalization of mesenteric Doppler flow with sildenafil after Fontan. *Ann Thorac Surg.* 2006;82(6):e39–e40. https://doi.org/10.1016/j.athoracsur.2006.08.043
50. John AS, Johnson JA, Khan M, et al. Clinical outcomes and improved survival in patients with protein-losing enteropathy after the Fontan operation. *J Am Coll Cardiol*. 2014:64(1):54–62. https://doi.org/10.1016/j.jacc.2014.04.025
51. Meadows J, Jenkins K. Protein-losing enteropathy: integrating a new disease paradigm into recommendations for prevention and treatment. *Cardiol Young.* 2011;21(4):363–377. https://doi.org/10.1017/s1047951111000102
52. Mery CM, Moffett BS, Khan MS, et al. Incidence and treatment of chylothorax after cardiac surgery in children: analysis of a large multi-institution database. *J Thorac Cardiovasc Surg.* 2014;147(2):678–686. https://doi.org/10.1016/j.jtcvs.2013.09.068
53. Liphultz E, Steven MD, Sleeper A, et al. The incidence of pediatric cardiomyopathy in two regions of United States. *N Engl J Med.* 2003;328:1647–1655. https://doi.org/10.1056/nejmoa021715
54. Miller TL, Neri D, Extein J, Somarriba G, Strickman-Stein N. Nutrition in cardiomyopathy. *Progr Pediatr Cardiol*. 2007;24(1):59–71. https://doi.org/10.1016/j.ppedcard.2007.08.007
55. Bhagavan HN, Chopra RK. Potential role of ubiquinone (coenzyme Q10) in pediatric cardiomyopathy. *Clin Nutr*. 2005;24(3):331–338. https://doi.org/10.1016/j.clnu.2004.12.005
56. Madmani ME, Yusuf Solaiman A, Tamr Agha K, et al. Coenzyme Q10 for heart failure. *Cochrane Database Syst Rev.* 2014;6:CD008684. https://doi.org/10.1002/14651858.cd008684.pub2
57. Bannister L, Manlhiot C, Pollock-BarZiv S, Stone T, McCrindle BW, Dipchand AI. Anthropometric growth and utilization of enteral feeding support in pediatric heart transplant recipients. *Pediatr Transplant*. 2010;14(7):879–886. https://doi.org/10.1111/j.1399-3046.2010.01361.x

58. Nucci A, Strohm S, Katyal N. Oncology, hematopoietic transplant, gastrointestinal supportive care medications, and survivorship. In: Corkins MR, ed. *The A.S.P.E.N Pediatric Nutrition Support Core Curriculum.* 2nd ed. American Society for Parenteral and Enteral Nutrition; 2015:459–494.
59. Anthony SJ, Annunziato RA, Fairey E, Kelly VL, So S, Wray J. Waiting for transplant: physical, psychosocial, and nutritional status considerations for pediatric candidates and implications for care. *Pediatr Transplant*. 2014;18(5):423–434. https://doi.org/10.1111/petr.12305
60. Chin C, Rosenthal D, Bernstein D. Lipoprotein abnormalities are highly prevalent in pediatric heart transplant recipients. *Pediatr Transplant.* 2000;4(3):193–199. https://doi.org/10.1034/j.1399-3046.2000.00112.x
61. Blume E. Current status of heart transplantation in children: update 2003. *Pediatr Clin North Am.* 2003;50(6):1375–1391. https://doi.org/10.1016/s0031-3955(03)00151-2
62. Sudan D, Bacha EA, John E, Bartholomew A. What's new in childhood organ transplantation. *Pediatr Rev.* 2007;28(12):439–452. https://doi.org/10.1542/pir.28-12-439
63. Capra ME, Pederiva C, Viggiano C, De Santis R, Banderali G, Biasucci G. Nutritional approach to prevention and treatment of cardiovascular disease in childhood. *Nutrients*. 2021 ;13(7):2359. https://doi.org/10.3390/nu13072359
64. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics.* 2011;128(suppl 5):S213–S256. https://doi.org/10.1542/peds.2009-2107c
65. NCEP Expert Panel on Blood Cholesterol Levels in Children and Adolescents. National Cholesterol Education Program (NCEP) highlights of the report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics*. 1992;89:495–501. https://doi.org/10.1542/peds.89.3.495

66. Reis EC, Kip KE, Marroquin OC, et al. Screening children to identify families at increased risk for cardiovascular disease. *Pediatrics.* 2006;118(6):e1789–e1797. https://doi.org/10.1542/peds.2006-0680
67. American Academy of Pediatrics Committee on Nutrition. Cholesterol in childhood. *Pediatrics.* 1998;101(1):141–147.
68. American Academy of Pediatrics. Cardiovascular risk reduction in high-risk pediatric populations. *Pediatrics.* 2007;119(3):618–621. https://doi.org/10.1542/peds.2006-3557

Test Your Knowledge Answers

1. The correct answer is **D**. Surgical correction has emerged as the most efficient method to improve the nutrition status of these infants. Surgical correction eliminates the cardiac factors contributing to malnutrition.
2. The correct answer is **C**. Children should be screened for cholesterol initially at ages 9 to 11 years and again at ages 17 to 21 years. Children 2 years or older who have a family history or medical diseases associated with CVD and children with overweight and high blood pressure should be screened as well.[35]
3. The correct answer is **D**. The exact etiology of growth impairment in children with CHD remains unclear. Many factors have been identified as contributing to growth failure in this population.
4. The correct answer is **C**. The use of an MCT–enriched diet is based on the understanding that enterocytes directly absorb MCTs into circulation, allowing adequate calories while reducing lymphatic flow to allow for healing. At least 3% to 4% of fat calories should come from LCTs to prevent essential fatty acid deficiency.

22

Renal Disease

Christina L. Nelms, MS, RD, LMNT/LD; Marisa Juarez-Calderon, MPH, RD, CSP, LD; and Bradley A. Warady, MD

Learning Objectives

1. Describe normal kidney physiology and causes of pediatric kidney failure.
2. Understand nutrition care for pediatric patients with chronic kidney disease, acute kidney injury, and those undergoing recovery following kidney transplantation.
3. Assess nutrition needs and specifications for infants, children, and adolescents with kidney disease who are receiving supplemental enteral and parenteral nutrition.
4. Examine specific nutrition needs for other kidney disorders in pediatrics, including nephrotic syndrome, nephrolithiasis, and renal tubular disorders.

Introduction

In this chapter we explore the distinct nutrition challenges associated with kidney disease in children, focusing largely on chronic kidney disease (CKD) and acute kidney injury (AKI). We will also cover other kidney-related conditions, including nephrotic syndrome, nephrolithiasis, and renal tubular disorders. CKD presents a distinct challenge in the pediatric population because of management difficulties in some patients resulting from other congenital anomalies and the possibility of deceptively mild

symptoms. While end-stage kidney disease (ESKD) is relatively uncommon in children, incidence rates are slowly rising on a global scale. Optimal patient care demands meticulous nutrition management for individuals with impaired kidney function, regardless of the cause of injury. This involves addressing diverse nutrition issues. Nutrition support must account for the distinctive metabolic and nutrition demands in infants and young children, the challenges encountered by adolescents, and the profound impact of altered micronutrient levels on the growth and development of children with kidney disease.

Background

CKD in children (as well as adults) is classified according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF KDOQI) 5-stage schema, with stage 5 CKD being at or near end-stage disease and requiring dialysis or transplantation to sustain life.[1] CKD is more common in Black children and males, with congenital disorders such as posterior urethral valves, prune belly syndrome, and renal dysplasia being major contributors.[1] On occasion, CKD may present acutely at an advanced stage, with children exhibiting only mild symptoms, such as fatigue or flu-type illness until substantial progression of kidney damage has occurred.

Pediatric ESKD (ages 0–19 y) is significantly less common than in the adult population, with children comprising less than 2% of the world's ESKD population (needing dialysis and transplantation). However, as in adult populations, the incidence of ESKD continues to increase, albeit at a slower pace. The prevalence in children in the United States is about 82 per million of the age-related population.[1] Although hard to quantify, earlier stages of CKD account for more cases than end stage. Children may also have sudden onset of acute kidney injury (AKI) from a variety of causes, including dehydration, the use of nephrotoxic medications, or severe infections giving rise to multisystem organ failure. In some cases, those patients who experience AKI go on to have CKD.

Irrespective of the cause of kidney injury, patients with impaired kidney function typically have a variety of nutrition issues that should be addressed

for optimal patient management. Infants and young children have substantial metabolic and nutritional demands associated with the promotion of normal growth and cognitive development. Inadequate intake related to anorexia is a common problem associated with CKD in children. These patients frequently require enhanced feeding regimens, such as fortified and nutrient-altered human milk and formulas as well as tube feedings. Adolescents often experience challenges related to puberty, high calorie needs, and adherence. Nearly all infants, children, and adolescents with kidney disease or other kidney-related conditions experience altered micronutrient needs and, often, altered fluid needs.[2,3] Protein-energy malnutrition or protein-energy wasting (PEW) produces profound effects on growth and development and may be associated with an increased risk of hospitalization and mortality in children on dialysis.[4–5]

Kidney Development and Function

Human kidney development, or nephrogenesis, begins during week 5 of gestation. The first functioning nephrons are formed by week 9, and the entire process is completed by 32 to 34 weeks of gestation. Once nephrogenesis has been completed, the kidney is unable to respond to injury by de novo generation of nephrons. Urine production begins at about 10 weeks of gestation, and by 20 weeks, it accounts for approximately 90% of amniotic fluid.[6] Kidney function, as measured by creatinine clearance, doubles during the first 2 weeks of life in term infants and reaches adult values by 2 years of age.[7] Normal serum creatinine values also increase with age.[8] Most important from the clinical perspective is the fact that the kidney is key to a variety of functions that, if impaired, may significantly alter body homeostasis. These functions influence solute removal; fluid and electrolyte regulation; calcium, phosphorus, and vitamin D metabolism; erythropoietin production; acid–base balance; and blood-pressure regulation. All these factors must be addressed medically if kidney function is decreased on an acute or chronic basis.

Acute Kidney Injury Physiology

Acute renal failure, now more accurately called AKI, is commonly characterized by an abrupt onset (within hours to weeks) and prolonged loss of kidney function that is reversible in most cases.[9] It is typically accompanied by a change in creatinine clearance and possibly urine output. The causes of AKI are divided into 3 categories:

1. Prerenal
2. Renal
3. Postrenal

The categories localize the predominant injury site and describe the mechanism of injury. For example, prerenal AKI primarily includes the state of reduced renal blood flow that might result from diarrhea and vomiting, burns, bleeding, or congestive heart failure. Insults to the renal glomeruli or tubules can give rise to so-called renal or intrinsic AKI. Sources of injury include glomerulonephritis (eg, postinfection, systemic lupus erythematosus, membranoproliferative diseases, and Henoch-Schönlein purpura), nephrotoxins (eg, aminoglycosides, amphotericin B, and heavy metals), interstitial nephritis, hemolytic-uremic syndrome, or acute tubular necrosis. Finally, postrenal or obstructive AKI can be the sequela of disorders such as nephrolithiasis, neurogenic bladder, hemorrhage, renal tumors, or posterior urethral valves in newborns. Strict attention to the etiology of AKI and prompt therapeutic intervention often results in a return to baseline kidney function.

Chronic Kidney Disease Physiology

While AKI is often reversible, CKD is characterized by an irreversible renal injury, persisting for 3 months or more, that is often progressive. The NKF KDOQI guidelines classify CKD in children >2 years of age, adolescents, and adults by the presence of kidney damage and the level of estimated glomerular filtration rate (GFR; see Table 22-1).[10] A GFR of 90 mL/min/1.73 m^2 or greater is considered normal. Stage 1 CKD is characterized by a GFR of less than 90 mL/min with evidence of kidney damage, such as protein in the urine. Additional clinical signs of impaired kidney function occur as GFR decreases. At stage 5, defined by a GFR of

less than 15 mL/min/1.73 m^2, children typically require the initiation of kidney replacement therapy (dialysis or transplantation).[11]

TABLE 22-1. NKF KDOQI Classification of the Stages of Chronic Kidney Disease

Stage	GFR (mL/min/1.73 m^2)	Description
1	>90	Kidney damage with normal or increased GFR
2	60–89	Kidney damage with mild reduction of GFR
3	30–59	Moderate reduction of GFR
4	15–29	Severe reduction of GFR
5	<15 (or dialysis)	Kidney failure

Abbreviations: GFR, glomerular filtration rate; NKF KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

Data from Becherucci.[13]

A variety of disorders are associated with the development of pediatric CKD, as reflected by data from more than 7000 patients enrolled in the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) registry as of 2008 (see Table 22-2).[12] The 2 most common diagnoses are congenital obstructive uropathy and aplastic, hypoplastic, or dysplastic kidneys,[13] while focal segmental glomerulosclerosis is the most common acquired cause. Clear evidence from clinical studies shows that both hypertension (HTN) and proteinuria play a key role in the progression of CKD to ESKD.[13] Developmental abnormalities of the urinary tract that account for the largest percentage of patients with CKD stages 2–4 similarly account for the largest proportion (eg, 30%–50%) of children with ESKD (stage 5 CKD). This results in a lifelong journey with kidney disorders for these children, necessitating long-term medical and nutrition intervention. Understanding the cause of a patient's kidney disorder helps inform nutrition management.

TABLE 22-2. Transplant Primary Diagnosis

Primary Diagnosis	All Patients	
	N	%
Aplasia/hypoplasia/dysplasia kidney	1769	15.8
Obstructive uropathy	1713	15.3
Focal segmental glomerulosclerosis	1308	11.7
Reflux nephropathy	576	5.1
Chronic glomerulonephritis	344	3.1
Polycystic disease	339	3.0
Medullary cystic disease	305	2.7
Congenital nephrotic syndrome	289	2.6
Hemolytic uremic syndrome	288	2.6
Prune belly	279	2.5
Familial nephritis	247	2.2
Cystinosis	225	2.0
Idiopathic crescentic glomerulonephritis	195	1.7
Membranoproliferative glomerulonephritis-Type I	191	1.7
Pyelo/interstitial nephritis	189	1.7
SLE nephritis	172	1.5
Renal infarct	144	1.3
Berger’s (IgA) nephritis	135	1.2
Henoch-Schonlein nephritis	115	1.0
Membranoproliferative glomerulonephritis-Type II	87	0.8
Wegener’s granulomatosis	71	0.6
GFWilms tumor	59	0.5
Oxalosis	58	0.5
Drash syndrome	57	0.5
Membranous nephropathy	51	0.5
Other systemic immunologic disease	34	0.3
Sickle cell nephropathy	16	0.1
Diabetic glomerulonephritis	11	0.1

Primary Diagnosis	All Patients	
	N	%
Other	1223	10.9
Unknown	692	6.2

Abbreviation: SLE, systemic lupus erythematosus.

Data from 2014 NAPRTCS.[12]

Chronic Kidney Disease and Dialysis

Hemodialysis

Hemodialysis (HD) is a form of kidney replacement therapy in which soluble substances and water are removed from the blood by diffusion through a semipermeable membrane. Some forms of renal replacement therapy use convection to remove solutes through ultrafiltration. Access to the patient's blood is achieved either through a surgically constructed arteriovenous fistula or with a central venous catheter. A single session of HD for pediatric patients typically lasts 3 to 4 hours and occurs 3 times per week. Young patients who receive most of their nutrition as formula often require HD more often because of the substantial fluid gains that occur daily. Alternatives to thrice weekly in-center HD include frequent home HD and nocturnal HD, both of which are uncommon in most pediatric dialysis programs.[14–16]

Peritoneal Dialysis

Peritoneal dialysis (PD) is typically prescribed for infants, toddlers, children, and approximately 50% of adolescents needing dialysis treatment. It is usually a nightly process that makes use of an automated cycling machine. PD involves the infusion of a glucose-based solution through a catheter that is surgically inserted into the peritoneal cavity. Diffusion across the peritoneal membrane allows for waste products (eg, urea nitrogen, creatinine) and water to cross from the patient into the dialysis solution before draining from the body through the catheter. Fresh dialysis solution is then infused and a defined number of cycles occur during the session. In most children, this process occurs over 10 to 12 hours while they

sleep. Some patients also maintain dialysis fluid in their peritoneal cavity throughout the day to permit additional dialysis; this is called a daytime dwell or last fill.[17]

The peritoneal equilibration test (PET) determines how rapidly solute (eg, creatinine, glucose) moves across the peritoneal membrane during a 4-hour period. This information can then be translated to classify patients' peritoneal transport rate as high, high-average, low-average, or low.[17] Patients with a high transport rate tend to have more porous peritoneal membranes and thus rapidly remove waste products along with significant amounts of potassium and protein. The rapid absorption of glucose from the dialysate in these patients decreases the osmotic gradient generated by glucose, resulting in decreased fluid removal. In contrast, patients with a low transport rate tend to remove less kidney waste but retain more protein and potassium. Because minimal glucose absorption preserves the osmotic gradient, they also tend to remove fluid well. The nutrition prescription for the PD patient is thus often influenced by the transport capacity of the patient's peritoneal membrane because potassium, protein, and other nutrient needs can vary greatly depending on the transport status.

Growth and Chronic Kidney Disease

Poor growth is a common manifestation of CKD in children. Growth velocity slows as GFR declines. Many factors contribute to growth failure, including decreased appetite with poor energy intake, acidosis, reduced residual kidney function, excessive urinary sodium losses, renal osteodystrophy, and abnormalities of the growth hormone (GH)–insulin-like growth factor (IGF) axis.[3,18,19] Infants with preterm birth and those born small for gestational age, as well as those with syndromes or co-occurring conditions that accompany CKD, demonstrate poor growth. Parental short stature and steroid use are additional independent risk factors for poor growth.[20,21] Over the past 25 to 30 years, we've seen improvement in final adult heights among pediatric patients with CKD. Yet, the fact that 35% to 50% of children with CKD grow into adults of small stature indicates significant room for further improvement. One factor may be late referral to pediatric renal specialists.[14,20] Notably, poor growth is associated

with an impaired quality of life and an increased risk of hospitalizations and mortality in children with CKD.[14]

Adequacy of Weight Gain

Overweight, obesity, and underweight are commonly found in children with CKD, with underweight being more common in eastern Europe and southeast Asia and overweight being more common in North America and the Middle East.[22] Weight gain in pediatric patients with CKD should be monitored often, especially among infants and toddlers. Dry weight should be used when assessing weight parameters. If poor weight gain occurs, contributing factors should be sought, identified, and corrected. Many patients with CKD have a dietary intake that is compromised, restricted, or both. In these cases, nutrition supplements are required to meet age-appropriate nutrition goals. Oral supplements should be provided first, followed by tube feeding (ie, nasogastric or gastrostomy) if deemed necessary. Infants with advanced CKD typically demonstrate delays in oral motor skills and often require enteral tube-feeding support for an extended period of time. In fact, tube feeding may also provide relief to parents and caretakers concerned about their child's poor intake. Some children may require more aggressive nutrition therapy to help reverse a catabolic state (see the "Intradialytic Parenteral Nutrition" section). It is important to recognize that all infants receiving a substantial portion of their daily nutrition needs by a nonoral route need to continue oral stimulation to promote normal oral motor development. As with linear growth, some preliminary evidence suggests that intensified and daily HD may be associated with improved weight gain and nutritional status.[16,23]

Linear Growth and Growth Hormone

In all cases of impaired growth associated with CKD, adequacy of nutrition should be assessed before considering GH therapy.[2] Evidence suggests that aggressive dialysis, as reflected by better solute clearance, along with caloric and protein intake at or above the recommended intake for age, helps prevent growth failure.[23] Nutrition support, primarily supplemental enteral nutrition (EN), may be required to meet nutrition needs. Increasing

evidence suggests that daily HD may improve linear growth. It achieves this result not only by removing solute in a more physiologic pattern but also by facilitating a reduction of cachexia, thereby improving nutrition intake.[14] Finally, in children with kidney disorders such as obstructive uropathy (eg, posterior urethral valves) or renal dysplasia, supplementation of water and 2 to 4 mEq of sodium (as chloride, bicarbonate, or both) per 100 mL of formula is recommended.[24] The NKF KDOQI pediatric nutrition guidelines also recommend correcting the serum bicarbonate level to at least 22 mmol/L.[10,25] Maintaining appropriate serum bicarbonate levels to avoid acidosis may be important not only in growth but also in the prevention of acceleration to ESKD.[26]

Insensitivity and resistance to GH and alterations in the somatotropic hormone axis are significant factors influencing the growth of children with CKD. Typically, growth occurs as a result of the action of IGF-1, a product released from the liver following stimulation by endogenous GH. In children with CKD, serum levels of IGF-1-binding proteins may be increased sevenfold to tenfold due to a reduction in their renal clearance. The increase in IGF-1-binding proteins decreases the free or bioactive levels of IGF-1 and consequently limits growth despite normal or elevated levels of circulating GH. Additionally, inadequate protein or caloric intake may impair GH's ability to stimulate IGF-1. In this situation, therapeutic doses of recombinant human growth hormone (rhGH) may be given to patients with CKD, resulting in improved height velocity.[24] The NKF KDOQI Clinical Practice Guideline for Nutrition in Children with CKD indicates that the following patients (including those who have undergone transplant) qualify for treatment with rhGH: those with a height or height velocity z-score below −1.88 or those who are below the 3rd percentile for height-for-age.[2]

A Cochrane Review of studies assessing the use of rhGH in children with CKD, including predialysis, dialysis, and transplant patients, indicates a significant increase in height standard deviation score (SDS) and height velocity at 1 year after starting the therapy.[27] Most importantly, the early initiation of rhGH therapy may result in a more optimal final adult height as well as an improved psychosocial status. However, GH can be quite expensive if not covered by insurance, which is a concern for families who

are often already burdened with other CKD-related costs (eg, medications, formula, transportation, respite care).

Although kidney transplantation may improve the growth of younger children, many older children do not achieve adequate catch-up growth with transplantation alone. The use of a steroid free immunosuppressive regimen or the introduction of rhGH >1 year after transplant has been associated with improved posttransplantation growth.[25] A dosage of 0.35 mg/kg/week is suggested for children with kidney disease.

Nutrition Assessment

No single measurement adequately characterizes the nutrition status of any child.[28] Assessing a child with CKD is especially challenging due to inherent metabolic and growth complexities. At the same time, early nutrition intervention may be critical to optimize growth and development. Trending growth parameters can help detect problems early. World Health Organization (WHO) growth charts should be used to plot patients younger than 2 years of age. and Centers for Disease Control and Prevention (CDC) charts should be used for children from North America who are older than 2 years of age. Other parts of the world may use growth charts more specific to ethnicity-related growth diversity for their populations. For all anthropometric measures, growth charts are a key tool. In children who have CKD in addition to other specific genetic conditions, such as Down syndrome or Turner syndrome, preference should be given to validated growth charts specific to those disorders, where they are available. Children who are preterm may have concurrent “adjusted” plotting, through 1 year of age for children who were born between 32 and 36 weeks gestation and through 2 years of age for those who were born earlier than 32 weeks gestation. Although this may give a more realistic picture of growth expectations, concurrent plotting with actual age also shows progression of catch-up growth.[28]

- The Pediatric Renal Nutrition Taskforce (PRNT) has recently sought to update management recommendations made by NKF KDOQI through topic-specific clinical practice recommendations (CPRs).[28] One recently

updated area is the assessment of children with CKD. The CPRs include a table with recommendations for frequency of assessment, noting that children who are younger, with more advanced CKD, and with associated concerns (eg, poor intake, history of poor growth, comorbidities) or other risk factors should be assessed more often. The CPR recommends the following areas for regular assessment:

- *Dry weight*: Dry weight is the patient's weight at an euvolemic state. Dry weight should be assessed regularly and used when assessing growth, including weight for age and body mass index (BMI) for age. Evaluating grams per day of weight gain, based on data collected for 1 week or more, can be a useful approach to follow weight gain closely in children younger than 2 years who are expected to gain weight rapidly. In oliguric or anuric patients who receive chronic dialysis, fluid overload will influence weight as well as other anthropometric measures, such as head circumference and midarm circumference. Fluid overload is the most common source of error in measuring anthropometric data in this population.[29] In other kidney diseases in which urine-concentrating capacity is impaired and volume depletion is common, dry weight is equally important in assessing growth.
- *Length or height*: Length or height should be measured regularly. Length-for-age and height-for-age trends reflect chronic nutrition status. Height velocity can be assessed using reference data from the Fels Longitudinal Study,[30] ideally with at least 6 months of data.[29] This can be assessed at 6-month intervals. As with dry weight, WHO and CDC charts should be used as appropriate for age, and z-scores provide a descriptive assessment for outliers. Because linear growth is a very important marker in children with CKD, height should be measured in children who are unable to stand using a surrogate marker (eg, recumbent length for children over 3 years of age or arm span or ulnar length for older children). Additionally, calculating midparental height can be useful in determining genetic potential and expected growth patterns.[28]
- *Weight for length (Wt/L)*: This calculation uses WHO growth charts to assess weight-to-length proportion in children younger than 2 years of age. Z-scores may be used to assess children whose weight/length fall

outside the typical distribution range. BMI for age should be used in children older than 2 years of age.

- *BMI for age*: BMI should be utilized to assess patients with kidney disease, just as it is in the healthy pediatric population. BMI should not be used for children over 2 years of age who are unable to stand because the error in height calculation is magnified by the BMI calculation. Dry weight should be used when calculating BMI for age. Because a predisposition for stunted growth and developmental delays accompanies CKD, BMI-for-height age (the age at which height has a z-score of zero) may more accurately assess BMI and ideal body weight when the child's height-for-age z-score is less than –1.88 (below the 3rd percentile). Using chronological age to assess BMI and ideal body weight may actually overestimate ideal body weight.[29] Studies have shown a U-shaped curve in BMI for age versus mortality risk, meaning that both very high and very low BMIs are associated with an increased risk of mortality in pediatric patients with kidney disease.[31] Additionally, z-scores are useful for weight, length, and BMI.[28]
- *Head circumference*: Regular measurements of head circumference should be taken through 3 years of age in children with CKD and plotted on the 2006 WHO head circumference-for-age curve.[28] Any variance not associated with a comorbidity in which large or small head size is expected should be noted, including the z-score.
- *Mid-upper-arm circumference (MUAC):* Although listed in the international CPRs as an emerging measurement, increasing evidence suggests that MUAC z-scores can be used to diagnose malnutrition in children. It is a recommended surrogate marker of nutrition status when height is not available to assess BMI or Wt/L or when a patient is edematous and weight is not an accurate marker.[32]
- *Dietary intake*: Dietary intake should be assessed regularly. Acceptable methods to estimate intake include a 3-day food diary or three 24-hour diet recalls with at least 1 weekend day. While both have limitations, they can clearly illustrate actual intake patterns and eating behaviors. As with anthropometric measures, children with more advanced CKD, younger children, and children with additional comorbidities or risks (especially for poor intake) should be assessed most often.

- *Biochemical parameters*: Studies underscore the limitations of relying on serum albumin as an indicator in children with CKD because readings may reflect dilution caused by fluid retention instead of actual protein depletion. Additionally, serum albumin may not be a straightforward nutritional marker in these patients because inflammation can reduce albumin levels independently of nutritional intake.[28,33] Other than the normalized protein catabolic rate (nPCR), good biochemical markers of nutritional status in children with CKD do not exist. To offset the limitations of nPCR, several biochemical markers may be used (after anthropometric and dietary evaluations) as secondary tools to identify nutrition concerns. Protein stores may be lower in the presence of inflammation. Trending blood urea nitrogen (BUN) levels may provide clues to protein status as well as low or low-normal transthyretin, bicarbonate, or creatinine levels; low serum cholesterol or iron indices; or elevated inflammatory markers (although these are less commonly measured).[28]

Normalized protein catabolic rate (nPCR): The normalized protein catabolic rate (nPCR) is a specific renal marker calculated to measure protein intake in grams of protein per kilogram per day. While it is useful for assessing nutrition status in children undergoing HD, its most significant utility is for adolescents. An nPCR value of less than 1 g/kg/d emerges as a strong predictor of weight loss in this patient group.[34] Evidence suggests that a 3-point nPCR measurement is a superior method of calculating nPCR.[35] This method, however, requires a computer algorithm to measure and may not be feasible or accessible to a clinician. In this case, the calculation below is appropriate. The nPCR value is determined by first calculating the urea generation rate (G), as follows:

$$G\ (\text{mg/min}) = [(C_2 \times V_2) - (C_1 \times V_1)]/t$$

where

C_2 = predialysis blood urea nitrogen (BUN) (mg/dL)

C_1 = postdialysis BUN

V_2 = predialysis total body water (dL; V_2 = 5.8 dL/kg × predialysis weight in kg)

V_1 = postdialysis total body water (dL; V_1 = 5.8 dL × postdialysis weight in kg)

t = time (minutes) from end of the dialysis treatment to the beginning of next treatment.

Then, using a modified Borah equation, nPCR is calculated as follows:

$$\text{nPCR (g/kg/d)} = 5.43 \times \text{est } G/V_1 + 0.17$$

where

V_1 = postdialysis total body water (L; V_1 = 0.58 × postdialysis weight in kg)

Similar to nPCR in HD, protein equivalent of nitrogen appearance (PNA) has been recommended to assess dietary protein intake in adults receiving PD. In adults, PNA is calculated by measuring urea nitrogen content of both urine and dialysate and then multiplying the result by 6.25; the same calculation, but with a modification, is used for pediatrics. However, it is only valid when the patient is not anabolic or catabolic, and it can have great variability.[2] Protein metabolism is age dependent, with younger children having greater differences of metabolism. Due to these factors and limited pediatric data, PNA is not routinely performed in pediatric patients.[36]

Additionally, grip strength,[37,32] waist-to-height ratios,[38] and physical examination have value and are emerging potential markers of nutritional status in the pediatric CKD population.[28] Specifics on nutrition assessment (see Table 22-3) are included in Chapter 30, "Assessment of Nutrition Status by Age and Determining Nutrient Needs." Unless specifically described, the calculation and assessment of these measurements apply to patients with kidney disease as well as other populations.

TABLE 22-3. Nutrition Assessment

Categories of Assessment	Factors
Anthropometrics	• Dry (target) weight and weight-for-age z-score • Length-for-age or height-for-age z-score • Length-for-age or height velocity-for-age z-score • Weight/length z-Score (for <2 y) • BMI-for-age z-score (for ≥2 y)[a] • SDS for all parameters • Ideal body weighta • Head circumference-for-age percentile (for <3 y) • Physical exam, hand-grip strength, mid-upper-arm circumference and waist-to-height ratio
Medical history	• Conditions relevant to nutrition status and care • Psychological and social factors affecting nutrition
Intake assessment tools	• Food diary for 3 d • Diet recall: 24-h recall for 3 d
Laboratory tests	• Electrolytes: Na, K, Cl, bicarbonate • Minerals: Ca, Phos, Mg • Glucose • Lipids: triglycerides, cholesterol • Renal function: BUN, Cr, Cystatin C • For ESKD, Kt/V for adequacy of dialysis • Malnutrition signs: nPCR (HD), CRP, proteinuria
Fluid status	• Blood pressure • Urine output • I/O • HD: noninvasive monitoring, intradialytic weight gain • Bioimpedance
Medications	Medications that may influence nutrition parameters

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein; ESKD, end-stage kidney disease; HD, hemodialysis; I/O, input/output; Kt/V, K is dialyzer clearance of urea, t is dialysis time, V is volume of urea distribution; nPCR, normalized protein catabolic rate.

[a] BMI-for-height age percentile and ideal weight based on BMI-for-height age may be more appropriate.

Data from the National Kidney Foundation,[2] Juarez-Congelozi et al,[34] Srivaths,[35] and Mendley and Majkowski.[36]

Nutrition Requirements

Macronutrients

Energy

The new PRNT CPR for energy and protein needs provides guidance for children across the stages of CKD.[18] The recommendations are characterized as "suggested dietary intakes" or SDIs, a new term to reflect an international population. The SDIs were determined by averaging recommendations from governmental scientific bodies in different countries/regions, excluding a couple of outliers, such as the American Institutes of Medicine's estimated energy requirements and dietary reference intakes, the Nordic Nutrition Recommendations, and the National Health and Medicine Research Council (Australia and New Zealand) and others.[18] No evidence exists to suggest that patients with CKD stages 3 to 5 have higher energy needs compared to healthy children. However, the range of calorie recommendations allows for clinical judgment to take into account various clinical factors such as overweight or underweight, level of activity, and comorbidities that may affect caloric needs. These patients need regular assessments to adjust for inappropriate weight gain or loss. If energy needs cannot be met with regular solid food intake, oral supplementation with a product that meets electrolyte, mineral, and/or fluid restrictions should be considered. Supplementation products can include modulars of glucose polymers, protein, or fat if necessary to meet nutrition needs. A balance of calories from all three macronutrients (ie, carbohydrate, protein, and fat) is desirable.[18]

Children receiving PD often consume less than 75% of their recommended caloric intake.[39] Insufficient energy intake is also seen in children undergoing HD, even after glucose calories derived from the dialysis fluid are accounted for. Additionally, research suggests that pediatric patients receiving PD may commonly experience malnutrition and PEW, which involves loss of lean body mass with normal or elevated fat mass, high basal metabolic rate, and poor nutrition response.[40] These nutrition challenges may be related to multiple factors, including a physiological sense of fullness from PD fluids, delayed gastric emptying,

hormonal imbalance, altered macronutrient intake, variation in peritoneal toxin removal, and inability to reach full dialysate prescription.[41]

The recommended range of intake of 45% to 65% of energy from carbohydrate and 20% to 35% from fat (25%–40% for infants and young children) has been set by the Institute of Medicine and is acceptable for children with CKD. Because cardiovascular disease (CVD) is a significant and frequent complication of CKD in children, carbohydrate and fat sources should be closely monitored and altered in the setting of dyslipidemia. Diet management of dyslipidemia should include heart-healthy fats such as monounsaturated and polyunsaturated fats rather than saturated or trans fats.[42,43] Complex carbohydrates should replace simple sugars. If carbohydrate and fat modulars are needed to increase calories to promote growth while conforming to fluid restrictions, they should be added proportionally to keep the macronutrient content consistent with the base or standard formula. (See the "Cardiovascular Disease and Lipid Management" section for further discussion.)

Protein

Children with CKD may demonstrate a lower dietary protein intake compared to healthy children without CKD. If children are unable to consume adequate amounts of protein to meet their needs, protein modulars or concentrated formula may be used. In contrast, if protein intake is high, it may be beneficial to limit dietary protein intake, especially in children with CKD who are not receiving dialysis. By restricting protein, phosphorus is also restricted, which may prove beneficial in terms of preventing CVD and helping control renal osteodystrophy.[53]

The new CPRs promote a range of protein intake to allow for lower intakes for CKD and higher intakes for patients receiving dialysis.[18] Other factors, such as inflammation or recent infection, which may contribute to protein catabolism, should also be considered when making recommendations on protein needs.

Patients on PD lose about 7% to 10% of protein intake (depending on body surface area) into the dialysis effluent, and inadequate caloric intake or uremia can affect amino acid and protein profiles negatively.[39] Infants on PD have twice the protein losses per square meter of body surface area than

full-grown adolescents[44] and thus may need greater protein supplementation per kilogram. However, it is important not to provide excessive protein intake. Excess protein has been shown to increase body acidity, creating poor bone mineralization. Sometimes patients may have extreme protein losses in urine or through the peritoneum. Increasing protein far above the DRI may just exacerbate further protein loss in these patients and create a high acid load. Use clinical judgment when assessing protein-related laboratory values to determine if added protein will benefit hypoalbuminemic patients. In summary, adequate but not excessive amounts of protein are important in this population.[45]

Carnitine is essential for transporting fatty acids into the mitochondria to produce energy. Seventy-five percent of carnitine is obtained through the diet exogenously and 25% is synthesized endogenously from the liver, kidney and brain. Patients with advanced ESKD are at increased risk for deficiency due to reduced biosynthesis in the kidney, losses in dialysis, insufficient intake due to diet restrictions, and decreased loss of acylcarnitine. Carnitine deficiency may lead to cardiovascular issues, muscle weakness, erythropoiesis-stimulating agent-resistant anemia, cachexia, and dyslipidemia in patients on dialysis. Although sufficient evidence does not exist on the treatment of this deficiency in pediatric dialysis patients, carnitine supplementation at a dose of 10 to 20 mg/kg/day is beneficial in cases of deficiency (ie, free carnitine is below 20 nmol/L or the acylcarnitine:free carnitine ratio is higher than 0.4).[46]

Micronutrients

Children with CKD are at risk for micronutrient deficiencies due to poor intake, poor absorption, abnormal renal metabolism, medication interactions, and dialysis losses. Adequate intake of fat-soluble and water-soluble vitamins, zinc, selenium, and copper should be encouraged. Growth and overall health are at risk if these micronutrients are deficient. Supplementation of these vitamins and minerals is necessary if dietary intake is low or if there is clinical evidence of deficiency and/or low blood levels. Because excess losses of water-soluble vitamins are possible during the dialysis procedure, children with stage 5D CKD (eg, patients receiving dialysis) who eat orally should take a water-soluble vitamin supplement.[2,47]

Children receiving enteral formulas are more likely to meet micronutrient needs and should be individually assessed.[48]

Fat-Soluble Vitamins

VITAMIN A Even with a normal intake of vitamin A, individuals undergoing dialysis or those with significant renal impairment before dialysis often experience high retinol levels. This elevation could be attributed to higher levels of retinol-binding protein levels commonly found in patients with CKD. While the general population might face liver toxicity risks from chronically high vitamin A levels, a more pressing concern for patients with CKD is how these levels affect serum calcium.[49] Vitamin A can increase osteoclastic action and decrease osteoblastic action, increasing bone turnover and calcium loss.[50] Studies have found elevated vitamin A levels even in children with CKD with vitamin A intake below recommendations. This may not be a significant clinical issue until hypercalcemia presents. Hypercalcemia is a risk for bone depletion and organ and soft-tissue calcification.[49,50]

VITAMIN D Vitamin D has a significant and unique role when discussed in the context of CKD. It is well known that vitamin D synthesis from the inactive to active form takes place in the kidney, and patients with CKD typically need supplementation with the active form of vitamin D, calcitriol. As GFR declines, plasma concentrations of 1,25-dihydroxyvitamin D (1,25-$(OH)_2D$) decline concurrently. There usually is a concurrent increase in the parathyroid (PTH) level, inducing secondary hyperparathyroidism.[51] Limiting of dietary phosphorus can improve 1,25-$(OH)_2D$ levels (see Phosphorus in the Fluid and Electrolyte Balance section later in this chapter).[52]

Research indicates that dietary or "inactive" vitamin D (25-hydroxyvitamin D) may also play an important role in bone metabolism and preventing inflammation and CVD in patients with CKD. Low plasma 25-hydroxyvitamin D is an independent and major risk factor for infection and autoimmune diseases, even in healthy children.[53–55] Multiple studies have previously shown that 25-hydroxyvitamin D is often deficient in children

with CKD and that supplementation may help reduce the incidence of secondary hyperparathyroidism.[2,56] The recent European Society of Pediatric Nephrology (ESPN) clinical practice guidelines (CPGs) recommend native vitamin D therapy as a first intervention for elevated PTH levels.[57] Work by Dibas and Warady supports this recommendation, noting that 78% of 51 pediatric patients receiving dialysis had low 25-hydroxyvitamin D levels. Sixty percent of these patients achieved a normal level after receiving a high dose of ergocalciferol once a month for 3 months and then continuing on a maintenance dose.[58] Older children of non-Caucasian descent on a longer length of dialysis were more likely to be associated with low levels.

VITAMIN E Serum vitamin E levels are often elevated in CKD, and vitamin E is not cleared well by dialysis.[59] However, recent evidence suggests that vitamin E benefit the treatment of anemia. In a single-center study of 10 children on HD, patients who received 15 mg/kg/d of vitamin E and erythropoietic stimulating agent (ESA) therapy experienced improved hemoglobin and hematocrit values compared to control patients who received an ESA alone. Vitamin E therapy was also found to reduce oxidative stress. Vitamin E utilization is often altered with altered lipids, which is common in CKD.[60] However, additional supplementation is not necessarily beneficial as an antioxidant. Accordingly, vitamin E supplementation may improve anemia in patients with CKD,[61] but excessive vitamin E intake is not recommended due to poor renal clearance. Generally speaking, vitamin E supplementation is not routinely required (and perhaps not appropriate), except in special circumstances.

VITAMIN K Vitamin K is synthesized by the intestine, and no evidence exists for dialysis losses. Vitamin K supplementation is not needed in children with CKD.[2] However, some evidence suggests that frequent antibiotic therapy, may increase the risk of abnormal coagulation related to vitamin K deficiency in children, regardless of diagnosis.[62] It may be prudent to bear in mind that children who receive antibiotics, such as children with CKD and those receiving dialysis, could potentially have vitamin K depletion in the same way typical pediatric patients might.

Water-soluble Vitamins

A water-soluble-vitamin supplement may be appropriate for children with CKD stages 3 to 5 if dietary intake and/or laboratory values are low. Low intake of many water-soluble vitamins is common in patients with CKD, often because of dietary phosphorus restrictions and poor intake due to uremia. Supplementation is recommended for patients with CKD stage 5D due to potential dialysis losses. Losses of vitamin C and B have been observed in patients undergoing HD , with low levels of B_{12} specifically reported in children.[63] However, low vitamin C and folic acid levels have been easily corrected with low-dose supplementation.[64]

Hyperhomocysteinemia is common in children with CKD. However, only a small percentage of these patients have low folate levels, and a smaller percentage have low vitamin B_{12} levels.[65] Treatment with 1 mg of folic acid has been shown to improve homocysteine levels significantly and to increase serum folic acid levels in pediatric patients.[66] Whether decreased morbidity and mortality occur as a result of this therapy is unknown. In fact, a large study of adult patients treated with high-dose folic acid, vitamin B_6, and vitamin B_{12} did demonstrate resultant lower serum homocysteine levels, but no evidence was found of decreased cardiovascular morbidity or mortality. These study results were consistent with studies in the general population regarding cardiovascular risk and homocysteine. High doses of folic acid can potentially mask a vitamin B_{12} deficiency.[67]

Another consideration for folic acid supplementation is to improve erythropoietin-resistant anemia. Five milligrams of folic acid has been found to improve hemoglobin and reduce ESA requirements in pediatric and adolescent HD patients.[68] In light of this evidence, pediatric patients likely benefit from a standard renal multivitamin supplement that includes moderate doses of folic acid.

Intake of vitamin C, like the B vitamins noted, is often poor in CKD. Vitamin C is also lost through dialysis. Supplementation of vitamin C, as part of a water-soluble-vitamin supplement, is recommended for patients with CKD stages 3 to 5 who are at risk for deficiency and for all patients with CKD stage 5D. However, excess amounts of vitamin C may be

detrimental. Ascorbic acid and amino acids are precursors to oxalate. Because advanced CKD and dialysis commonly reduces oxalate clearance, further elevation of blood oxalate levels from high doses of vitamin C may contribute to secondary oxalosis. Therefore, assessing pre-dialysis patients for adequate vitamin C intake is crucial to determine if supplementation is necessary. Supplementation should meet the DRI or be slightly higher for individuals undergoing dialysis and should take nutrient losses from HD into account. [2] Some reports recommend using as much as 250 mg of vitamin C daily[69] while others warn against minimal tolerance for additional vitamin C.[70]

Pediatric renal vitamins are not currently available on the market in the United States. However, many vitamins formulated for adults are appropriate for older children and adolescent patients. The goal is to find a vitamin for the patient that contains close to or slightly above the DRI for their age. Smaller doses of more widely available adult liquid renal vitamins can be titrated to more closely meet the DRI requirements for younger children and infants.[2] Many "adult" renal vitamins provide much more than the DRI for younger children, and supplemented children may consequently have normal or above-normal serum concentrations of vitamins, including thiamin, riboflavin, vitamin B_6, and folic acid. Because these vitamins are water soluble, they are not likely to cause harm.[71] Infants being fed with infant formula may receive more vitamins and minerals than older children.[61] Similarly, older children on dialysis who receive nutrition supplementation have been shown to achieve higher-than-adeqaute vitamin B intakes.[63]

Minerals

An inadequate intake of zinc and copper is frequently found in patients with CKD due to diet restrictions, dialysis losses, and poor oral intake. These patients, as well as those with nephrotic syndrome, may also experience low serum levels of zinc because of altered zinc metabolism especially in the face of proteinuria and uremia. Zinc deficiency is associated with many problems, including impaired wound healing, anemia, delays in growth, skin changes (eg, dermatitis), and altered taste perception (ie, dysgeusia).

Low serum zinc levels have been found in children undergoing PD due to zinc loss across the peritoneum. These levels improve with supplementation of zinc.[72] Additionally, in a randomized controlled trial, one group found that zinc supplementation resulted in improvement in BMI scores and serum albumin levels.[73] In adult patients, supplementation of zinc not only improves serum levels but is also associated with reduced oxidative stress.[74] A small single-center study also found that copper levels may be low in patients with CKD stage 5D due to medication interactions.[75] Thus, assessing both zinc and copper levels on a regular basis (semi-annually) in patients receiving dialysis is suggested. Supplementation to the DRI (for low levels) or to therapeutic levels (for severely low levels) is recommended.[2] Zinc levels should be checked in patients who have CKD but are not yet on dialysis if they present with poor dietary intake or show clinical symptoms of zinc deficiency.

Abnormalities of selenium metabolism have also been noted in patients with CKD. In a study of adult HD patients, plasma selenium levels were found to be significantly lower than in the control group but could be corrected with supplementation.[76] Selenium is involved with the regulation of thyroid function, and low thyrotropin levels and increased triiodothyronine levels were found in these patients. However, no studies have been done on selenium in children with CKD, and supplementation needs are not known at this time.[2]

Iron deficiency, which often complicates anemia management, is frequently present in patients with CKD. Poor dietary intake and blood loss from medical procedures can contribute to low serum iron levels.[77] Specific information regarding the titration of iron supplementation and its influence on erythropoiesis is outside the scope of this chapter, but can be reviewed in the NKF KDOQI or KDIGO) guidelines. Notably, pica, which is the tendency to crave, chew on, or eat non-nutritive, non-food items, is a common symptom of iron deficiency. It has been reported in 46% of patients on dialysis but is more likely in those undergoing HD. Depending on the item and whether it is actually ingested (eg, chewing ice or swallowing pebbles), pica may cause harm to the patient.

Other Electrolytes of Concern

MAGNESIUM Magnesium metabolism is often altered in patients with CKD, resulting in low ionized levels and high total circulating levels.[79] Typically, serum magnesium levels will be elevated or high-normal in patients receiving dialysis. Although symptomatic hypermagnesemia is rare, case reports indicate the possibility of symptomatic elevated magnesium levels in young children on PD, especially those who are enterally fed.[80] A recent study looking at adult patients undergoing HD determined that elevated serum magnesium levels were consistent with high dietary magnesium intake, notably when magnesium intake exceeded recommended intakes. A high-protein or high-lactose diet, as well as vitamin B_6 supplementation, may increase intestinal absorption of magnesium. Some phosphate binders contain magnesium and are considered safe in the absence of hypermagnesemia.[81]

HEAVY METALS Other minerals of concern are those that may be impacted by ongoing dialysis treatments. Elevated levels of minerals such as lead, mercury, and cadmium have been observed in patients receiving long-term dialysis. Contamination of dialysis fluids may contribute to these mineral abnormalities.[82]

Aluminum has been found to be very harmful to patients with renal impairment, and toxicity has caused severe bone disease and encephalopathy in patients with severe impairment of kidney function. Preventing excessive aluminum intake by choosing non-aluminum-based phosphate binders and avoiding aluminum contamination of dialysate or parenteral solutions is critical.

Fluid and Electrolyte Balance

Fluid and electrolyte restrictions will vary among individuals according to urine output, stage of CKD, primary disease, and serum levels. In patients on dialysis, sodium and fluid control is particularly important to help control blood pressure and decrease the risk for CVD. Fluid overload contributes to cardiovascular complications and mortality. In patients receiving dialysis, intradialytic weight gain and ultrafiltration rates (UFR)

must be managed diligently.[83,84] Pediatric patients on HD can also experience intradialytic hypotension which in turn leads to left ventricular dysfunction.[85] Thus, rapid and excessive ultrafiltration is not recommended. An ultrafiltration rate (UFR) lower than 13 ml/kg/h is recommended for adults; however, more studies are needed to determine an ideal rate for children. Relative blood volume monitoring is an important tool. Bioimpedance and lung ultrasound are promising techniques for monitoring fluid status, while the inferior vena cava collapsibility index, a measurement derived from ultrasound, also offers valuable insights. However, each has limitations and disadvantages.[84]

Sodium

Sodium is often restricted to help control volume overload and blood pressure. According to the Dietary Guidelines for Americans, 2020–2025, individuals should limit sodium intake to 1200 to 2300 mg/d depending on age.[86] Adherence to this recommendation is complicated by the environmental cues and peer pressures that promote high sodium intake, especially when fast food is concerned. Stringent sodium restrictions are challenging. A more reasonable sodium restriction of 2000 to 3000 mg/d may be better accepted and hence adhered to in older children or adolescents who face multiple restriction requirements (eg, potassium, phosphorus). The amount of sodium restriction should be based on individual patient parameters such as blood pressure, fluid gains, and nutrition intake. Most sodium in the diet comes from processed foods. Therefore, increasing fresh food intake and decreasing processed[86] or canned foods will decrease dietary sodium intake. Using natural herbs and spices to season foods instead of table salt is extremely helpful in reducing sodium content in foods.

In addition to educating patients about low-sodium foods, patients should also learn to interpret nutrition facts on food labels. According to the U.S. Department of Agriculture, foods with less than 5 mg of sodium per serving are considered sodium or salt-free. Foods with less than 35 mg of sodium per serving are considered very low sodium, and foods with less than 140 mg of sodium per serving are low sodium.[87] The use of salt substitutes is often contraindicated in patients with CKD because potassium

chloride is typically substituted for sodium chloride. Potassium chloride can cause hyperkalemia in those at risk for the condition.

In patients with polyuria and salt wasting disorder, adequate hydration and salt supplementation is crucial to prevent growth impairment.[88] Parekh et al described an intervention of supplementing volume and salt in patients with chronic volume depletion and a negative sodium balance while maintaining normal macronutrient intake to obtain normal linear growth in the treatment group.[89] Salt depletion in infants on PD can also result in hypotension and severe complications related to the central nervous system (eg, blindness), necessitating attention to substantial supplementation as part of routine PD management.[90]

Potassium

Dietary potassium is often restricted in patients with CKD to prevent hyperkalemia because the ability to excrete potassium is decreased as kidney failure progresses. Hyperkalemia can, in turn, lead to impaired muscle function, including of the heart, which can result in cardiac death. The PRNT CPR for potassium management[87] recommends a stepwise approach for potassium management. Assessing intake and evaluating likely sources of potassium, including potassium food additives, is the first step to determine the cause of dyskalemias. Next, nondietary causes for potassium level alteration (eg, medications or medical conditions outlined earlier in this section) should be considered. Adjustments in diet and medications are only necessary if serum potassium levels are out of range. If elevated potassium levels are observed in an infant or child requiring EN support formula or human milk can be modified with a low-potassium formula. Once an infant has started solid foods, lower potassium foods should be encouraged. However, if serum potassium levels remain within normal ranges, nutrient-dense higher-potassium foods can be introduced in moderation. For the older child who eats orally, families should be advised to limit or avoid foods with potassium additives and to encourage nutrient-dense lower-potassium alternatives. Food-preparation methods that promote lower-potassium contents may be considered as well. Foods with potassium additives have more bioavailable potassium than plant-based foods and are therefore a potentially problematic source of hidden potassium in the diet. It

is not appropriate to encourage empty-calorie food only because of low-potassium content. A last option for controlling potassium when other alternatives have been considered is a potassium binder. This can be taken orally or used to decant formula or human milk.[87]

It is important to remember that certain medications, such as steroids, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme (ACE) inhibitors, and β-blockers, have a drug–nutrient interaction that can result in hyperkalemia. Other medical conditions such as hypoaldosteronism, constipation, acidosis, and rhabdomyolysis may also cause hyperkalemia. Some patients receiving PD may not need to limit potassium and may even require a supplement if they experience high dialysis losses.[87]

Adult patients are typically advised to limit potassium to 2000 to 3000 mg/d. No direct evidence is available for appropriate amounts for children. However, an extrapolation of the adult recommendation to children is less than 30 to 40 mg/kg/d or 0.8 to 1 mmol/kg/d. For infants and young children, 1 to 3 mmol/kg/d may be an appropriate place to start.[2] Restriction can be adjusted based on individual tolerance and serum laboratory values.

Bone Mineral Management

Phosphorus

Elevated phosphorus values are well known to be associated with increased PTH levels as early as stage 3 CKD. Beyond poor growth, elevated PTH levels lead to high bone turnover, increasing risk for bone calcium loss and consequent chronic kidney disease mineral bone disease (CKD-MDB), where calcium is deposited in organs and small vessels. A low intake of dietary phosphorous can help control serum phosphorus and PTH levels. Even when phosphorus levels are normal in the earlier stages of CKD, limiting phosphorus intake can improve PTH values and increase 25-hydroxyvitamin D levels.[52] Supplementation with active vitamin D (calcitriol) is necessary to increase calcium uptake by the gut and further suppress the PTH level to prevent calcium bone loss. The downside of vitamin D therapy is that it also increases phosphorus absorption, typically increasing serum phosphorus levels and fibroblast growth factor 23 (FGF

23) levels. FGF 23 is a hormone that suppresses phosphorus resorption. However, elevated serum FGF 23 is associated with higher mortality risks and accelerated aging.[56] Calcimimetic drugs are used to lower PTH levels, but their use carries a risk of severe hypocalcemia. Determining indication for use requires weighing that risk with the possibility for prolonged severe hyperparathyroidism. Calcium supplementation may be indicated.[91]

Consequences of excess phosphorus intake in patients with advanced stages of CKD include increased cardiovascular morbidity and mortality. The PRNT CPRs for the dietary management of calcium and phosphorus aim to maintain serum phosphorus levels within age-normal values, while ensuring nutritional needs are not compromised.[92] For some children and adolescents, especially those with minimal or no urine output and those with high caloric needs, maintaining a "normal" serum phosphorus could put them at risk for inadequate nutrition and inappropriate weight status. Nonetheless, an improved serum phosphorus level should still be the goal in these patients. When considered in the context of dietary counseling, serum values should be assessed as trends and not as individual values. Patients with hyperparathyroidism and/or hyperphosphatemia should be counseled to limit phosphorus more diligently. In contrast to elevated phosphorus levels, hypophosphatemia can also arise, most commonly due to phosphate-wasting disorders or overcorrection of high levels. This too should be addressed because hypophosphatemia can be associated with bone abnormalities and poor growth.[92]

The PRNT CPRs have also developed SDIs for phosphorus and calcium based on international ranges.[92] Limiting phosphorus toward the lower end of the SDI is appropriate when hyperphosphatemia and hyperparathyroidism are present. It is not necessary to overrestrict phosphorus when serum values are appropriate, so these children can be liberalized toward the higher end of the SDI. Given that young children typically have low phosphorus needs compared to calorie needs, a balance must be considered when trying to meet calorie needs without overrestricting phosphorus. This balance is often difficult to achieve with oral feeding. By contrast, enteral formula allows more specific control of phosphorus intakes.[92] Overrestriction of protein-rich foods in an effort to control serum phosphorus levels may also lead to PEW.[93]

Limiting phosphorus in the pediatric diet may be a challenge, especially because consumption of fast food and convenience food increases with age in the usual diet of children and adolescents. Foods high in protein typically contribute the most phosphorus in a natural diet, with dairy and meats, including fish, providing 20% to 30% of the usual daily intake. These numbers are increasing as more instant and processed foods and colas, all of which have phosphate additives, are on the market. Foods made with phosphate additives are characterized by almost 100% absorption of their phosphate content. Foods with phosphate additives are nearly 70% higher in phosphorus than the comparable "natural" food product of equal size.[94] The differences in these products are not accounted for in standard nutrition databases.[95] These foods are estimated to add about 1g/d to dietary phosphorus intake, even with unchanged protein and calcium intakes.[96] Considering these factors, it is difficult to estimate phosphorus content of foods and to advise patients who need to limit dietary phosphorus. The increased presence of phosphate additives in processed foods is perhaps mitigated by intensified education regarding phosphorus management. Evidence suggests that such measures increase patient and family knowledge of phosphate-containing foods.[97]

In addition to dietary modification, a common treatment for elevated serum phosphate levels phosphorus binders. These medications induce excretion of phosphorus through fecal elimination when taken with food and formula. Frequently used phosphorus binders include calcium-based binders, notably those using calcium carbonate (eg,Tums, Calcarb) and calcium acetate (Phoslo). Non-calcium-based binders, include sevelamer carbonate (Renvela) and lanthanum carbonate (Fosrenol). Lanthanum carbonate is not currently recommended for pediatric patients. A small study found that iron-based binders, namely ferric citrate, may improve both phosphorus and iron levels; however, more research is needed before these can be routinely recommended in a pediatric population.[98]

The National Kidney Foundation's guidelines for bone metabolism and disease in children with chronic kidney disease recommend that calcium-based binders should be the initial therapy in infants and young children. However, non-calcium-based binders (eg, sevelamer) may be used if further correction of hyperphosphatemia is needed, especially if serum calcium

levels are elevated.[99] Either type of binder may be used in adolescents. Calcium acetate has a higher binding capacity than calcium carbonate. For example, it takes 667 mg of calcium acetate to bind 45 mg of phosphorus, while only 1250 mg of calcium carbonate is required to bind 39 mg of phosphorus. The body absorbs 25% calcium from calcium acetate, compared to40% from calcium carbonate, resulting in a lower calcium load from calcium acetate.[100]

Adherence with binder use is often poor in children, especially in adolescents. A novel approach to manage adherence with binder therapy focuses on patient empowerment. Children and adolescents who are taught binder self-management, which includes adjusting the dose to the estimated amount of phosphorus consumed, may demonstrate greater adherence levels and consequently improved phosphorus values.[101]

Factors such as residual kidney function and dialysis also play a large role in determining serum phosphorus levels. When serum creatinine levels are higher, patients often experience reduced phosphorus elimination through both urine and dialysis. Patients receiving PD who have high transport rates also experience greater phosphorus clearance than patients who have low or average transport rates.[102] Additionally, increased dialysis time improves phosphorus clearance. Patients receiving nocturnal HD, which is usually 6 to 10 hours nightly during sleep, typically have twice the phosphorus clearance of patients who receive standard HD 3 times per week.[103]

FGF 23 is a more recently discovered hormone that has received attention in the CKD population because it may be elevated as early as CKD stage 2 in association with impaired phosphorus excretion; FGF 23 values increase as CKD progresses. FGF 23 levels are elevated in earlier stages of CKD compared with PTH levels.[104] This early marker may, in turn, strengthen early dietary intervention and help prevent or delay associated kidney damage. Early intervention may be important; one study showed that increased FGF 23 levels were associated with increased coronary calcification.[105]

Calcium

Insufficient dietary calcium intake may result in poor bone mineralization. However, excess intake may contribute to an increased risk for CVD. Consequently, close monitoring of the intake of calcium is important for children with CKD. The calcium and phosphorus management recommends 100% to 200% of the SDI for age for calcium intake; however, many sources may contribute to calcium intake and thus increase the risk for the ingestion of an excessive amount.[92] The total elemental calcium intake derived from dietary intake, enteral supplementation, and calcium-based phosphorus binders should not provide more than 200% of the SDI for calcium.[92]

If intake is inadequate because of poor appetite and dietary restrictions, calcium supplementation is recommended. A supplement may be offered away from mealtimes and apart from iron supplements to allow for maximum calcium absorption. Iron should also be given apart from phosphorus binders. Calcium gluconate, lactate, acetate, or carbonate are all reasonable alternatives and should be given in doses not exceeding 500 mg of elemental calcium at optimal time for absorption. As already noted, calcium carbonate (eg, Tums) and calcium acetate (Phoslo) are often used as phosphorus binders in children with CKD. Research indicates that the use of calcium-based binders may contribute to hypercalcemia and as mentioned previously, may contribute to the development of soft tissue calcification with organ and small-vessel damage. Also as already noted, some calcium-containing binders containing less calcium should be considered if the patient's calcium load needs to be decreased. In cases of prolonged hypercalcemia, calcium supplementation below the SDI may be appropriate. Likewise, with prolonged hypocalcemia, supplementation above the SDI may be necessary for correction.[92]

Calcium citrate should not be given because it can increase aluminum absorption. Calcium chloride should also be avoided because it can contribute to metabolic acidosis.[2] If patients are hypocalcemic (below 8.8 mg/dL, corrected calcium value), combined calcium and vitamin D therapy should be considered.[88] Intestinal calcium absorption is suboptimal in patients with CKD, especially as kidney failure advances, due to low levels of 1,25-$(OH)_2$D. Higher doses of active vitamin D can decrease the

patient's need for calcium supplements.[2] At the same time, the NKF KDOQI pediatric bone guidelines indicate that serum calcium levels should not exceed the norms for age in CKD and should be on the lower end of normal in ESKD patients.[99]

When serum calcium levels are elevated and the PTH level is low, adynamic bone disease (where bone does not turn over at a rate necessary for proper growth and bone maintenance) is indicated. Because calcium is not incorporated into bone appropriately in this state, excessive calcium and vitamin D should be discouraged.[99]

Cardiovascular Disease and Lipid Management

Cardiovascular Disease

In CKD, approximately 40% of mortality is related to CVD.[106,107] Children with ESKD have a thousandfold higher risk of cardiac death compared to children without ESKD.[106] Traditional risk factors including HTN, left ventricular hypertrophy (LVH), and dyslipidemia are highly prevalent in adult patients with CKD. However, recent data show that nontraditional markers or uremic factors also contribute to CVD in pediatric patients. These factors include abnormal calcium and phosphorus levels, secondary hyperparathyroidism, vascular injury due to vascular calcifications and arteriosclerosis, inflammation, anemia, fluid overload, hyperhomocysteinemia, and proteinuria.[108] CVD risk factors increase in prevalence twofold to fourfold with decreasing GFR. Adolescents are at higher risk for CVD than younger children with CKD.

Uncontrolled HTN increases the progression of CKD and is exacerbated by decreased kidney function. HTN appears to be the main risk factor for CVD and LVH. Volume and pressure overload contribute to the HTN and LVH present in many children, and if uncontrolled, LVH may lead to cardiomyopathy and cardiac failure. Therefore, blood pressure and volume control are needed to help reduce the manifestations of CVD.

Dyslipidemia also occurs in association with the development and progression of CKD, and it is an important risk factor for the development

of CVD. The Chronic Kidney Disease in Children (CKiD) study has shown a significant association between dyslipidemia and both lower GFR and nephrotic-range proteinuria.[109] Triglyceride levels were also shown to be increased by 8% for every 10 mL/min/1.73 m^2 decrease in GFR. Elevated triglyceride levels are also associated with increased age and obesity. According to the American Heart Association (AHA), the treatment of dyslipidemia starts with lifestyle changes consisting of dietary modification and exercise.[42] The NKF KDOQI guidelines do not recommend dietary intervention for dyslipidemia in malnourished children with CKD. However, in well-nourished children, a change to a diet characterized by heart-healthy fat, increased fiber, and a limitation in sugar intake is recommended.[2,43] Pharmacological agents have not proven effective in reducing mortality in children with dyslipidemia. Research in this area is ongoing.

Children on PD are notably at risk because serum triglycerides and cholesterol are often elevated in this population, likely due to dextrose infusion of PD. Younger children (under 10 years of age) often have more lipid abnormalities than older children despite greater CVD risk in adolescents.[39]

Other risk factors

Obesity, especially in the posttransplant population, contributes to CVD risk and the development of other risk factors for CVD including dyslipidemia, HTN, and diabetes mellitus. Therefore, weight management is a key component of the nutrition intervention (see the "Kidney Transplant" section). Evidence also exists for reverse epidemiology for low serum cholesterol levels, low serum homocysteine levels, and low BMI, suggesting that malnutrition is also a risk factor for CVD.[31,108]

As mentioned previously, a nontraditional risk factor for CVD is abnormal calcium and phosphorus metabolism. Calcifications form in the vessels and soft tissues, including the heart. As many as 60% of pediatric patients on dialysis have soft-tissue calcifications at the time of death (see the "Phosphorus" and "Calcium" sections).[110]

Inflammation is another nontraditional risk factor that appears to contribute to CVD risk. Systemic inflammation is often characterized by

elevated serum C-reactive protein (CRP) levels. Evidence suggests that an elevated CRP level is associated with cardiac morbidity and mortality in patients with CKD.[111] Causes of inflammation include the presence of uremic toxins increasing oxidative stress, chronic infections, increased presence of proinflammatory cytokines, and abnormal calcium and phosphorus metabolism.[112]

Finally, a syndrome known as malnutrition, inflammation, and atherosclerosis syndrome (MIA) is thought to be one of the main causes of mortality in adults. This syndrome is based on evidence of a strong link between these 3 factors and an increased risk of mortality in patients with CKD.[113] Recent pediatric studies suggest MIA may contribute to cardiac calcifications and thus greater CVD risk[113]; however, more studies in this area are needed.

Kidney Transplant

The ultimate medical goal for children with ESKD is kidney transplantation, either from a living or deceased organ donor. However, transplantation is considered a treatment modality and not a cure for CKD. Children who have received a kidney transplant are still considered to have CKD. Unfortunately, until advances in medicine provide improved medication treatment options or alternatives to human organs, slow deterioration of kidney transplant function and the need for another transplant for the pediatric transplant recipient is probable. Close attention to the nutrition and overall health care of the transplant patient is often paramount to the longevity of the transplanted kidney.

General Issues of Concern

CVD is not only a significant risk for morbidity and mortality in pediatric and young adult ESKD patients but is also more prevalent in kidney transplant patients than in the general population. The reduced risk (eg, for CVD, infection, and psychosocial issues) in transplant may present a desirable alternative for kidney replacement therapy. However, patients who receive kidney transplant face new or continued risks such as hyperlipidemia, inflammation, malnutrition, anemia, and hyperglycemia or

insulin resistance. These factors may contribute to the development or continuation of CVD in this population.[114]

Several immunosuppressive medications are associated with potential side effects that can be damaging to the kidney and to the overall health of the patient who receives a transplant. These include the following: growth delays, compromised bone health and/or osteoporosis, poor lipid and glycemic control, increased blood pressure, increased appetite leading to weight gain, peptic ulcer disease, muscle wasting, and an increased risk of infection.[115] Although many centers have developed protocols that minimize corticosteroid use, patients who receive a transplant still frequently receive these medications.[115] Calcineurin inhibitors such as cyclosporine and tacrolimus can cause hyperglycemia, hypomagnesemia, hyperkalemia, HTN, and nephrotoxicity. T-cell receptor (mTOR) inhibitors (eg, sirolimus) have additional potential side effects, including hypertriglyceridemia, hypercholesterolemia, diarrhea, delayed wound healing, and mouth ulcers. The use of antiproliferative agents (eg, mycophenolate mofetil, azathioprine), may result in gastrointestinal (GI) side effects such as nausea and diarrhea, sore throat, or altered taste acuity.[115] A clinician must be aware of these potential side effects and work with the patient to minimize medication-related complications as part of optimal nutrition management. The NKF KDOQI guidelines provide a more extensive review of immunosuppressive medication side effects than is appropriate for the scope of this chapter.[2]

Because patients who have received a transplant are immunosuppressed, food safety and hygiene are especially important. Many of these patients are receiving treatment for GI reflux and related conditions, specifically with medications that lower gastric pH, thereby reducing natural resistance to foodborne pathogens. Unfortunately, symptoms of foodborne illness can interfere with the administration or absorption of critical antirejection medication. Thus, education about food-safety practices is important, especially when patients are receiving high doses of immunosuppressive therapy.[116] The U.S. Food and Drug Administration has created an educational booklet on food safety for compromised populations, including those with solid organ transplants that is accessible for free.[116]

Notably, some practitioners may be caring for the kidney donor when living donation takes place. Although no specific nutrition regimen is recommended for organ donors, the donor should be aware of the positive impact that proper nutrition has on healing. In the long term, kidney donors should ideally limit dietary sodium intake to help prevent future HTN. Their diet should also be characterized by moderate protein intake, adequate fluid intake, and adequate micronutrients and fiber. Donors should also strive to maintain a healthy weight because overweight or obesity can contribute to future kidney disease.[117]

Growth

Although growth may improve posttransplant, pediatric patients receiving a transplant should undergo frequent growth assessment followed by intervention as deemed appropriate. For children younger than 3 years of age, the KDIGO transplant guidelines recommend monitoring weight, length, and head circumference at least every 3 months. For children 3 years of age and older, these parameters should be measured every 6 months. [118]

It is approved and appropriate to treat slow growth posttransplant with rhGHafter the first-year post-transplant if impaired growth persists despite adequate nutrition, the correction of acidosis or salt depletion, and minimized doses of medications associated with poor growth velocity (eg, corticosteroids and sirolimus). A very small concern exists for greater rejection risk with rhGH use in patients who have had multiple prior rejection episodes.[119]

Rapid weight gain and obesity are common posttransplant. Transplant medications such as tacrolimus and especially corticosteroids may increase appetite or alter glucose and lipid metabolism and encourage weight gain. Other speculative contributors included relaxed dietary restrictions, improved appetite, and reduced feelings of malaise. Although some patients continue to struggle to gain adequate weight, the majority reach or exceed an appropriate weight and/or rate of weight gain posttransplant. Dietary counseling should focus on a healthy diet with appropriate caloric intake.[2] A weight-reduction program should be offered to all patients with obesity.[118] A recent report of international peritoneal dialysis data in

children revealed that tube feeding is a risk for obesity. Therefore, the astute clinician will ensure that tube feeding prevents inadequate intake and underweight while making sure not to "overcorrect" by pushing caloric intake too high.[22]

Because obesity is so prevalent posttransplant, metabolic syndrome is a significant concern for pediatric patients who receive a transplant. It has been estimated that as many as 38% of posttransplant adolescents may have metabolic syndrome.[120] While obesity and metabolic syndrome are a problem in the pediatric CKD population, the rate of these complications is fairly similar to what occurs in the general population. The PRNT CPR for obesity and metabolic syndrome assessment and management outlines principles for nutrition management of this condition. Notably, the best diet plan is realistic, ie, individualized for patient preferences and family needs. Its focus should be the provision of a well-rounded diet of nutrient-dense foods. Exercise, sleep hygiene, and management of psycho-social factors are important considerations that must work in tandem with dietary change. Medications are not routinely recommended at this time for weight management; however, in certain cases involving extreme obesity, weight-loss surgery may be a viable therapeutic option.[121]

Physical inactivity is common in patients who have received a transplant. For example, they may have a history of CKD- or dialysis-related lethargy and malaise or limit involvement in sports or similar activities out of concern for protecting the transplanted kidney. However, patients who have received a transplant should be encouraged to engage in physical activity because of their increased risk for CVD, obesity, and HTN. Achievement of appropriate muscle mass is a similarly important goal and should thus be monitored.[122]

Macronutrient Needs

The NKF KDOQI nutrition guidelines recommend that pediatric transplant recipients have macronutrient intakes consistent with the acceptable macronutrient distribution ranges for the general population. While they should balance carbohydrates, fats, and proteins, a focus on healthy fats and carbohydrates is emphasized.[2]

Patients who have received a transplant should be advised to limit concentrated sweets, especially when immunosuppressive medication dosages are highest, such as soon after transplant or when treating transplant rejection. Unless patients are underweight, water and other fluids low in calories and simple sugars are recommended to control weight gain, limit hyperglycemia, and promote good dental health.[114]

In the setting of prevalent cardiovascular risk, a diet low in saturated and trans fat is recommended.[2] Hyperlipidemia can be treated with diet modification (eg, increase in polyunsaturated fats and decrease in saturated fat) and medication. The use of 3 to 4 g of ω-3 fatty acids daily or at least 2 servings of fatty fish weekly may also lower triglyceride and cholesterol levels.[118,123]

Although no definitive evidence supports limiting dietary protein posttransplant, high-protein diets should be avoided. Protein supplementation beyond age-appropriate needs should be discouraged to protect long-term viability of the transplanted kidney. At the same time, adequate protein intake is important for healing immediately following the transplant procedure.[2,114]

Micronutrient Needs

After receiving a kidney transplant, patients often need to continue limiting dietary sodium intake to prevent or control HTN. Intakes below the upper limit for age are appropriate, with adjustment as needed based on blood pressure response and kidney function. Measuring blood pressure at every clinic visit is recommended.[118] Infants who receive an adult transplanted kidney may require additional salt to optimize kidney function. Correcting abnormal mineral or electrolyte concentrations is also recommended.[2]

Laboratory values may dictate dietary inclusion of foods containing high magnesium and the limitation of foods containing high potassium. However, pharmacological management may be necessary to treat hypomagnesemia, either with magnesium oxide or, less frequently, gluconate-based magnesium preparations. Persistent or severe hyperkalemia can be treated with medications such as fludrocortisone or with modified potassium formula for the infant or tube-fed patient.

Adequate intake of calcium is important for bone health. This is because of the potential for transplant-medication-related side effects (eg, osteoporosis), but also because of the high likelihood of preexisting bone damage. Calcium and vitamin D intakes of at least 100% of the DRI are typically suggested. However, if transplant function has deteriorated to the degree that serum phosphorus and PTH levels are elevated, total elemental calcium intake should not exceed 200% of the DRI, as indicated for other patients with CKD at a similar stage.[2,92] Hypophosphatemia is common posttransplant, with approximately 46% of patients needing phosphate supplements within the first 6 months posttransplant. This need is thought to be related to elevated PTH levels pretransplant and to the function of FGF 23. PTH levels are slow to change: 69% of patients experience elevated PTH values at transplant, 59% at 6 months posttransplant, and 47% at 1 year. This situation exacerbates calcium (and phosphorus) loss from the bone and into the urine. Supplementation of calcium is important for bone health, especially if dietary intake is limited.[124] Like all patients with CKD, laboratory values of phosphorus and PTH may indicate the necessity of limiting phosporus as the function of the transplanted kidney function declines over time.

Some transplant patients may experience issues with iron deficiency and anemia, which mandate treatment similar to that of other children with CKD. In most cases, vitamin and mineral supplements are not required in the posttransplant population until transplant kidney function has deteriorated significantly or unless the diet is significantly limited. The clinician should regularly assess dietary adequacy and supplement to 100% of the DRI for specific vitamins or minerals found to be inadequate.[2]

Fluid Needs

Fluid intake is key for the transplant recipient to ensure the adequate perfusion of the transplanted kidney. In pediatric patients, this intake is typically 1.5 to 4 L/d depending on the size and activity of the child.[125] A recommended intake of 2 to 3 L is typical for adult-sized adolescents. In young children, including infants and toddlers, adequate fluid intake may be especially important to prevent acute tubular necrosis, graft thrombosis, and graft nonfunction. Transplant success in this age group is best when adult-

sized donor kidneys are used. However, due to a child's small heart, blood volume, and blood vessels, meeting the kidney's requirement for a large blood flow may be difficult, resulting in loss of kidney function. One center indicates prevention of these complications with a total daily fluid intake (enteral formula and water given orally and via tube feeding) of 2500 mL per body surface area (2500 mL/m^2/d) and a sodium intake of 8 to 10 mEq/kg/d.[126,127] This type of protocol may be necessary for 6 months to 1 year after transplant in the youngest patients.[126]

Acute Kidney Injury

AKI is a temporary condition of kidney dysfunction typically characterized by electrolyte imbalances, an increase in BUN and serum creatinine, and a decrease in urine output.[128] (For further discussion of physiology, refer to the "Kidney Development and Function" section.) The incidence of AKI in intensive care units (ICUs) is approximately 30%. Although kidney function is usually restored once the etiology of AKI is eliminated or corrected, supportive therapy is required in the interim. Therapy may or may not include temporary dialysis. If dialysis is required, PD, HD, or continuous kidney replacement therapy (CKRT) may be used, the specific choice being dependent on specific patient characteristics, clinical status, and the resources of the treatment center. CKRT is chosen by an increasing number of pediatric centers because of the safety and efficacy of the technique, even in patients who are experiencing hemodynamic instability.[129]

Nutrition assessment and planning for patients with AKI typically follows the same guidelines as for patients with CKD stage 5D and critical illness. Hypercatabolism and alterations in metabolism are common in AKI. Some of the alterations of metabolism that occur include decreased protein synthesis, inefficient cellular utilization of protein, altered amino acid pools, hyperglycemia secondary to insulin resistance, lipid alterations caused by impaired lipolysis, acidosis, and electrolyte imbalances. The primary goal of nutrition therapy in patients with AKI is to optimize nutrition intake, prevent PEW, provide immune support, enhance wound healing, and reduce inflammation and mortality.[130] Critically ill patients are at risk for

underfeeding. This may occur due to fluid restriction, gastrointestinal intolerance, lack of feeding protocols, or interruptions due to procedures. Kyle et al reported underfeeding of energy and protein in the pediatric intensive care unit (PICU) observing that underfeeding was greatest in those with AKI.[131] More recently, Kyle et al reported that higher protein intake in pediatric patients with AKI was not associated with a delay in kidney recovery.[132] Because critically ill patients and those with AKI are at increased risk for PEW and PEW is associated with increased morbidity and mortality, improved outcomes require close attention to adequate nutrition. Additionally, improved protein intake is associated with an interdisciplinary care team and nutrition protocols individually tailored to patient needs.[132,133]

The patient with AKI who is not on dialysis may need more rigid electrolyte and fluid restrictions. If a nutrition supplement is required, a nutrient-dense renal supplement with low renal solute load is recommended. Once kidney function is restored, a regular diet and/or supplement is appropriate. However, restrictions may vary when dialysis is performed, depending on the modality (see the "Continuous Kidney Replacement Therapy," "Hemodialysis," and "Peritoneal Dialysis" sections). Fluid and electrolyte concerns, as well as prevention of catabolism, take priority in the setting of AKI in contrast to more long-term concerns associated with CKD, such as CVD, growth, and renal osteodystrophy.[128]

Continuous Kidney Replacement Therapy

CKRT is an umbrella term that includes a variety of continuous therapies, including continuous arteriovenous hemofiltration (CAVH), continuous venovenous hemofiltration (CVVH), slow continuous ultrafiltration (SCUF), continuous arteriovenous hemodiafiltration (CAVHDF), continuous venovenous hemodiafiltration (CVVHDF), continuous arteriovenous hemodialysis (CAVHD), and continuous venovenous hemodialysis (CVVHD). CKRT replaces kidney function (ie, solute and fluid removal) on a continuous or near-continuous basis. It has been found to increase survival in critically ill children and even infants weighing less

than10 kg.[134] The Cardio-Renal Pediatric Dialysis Emergency Machine (Carpediem) is a CKRT device designed for patients weighing 2.5 to 9.9 kg. Carpediem shows promise in improving survival rates in patients weighing less than 10 kg compared to adult CKRT modalities that have been adapted for children.[135] Because Carpediem is a relatively new technology, literature does not yet exist regarding associated nutrition needs.

Caloric needs related to the patient's primary condition and nutrition status prior to commencing CKRT should, in large part, determine caloric needs associated with the use of CKRT. Indirect calorimetry (IC) is the "gold standard" for measuring caloric needs in critically ill patients; for those on CKRT, the IC rarely exceeds 1.3 times basal energy expenditure.[130,136] If IC is not available, the Schofield equation is preferred.[137] Nonintentional calories such as those from citrate, glucose, and lactate-containing fluids should be considered because they can contribute substantial calories.[136] Hypothermia is common in CKRT and should also be considered in determining caloric needs.[136] Evidence suggesting that CKRT alters fat metabolism does not exist. Fats should provide 30% to 40% of total calorie intake.[136] EN is the preferred route of nutrition support in children receiving CKRT. Parenteral nutrition (PN) should be reserved for those who experience GI intolerance or who are unable to receive adequate nutrition through EN alone. The high osmolality of renal formula may increase GI complications, such as diarrhea or emesis. A standard tube-feeding formula started at a slow, continuous rate and monitored for tolerance is optimal, even for children on vasoactive and sedative drugs. Gastric emptying can be problematic in patients with kidney failure, may be alleviated by using transpyloric feedings.[138]

Protein losses may be very high in patients receiving CKRT. Maxvold et al attempted to assess nitrogen balance and amino acid loss in pediatric patients.[139] In this study, children receiving 120% to 130% of indirect-calorimetry-predicted resting energy expenditure and 1.5 g/kg protein were in negative nitrogen balance. These results suggest the need for even greater protein intake. A study with adult patients indicates that at least 2.5 g/kg protein may be necessary to achieve a positive nitrogen balance.[140] Thus, protein needs for children receiving CKRT are likely to be at least as high–

and likely higher–than adult needs because the baseline protein needs per kilogram are greater in children than adults. Studies in both adults and children demonstrate a 10% to 25% loss of amino acids in CKRT via the dialysis filter.[141,142] Zapatelli et alreported that 10% of prescribed protein was lost in children receiving CVVHD.[141] A recent study on pediatric patients receiving CVVHDF reported 2 findings: 14.6% removal of prescribed protein, and a positive correlation between rates of protein loss and rates of dialysis dose and blood flow.[142]

Minimal published studies have assessed the micronutrient needs for children receiving CKRT. More than 50% of patients on CKRT experience electrolyte and mineral imbalance. Sodium, potassium, phosphorus, calcium, and magnesium are lost in the effluent and may need to be supplemented. A single pediatric study did demonstrate hypophosphatemia in two-thirds of pediatric CKRT patients finding supplementation to be safe and efficacious in replacement or dialysis fluids.[143] Hypokalemia is common in patients on CKRT due to inadequate potassium supplementation. Potassium may be provided in replacement fluids or as a supplement.[144] Hypocalcemia is common especially with the use of citrate anticoagulation because citrate chelates calcium. High losses of trace elements and vitamins, such as selenium, copper, and thiamin, and other water-soluble vitamins are common.[136,145,146] Experts recommend supplementation of thiamin, selenium, folic acid, vitamin C, and potentially other water-soluble vitamins to compensate for losses on CKRT (see Table 22-4).[144] Manganese may accumulate in CKRT, and higher levels may be neurologically toxic.[141,144] Carnitine deficiency is common in dialysis, and due to continuous removal, patients on CKRT are at increased risk for carnitine deficiency. Sgambat has reported carnitine deficiency with increased length of time on CKRT and increased mortality with deficiency.[147] Sgambat also reported improved myocardial strain in patients on CKRT supplemented with levocarnitine.[148] A dose of 10 to 20 mg/kg/day of IV levocarnitine is recommended for patients on CKRT; however, more pediatric studies are needed to determine an optimal dose for children.

TABLE 22-4. General Nutrition Management of Patients With Renal Dysfunction

	Nephrotic Syndrome	AKI, No Dialysis	AKI, PD or HD	AKI, CKRT	CKD (Stages 3–5)	CKD5, HD	CKD5, PD
Energy[a]	EER for age	EER for age or original disease state	EER for age or original disease state	EER for age or original disease state	SDI for age	SDI for age	SDI for age
Protein	DRI; do not supplement to replace urinary losses	DRI or less per BUN monitoring	DRI with 0.2 g/kg increases for HD, 0.4 g/kg increases for PD	At least 2.5 g/kg or greater	Stage 3: Lower end of SDI	Higher end of SDI	Higher end of SDI
Sodium	1–3 mEq/kg; will vary according to edema or HTN	Will vary; consult with renal/primary team to determine	Will vary; consult with renal/primary team to determine	Typically, no restriction; may need electrolyte supplementation	1–3 mEq/kg; will vary according to edema or HTN unless sodium wasting	1–3 mEq/kg; will vary according to edema or HTN unless sodium wasting	1–3 mEq/kg; will vary according to edema or HTN unless sodium wasting
Potassium	Restriction not needed	Tightly limit	Limit		Most will tolerate > 3 mEq/kg/d	1–3 mEq/kg but will vary according to serum levels and age	Generally unrestricted unless low transporter; will need to be monitored
Phosphorus	Restriction not needed	Tightly limit	Limit		Limit to SDI to keep serum levels WNL		
Fluids	Will vary according to UOP; consult with renal team to determine	Will vary according to UOP; consult with renal team to determine	Will vary according to UOP; consult with renal team to determine.	May need additional replacement fluids	Generally unrestricted	Replace UOP, insensible losses, + UF	Replace UOP, insensible losses,
Micronutrients[c]	DRI	Tightly limit fat-soluble vitamins	Limit fat-soluble vitamins	May need supplementation selenium 20–100 µg thiamin 100 mg riboflavin 2 mg Niacin 20 mg B5 10 mg Folic acid 1 mg B12 4 µg Vitamin C 90–250 mg Vitamin E 10 IU Vitamin K 4 mg/wk	100% DRI; supplement water-soluble vitamins if needed	100% DRI; water-soluble vitamin supplement recommended	

Abbreviations: AKI, acute kidney injury; BUN, blood urea nitrogen; CKD, chronic kidney disease; CKD5, chronic kidney disease stage 5; CKRT, continuous kidney replacement therapy; DRI, dietary reference intake; EER, estimated energy requirement; HD, hemodialysis; HTN, hypertension; IBW, ideal body weight; PD, peritoneal dialysis; UF, ultrafiltration; UOP, urinary output; WNL, within normal limits.

[a] Energy requirements may need to be adjusted for physical activity level and/or based on rate of weight gain or loss.

[b] Protein requirements may need to be adjusted according to dialytic protein and amino acid losses.

[c] DRI typically appropriate unless otherwise noted.

Neonatal Issues

AKI is common in the neonatal intensive care unit (NICU) and may be of primary origin, such as in the case of congenital kidney disease, or secondary to conditions such as sepsis, drug toxicity, obstruction, hypoxia, or respiratory distress.[149] Many of these patients will continue to be treated for CKD.[20] Twenty percent of new dialysis cases are reported to be in newborns.[150] Mortality is high (46%) in neonates and low-birth-weight infants with AKI requiring dialysis.[151] Dialysis, including PD, CKRT, or less commonly HD, may be used to maintain fluid, acid–base, and electrolyte balance, as well as to remove toxins in the short or long term. It is important to remember that serum laboratory values, such as phosphorus and potassium, may have higher normal ranges for neonates than for older infants and children. Strict attention to fluid balance is important because patients may exhibit an exceptionally high urine output due to sodium and fluid-wasting kidney disorders, stomas, repeated emesis, or suction. This may necessitate a high fluid intake, consisting of replacing losses and providing maintenance needs. Poor urine output or additional sources of fluids, such as medication drips, may lead to the need for fluid restriction and the need to concentrate formula with additives.[152,153] Oliguric and anuric infants typically should receive only 25 to 30 mL/kg/d, with infants younger than 26 weeks gestational age possibly needing more.[154] Avoiding hyperglycemia, measuring urine output and weight daily, and carefully monitoring electrolytes are key targets for this population.

Controlling HTN and edema in this population is important, and maintenance fluid needs are a good starting point, with adjustment based on clinical conditions.[155] Children with high fluid and sodium losses often require sodium supplementation of 1 to 3 mEq/kg/d.[154] Correcting of acidosis with sodium bicarbonate is often necessary,[150] and sodium bicarbonate supplementation of 1 to 2 mEq/kg/d may be needed to prevent hyperkalemia. If serum potassium levels are high, potassium intake should be limited to 1 to 2 mEq/kg/d.[154] Evaluating sodium from medications and intravenous fluids is important in determining total sodium intake.[153]

It is important to be aware of medications that may affect nutrition in neonates with AKI. Pressors or narcotics may decrease gastric motility and

may affect tolerance to enteral feeding. Continuous jejunal or transpyloric feedings may be better tolerated than nasogastric feedings when this occurs. Antihypertensive agents, specifically ACE inhibitors and angiotensin II receptor blockers, can increase serum potassium levels. Diuretics may cause potassium and chloride losses that need to be replaced. Antibiotic therapy may result in the need for vitamin K supplementation, especially because gut flora and vitamin K production may not be established in the neonate.[152]

The energy and protein needs for a neonate with AKI are estimated to be 120 kcal/kg/d and 2.5 g/kg/d, respectively.[152,153] Another proposed guideline has been 8 to 12 kcal/cm^2/d.[154] It is important to provide adequate but not excessive protein and calorie intake to not only children with AKI but also preterm infants in general because inadequate nutrition has been associated with chronic kidney damage later in life.[155] Patients on PD may receive some carbohydrate calories from the dialysate solution, but the same patient may need greater amounts of protein because of urine and dialysate protein losses.[154] Although the protein-related recommendations are a good starting place, the quantity of protein administered may need to be adjusted based on laboratory values and individual needs. For example, a child with poor urine output not receiving kidney replacement therapy will need reduced amounts of protein in contrast to the child receiving continuous dialysis therapy.[152]

Oral intake alone is commonly unable to meet nutrition needs, and tube feeding is a frequently used alternative route to meet nutrition demands. It should be emphasized that neonates who are tube fed should still be encouraged to take at least a portion of their feedings by mouth. Human milk is the optimal choice, and partial breastfeeding or bottle-fed human milk should be considered.[153] If oral intake is not well tolerated, regular oral stimulation is necessary. If human milk is not an option, a whey-based formula, especially one low in electrolytes, aluminum, and vitamin A is the next best option. Caloric density of human milk or formula can be gradually increased from 20 kcal/oz to more than 30 kcal/oz as needed due to volume intolerance or restriction. In order to reduce renal solute load, this is best accomplished with glucose polymers or fat modulars (as opposed to volume concentration).[156] Some concentration of formula may be acceptable in

preterm infants with increased calcium and phosphorus needs for bone accretion. This is especially true if serum phosphate levels are appropriate and the risk for phosphate retention related to kidney failure has been weighed. Calcium needs should be closely assessed, and supplementation may be required.[154] However, patients with kidney disease who receive calcium-based medications and vitamin D supplementation may experience increased calcium uptake. Consequently, calcium supplementation may be less necessary compared with that of other preterm infants. Because other solute concentrations increase, increasing formula concentration may not be appropriate even if higher phosphate and calcium load is necessary. Non-renal-preferred products may pose a greater risk.

Feeding tolerance should be closely monitored. Reflux and delayed gastric emptying are common in patients with renal impairment and should be treated if they are contributing to a suboptimal nutrition status.[152] Treatment options include decreasing concentration of the formula with a slow increase back to the desired concentration, slowing the rate of delivery by using continuous feeds, considering post-pyloric feeding access, and possibly adding medications to enhance gastric motility.[152,156] Bolus feeds, if tolerated, are the most physiologic. Some infants may do best with a combination of bolus feeds during the day and continuous feeds overnight.

In some cases, oral and/or tube feeding cannot meet the nutrition needs of the neonate, mandating the use of PN support. Glucose monitoring with PN is mandatory, with consideration for the use of an insulin drip if needed to provide adequate carbohydrate calories, while keeping serum glucose levels normal. Use of a neonatal amino acid solution, such as TrophAmine, is appropriate, as is the use of 20% intralipids to provide energy and essential fatty acids. Intravenous fat emulsions (IVFE) are started at 1 g/kg and can be increased to increase caloric intake, but typically not to an amount exceeding 3 g/kg. Triglycerides should be monitored, and IVFE should be advanced only if triglyceride values are below 250 mg/dL. If triglyceride values are above 300 mg/dL, IVFE should be reduced or stopped[152] (although some clinical guidelines indicate 400 mg/dL as an upper limit). The provision of parenteral solution additives, particularly micronutrients that are cleared by the kidney, should be based on an individual patient's response. A small amount of potassium in the parenteral

solution is often appropriate, especially if the patient is on dialysis. It is best to start with half the standard amount or less than what is typically provided for neonates without renal impairment. Likewise, a reduction of magnesium and phosphorus in PN to one-third or one-half of the normal amount may be wise to decrease the risk of toxicity while prevent low serum levels. Selenium, chromium, and molybdenum may need to be intermittently given or avoided due to impaired renal clearance. Zinc and copper intake should remain standard unless liver impairment is present, in which case copper may need to be limited. In high-output renal failure, additional zinc may be needed and assessing serum values may be beneficial.[150,154] Providing water-soluble vitamins separately on a daily basis, while limiting the quantity of fat-soluble vitamins, is most appropriate[152,153] (see the discussion on micronutrients in the "Chronic Kidney Disease" section).

Close follow-up of a neonate with previous or ongoing renal impairment is important, and growth and feeding tolerance should be monitored postdischarge. Formula mixing instructions in household measurements should be easy to read. Demonstrating mixing is also important.[152] Preterm or low-birth-weight infants who experience AKI may be at particular risk for medical complications later in life, likely due to the loss of renal mass from the early insult or as a result of failure to complete glomerulogenesis.[151] Problems that may occur include high blood pressure and proteinuria associated with a low GFR. Height and weight gains tend to be impaired in these patients, mandating close nutrition status monitoring and supervision. Growth goals are the same as for other neonates.

Enteral Nutrition

Inadequate dietary intake is common in children with CKD. Gastroesophageal reflux, medication taste, and uremia, as well as thirst for water instead of formula, may contribute to this problem. Gastroesophageal reflux and delayed gastric emptying can contribute to vomiting, which has been associated with as much as one-third of feedings being lost. Many children also need water and salt supplementation, which may be difficult to achieve completely by means of the oral route.[157] The PRNT CPRs that focus on the delivery of the nutrition prescription recommend oral or enteral

supplementation of formula or exclusive enteral formula feeding when children are not able to meet their nutrient needs orally.[158] Intervention should take place if growth decline is noted.

The majority of infants and young children who receive PD as treatment for ESKD require supplemental enteral feedings to help achieve adequate growth. A gastrostomy device is recommended for long-term feeding needs, which is the case for most children with ESKD. Also, nasogastric feedings should only be used overnight with close supervision, as aspiration is a risk.[158] Some concern exists that placement and use of a gastrostomy tube may be a risk factor for the development of peritonitis. Peritonitis is the most significant complication of PD and can permanently damage or alter a patient's peritoneal membrane and limit the use of this dialysis modality in the future. Consequently, most experts recommend placing a percutaneous gastrostomy or an open gastrostomy prior to the initiation of PD, if possible. If a gastrostomy is needed after initiating dialysis, an open gastrostomy along with antibiotic/antifungal prophylaxis may be associated with a lower risk of peritonitis than a percutaneous gastrostomy placement.[157,158]

When supplemental feedings are given via tube feeding, intake needs can typically be met in young children. In one study, both caloric and protein needs were met or exceeded in infants and young children receiving gastrostomy feeding, with 61% of needs coming from supplemental feeding.[152]

Infant and Toddler Feeding

Frequent nutritional assessment and revision of the plan of care is essential for optimal management of the infant and young child with CKD or on dialysis. One dialysis center reported that dietetic contacts, including direct, phone, and patient-related activities (such as school or daycare contacts), averaged about 6 per month for children younger than 5 years of age, as opposed to about 3 per month for children older than 5 years of age.[159]

Human milk, which is low in phosphorus, calcium, and other minerals, is an optimal food source for infants with CKD. As a second choice, a whey-based formula is most appropriate for this population. Of note, the

potential for aluminum toxicity is an important concern for patients with kidney impairment. Human milk has the lowest content of aluminum, and infants fed human milk have the lowest serum aluminum levels.[160] Whey-based formulas have the next-lowest aluminum concentration, followed by whey-based formulas fortified with carbohydrate and lipid modulars. Preterm formulas are higher in aluminum, followed by casein hydrolysate formulas. Consequently, soy and casein hydrolysate formulas are not recommended for children with renal impairment.

As noted in the discussion of neonates, concentrating formula with a reduction of the water-to-formula ratio is not an ideal approach for patients with CKD due to the electrolyte and renal solute load. Adding fat and carbohydrate modulars as well as protein modulars as needed based upon the protein needs of the infant is the most appropriate way to increase caloric intake or to concentrate the formula density in this population.[156]

Infants often require supplemental tube feeding to meet nutrition needs, as already discussed. Infants may benefit from continuous overnight feeding and bolus feedings during the day.[2,161] However, the feeding method and regimen should be determined jointly with the family and should meet the individual's needs. Some children may use overnight feeds to allow for oral intake during the day, while bolus feeds may help the child transition to an oral diet. When a child consumes food that is then followed by bolus feeding, children may associate eating orally with fullness, encouraging further oral intake.[156] Renal wasting disorders, such as renal dysplasia, are a common cause of renal impairment in this age group, and sodium supplementation using sodium bicarbonate or sodium chloride is often needed.[89] Phosphate additives are also sometimes needed to correct serum phosphate levels in patients who use a low-phosphorus formula.

Infants and toddlers with severe renal impairment often experience high potassium levels. The preferred means to improve serum potassium levels is to use a low-potassium feeding or to use a very-low-potassium feed to modulate another formula, thereby reducing the total potassium content. Another method to reduce potassium content of the formula is to treat it with sodium polystyrene sulfonate (SPS or Kayexalate).[156] Work by Bunchman et al indicates the following method may effectively reduce potassium content of liquid beverages, including human milk and formuls:

add Kayexalate to formula, allowing it to precipitate for 30 minutes in a refrigerator, then pour off the formula from the residue that has settled to the bottom of the container.[162] This method may be needed when low potassium formulas are not appropriate for use. For example, no milk-protein-free renal formulas currently exist. Although potassium content reduces significantly (and calcium and magnesium to lesser degrees), sodium content of the treated formula greatly increases because of the exchange of sodium for potassium. Bunchman and colleagues used Kayexalate in the amount of 1 g/mEq of potassium in the formula;[162] however, this approach may overcorrect serum potassium levels if potassium is only moderately elevated. As such, the dose should be adjusted on an individualized basis per patient tolerance and requirement. It is important to keep in mind that the use of SPS has been shown to result in biochemical derangements, even for sentinel events[163] and may potentially alter other micronutrient content.

Fewer infants and young children experience elevated serum phosphorus levels. However, for those who do, some data suggest that treating formula or other beverages with sevelamer or calcium carbonate can effectively lower phosphorus content similar to potassium decanting.[164]

Introduction of solids

Introducing solids at age-appropriate times is important. Foods high in electrolytes or protein should be limited but not avoided based on the child's underlying renal condition.[2] It is important to offer a wide array of foods, increasing texture gradually, and to allow infants to experience food exploration and other good feeding habits such as family mealtimes. Children with CKD may have oral hypersensitivity and exhibit food-aversive behavior, thus speech, occupational, and/or child psychology therapists may aid normal feeding-skill advancement. The need for intervention should be identified in a timely manner to prevent more lengthy feeding delays. Even for children who are tube fed, oral stimulation (including nonthreatening contact with food or pacifier use), helps encourage oral development. Oral feeding acceptance should be positively reinforced, while feeding refusal should be ignored. Although growth and adequate intake goals may compel a decision to rapidly discontinue tube

feeding in children with food aversion, gradually introducing oral feeding is preferred. Many children advance to an oral diet after transplantation, when factors such as uremia, excess thirst, or GI reflux may be reduced.[2,157,161] GI reflux may occur in as many as 70% or more of infants with CKD and may result in impaired intake, increased feeding refusal, and excess emesis. The potential need for standard reflux precautions, medication, or even surgical intervention should be assessed in this situation.[165]

Tube Feeding for Older Children

Older children and adolescents may benefit from tube feeding to meet their nutrition needs, but social and cosmetic reasons often prevent the initiation of tube feedings in this age group. However, some children who experienced CKD or dialysis as infants or toddlers continue tube feeding past toddler years because of parent and patient desires or when inadequate intake is an issue. Some children may have comorbidities that never allow total discontinuation of tube feeding. While oral intake should always be prioritized and tube feeding is preferred for younger children, newer research indicates that improved growth is indeed possible with this supplementation, even in older children.[166]

Parenteral Nutrition

Malnutrition is common in patients with CKD. Its prevalence varies between 6% to 65%, depending on the definition of malnutrition and the study population. Malnutrition is caused by multiple factors, including anorexia, poor food intake, the catabolic effects of dialysis, altered growth hormone levels, bone mineral disease, and the demands of growth.[164167,168] Because of these issues, meeting the needs for catch-up growth can be challenging with oral and enteral supplementation alone. In the case of mild to severe intolerance of oral or enteral supplements due to GI dysfunction, PN may be necessary to ensure the provision of adequate nutrition. Patients with CKD stage 5 often have a fluid restriction. Therefore, this approach to therapy requires central venous access to accommodate the concentrated high-osmolarity parenteral solutions that are often used.

The guidelines presented in this chapter provide general recommendations for patients with CKD or AKI. For specific recommendations for PN for neonates or in association with CKRT, see "Neonatal Issues" and "Continuous Kidney Replacement Therapy" sections.

Intradialytic Parenteral Nutrition

Intradialytic parenteral nutrition (IDPN) is a noninvasive method of providing carbohydrates, protein, and lipids to undernourished patients during HD via venous access.[169] It is supplemental to other forms of nutrition, including PN. The main goals of this therapy are to replace nutrients lost during HD, increase dry body weight, prevent further muscle wasting, improve the patient's appetite and strength, increase albumin and nPCR, and decrease hospital admissions.

IDPN is typically composed of a concentrated dextrose and amino acid solution and a separate IVFE.[170] The solution must be formulated based on the patient's needs and tolerance. Concentrated dextrose is used to minimize the amount of free water given and to keep the glucose infusion rate at 5 to 9 mg/kg/min. While the energy provided may seem minimal, its purpose is to maximize protein utilization. Serum glucose levels must be monitored because of the potential for hyperglycemia. Serum glucose levels should be maintained below 200 mg/dL, using insulin if needed. Because of increased insulin levels, a potential exists for the development of hypokalemia and hypophosphatemia; therefore, serum potassium and phosphorus levels should be monitored as well. Amino acids typically provide about 1.3 g protein per kilogram per treatment. IVFEs are given as a 20% intralipid solution. Triglycerides must be monitored before and after the initial IVFE infusion to assure tolerance. If levels increase 50% above the baseline, inadequate clearance of fat may be indicated, and IVFE should be discontinued.

IDPN has been shown to be an effective and safe treatment for adults on chronic HD with protein-energy malnutrition.[141,171] The NKF KDOQI nutrition guidelines provide recommendations for its use in children.[2] The use of intralipid therapy may improve nutrition status when resources are

limited. Haskin reported improved nutrition parameters in malnourished pediatric patients receiving HD when intralipid therapy was used without IDPN.[172] Intraperitoneal nutrition during PD is another treatment that may be considered, but no recent data in children currently exists.

Nephrotic Syndrome

Nephrotic syndrome (NS) is a combination of symptoms occurring in association with various kidney and systemic disorders rather than a single disease. NS is characterized by proteinuria, hypoalbuminemia, hyperlipidemia, and anasarca. It is defined by KDIGO as having edema, urine protein greater than or equal to 300 mg/dL or 3+ protein on a urine dipstick, and hypoalbuminemia or a serum albumin less than or equal to 2.5 g/dL.[170,173] Most children with NS have a kidney disorder known as minimal change disease. The cause of minimal change disease is unknown. Although most patients will have more than one episode of severe proteinuria, the majority of patients with minimal change disease will outgrow it and not develop permanent kidney damage.[174]

The main treatment goals are to decrease or correct proteinuria and minimize fluid retention. The DRI for age based on ideal body weight is the appropriate standard for energy and protein needs. Although proteinuria and hypoalbuminemia may be present, a high-protein diet is not recommended because it can contribute to further kidney damage. Edema and diuretic therapy may make the patient's weight parameters unreliable. Sodium and fluid are usually restricted to control edema. As a guide to sodium restriction, a sodium content of 1 to 2 mEq/kg is used in most circumstances (see Table 22-4). Fluids are restricted if a patient is fluid overloaded.[174] The Pediatric Nephrology Clinical Pathway team from BC Children's Hospital in Vancouver has developed a protocol for limiting sodium that is successful according to their evaluation of postdiagnosis sodium intakes.[175] It recommends limiting sodium to no more than 1 mg of sodium consumed per calorie consumed. This lines up well with sodium requirements and is also easy to teach families learning to interpret food labels. Notably, the BC Children's hospital team found that calcium and vitamin D intakes are often low in children with nephrotic syndrome. Thus,

careful evaluation of calcium intake and consideration for vitamin D and possibly calcium supplementation may help mitigate bone loss from steroid treatment.[175]

Hyperlipidemia is also commonly present and is secondary to the increased hepatic synthesis of cholesterol, triglycerides, and lipoprotein with the concurrent decreased catabolism of lipoproteins and lipase activity. Lipid levels typically return to normal once NS resolves, and diet therapy is not indicated unless hyperlipidemia persists.

Corticosteroids are the primary medications used to treat NS that is secondary to minimal change disease. From a nutrition perspective, it is important to consider the effects of prolonged corticosteroid use, such as growth delay, HTN, obesity, impaired glucose tolerance, and decreased bone mineral density. It is also important to be mindful of drug–nutrient interactions that warrant education.

Patients who have steroid-resistant NS may actually have a disease process that is more serious causing the nephrotic syndrome, such as focal segmental glomerulosclerosis, which may progress to ESKD; thus, further medical investigation may be needed for patients with steroid-resistant NS. Posttransplant, these patients have an increased risk of recurrence of disease.[173]

Congenital Nephrotic Syndrome

Congenital nephrotic syndrome (CNS) is a rare kidney disorder characterized by heavy proteinuria in the first 3 months of life. It may be diagnosed prenatally by amniocentesis. Other characteristics include hypoproteinemia, hyperlipidemia, and edema. The majority of cases are genetic in origin. Most of these cases are due to a podocyte gene mutation such as those which occur with CNS of the Finnish type, focal segmental glomerulosclerosis, Pierson's syndrome, and Wilms's tumor. Nongenetic forms are primarily caused by infections such as congenital syphilis, congenital rubella, human immunodeficiency virus, or hepatitis B. Genetic testing is the best diagnostic method for the etiology of CNS. Irrespective of etiology, the nutrition management goal is to promote age-appropriate growth and maintain normal electrolyte, mineral, and protein levels.

Nutrition management in turn, typically includes a hypercaloric diet (100 to 150 kcal/kg/day), dietary protein intake up to 4 g/kg/d, and calcium and magnesium supplementation. Supplemental vitamins A, D, and E and water-soluble vitamins may also be required.[176,177]

Edema caused by proteinuria in these patients is often treated with albumin infusions and fluid restrictions. Fluids should be limited by concentrating feeds and providing only the minimum fluid amount needed to promote growth. Limiting sodium intake is also recommended. Treatment may include a unilateral or bilateral nephrectomy in patients with severe complications. However, some centers choose to delay nephrectomies prior to transplant or until the child reaches an approximate weight of 7 to 10 kg, whichever comes first.[177,178]

Nephrolithiasis

Nephrolithiasis refers to kidney stones or calculi within the urinary tract. Calcium and oxalate are the primary components of the most common kind of stone in all age groups (50%–75%), followed by uric acid stones (10%–20%), struvite (ammonium-magnesium phosphate) stones (5%–10%), and cystine stones (1%–2%). Nephrolithiasis is most common in Caucasians and males. Overweight, HTN, and living in a warm climate are additional risk factors for stone formation. Although the majority of stones are primary and idiopathic in nature, a variety of kidney or urinary tract disorders can be associated with the development of stones; these include medullary sponge kidney, distal tubular acidosis, secondary hyperuricemia, and obstructive uropathy. Other disorders such as sarcoidosis, Crohn's disease, thyroid or parathyroid disease, disorders of calcium or vitamin D metabolism, short bowel syndrome, and drug ingestion may contribute to stone formation as well. Nephrolithiasis may lead to CKD with some conditions, such as struvite calculi and primary hyperoxaluria.[179]

Renal stone disease appears to be increasing in pediatric patients. In 1 center, the overall incidence of kidney stones increased more than fourfold, with the most significant increase present in children younger than 10 years old. There was a distinct familial tendency for stone formation, and children with obesity comprised 31% of the patients with stones.[180] In children with

hypercalciuric kidney stones, 77% were either at risk for obesity or obese, with 74% having an increased percentage of body fat.[180] However, another study has suggested that malnutrition is also not uncommon in this population, noting about a 10% incidence of it in association with factors such as stomach pain or other GI symptoms contributing to poor nutrition intake. Malnutrition was more common in younger children with kidney stones.[181]

Hypercalciuria and hypocitraturia are commonly found in children who form kidney stones.[182,183] Changing societal and environmental dietary habits in children, such as increased sodium and animal protein intake, as well as decreased fruit and vegetable intake, may play a role. Such habits reduce potassium and citrate intake and increase sodium and acid load in the typical childhood diet. Children who form kidney stones are likely to experience repeat kidney stones. However, proper nutrition care is paramount in treatment and may significantly reduce or eliminate the recurrence of stone formation (see Table 22-5).[182]

TABLE 22-5. Nutrition for Kidney Stone Management

	Increase Fluid (at least 1 oz/kg)	Increase Fruit and Vegetable Intake	Limit Acid-Based Foods	Limit Meats and Protein	Limit Oxalate	Limit Sodium	DRI Calcium Intake[a]
Calcium-based stones	X	X	X	X	X	X	
Oxalosis or hyperoxaluria with calcium-based stones	X	X	X	X	X	X	X
Uric acid stones	X	X	X	DRI, especially limit purines			
Cystine stones	X	X	X	X		X	
Struvite stones	X						
Other kidney stones	X	?	?	X		?	

Abbreviation: DRI, dietary reference intake.

[a] Although DRI calcium intake is appropriate general medical management for general pediatric health, including patients with a variety of kidney stone disorders, the avoidance of excessive or inadequate intakes of calcium are especially important with the types of kidney stones noted.

Data from Hawkins et al,[160] Warady et al,[161] Raaijmakers,[164] Ruley et al,[165] Marlais et al,[166] Brewer,[167] Juarez,[169] and the Council on Renal Nutrition of New England.[170]

Fluid intake is an especially important preventive measure for all types of kidney stones. Adequate fluid intake is shown to almost eliminate supersaturation of stone-forming elements.[183] One center finds that urine output, and thus fluid intake, appears to be inadequate in more than half of children who form kidney stones. A urine output of 1 mL/kg/h is suggested to be adequate for avoiding saturation of stone components in the urine, thus limiting stone formation.[183] Another recommendation suggests that the urine output should be as high as 35 mL/kg/d. For practical purposes and taking insensible losses into consideration, the rule of 1 mL/kg/h rule can be equated, to a recommendation of 1 oz/kg of body weight or more per day.[183] For an infant, more than 750 mL of urine output is expected; for a

child 1 to 4 years of age,1000 mL; for a child 5 to 10 years of age, 1500 mL.[184] Another guideline for fluid intake is 2 L per day or more for adults or adult-sized adolescents.[185] A more general qualitative guideline is that children and teens should be encouraged to consume enough fluid so that their urine is nearly colorless.[182] Sugar-sweetened beverages should be avoided as they can increase stone risk, decreasing urine volume.[184]

Hypercalciuria and Calcium-Based Stones

Hypercalciuria, or an excessive loss of calcium in the urine, predisposes a patient to calcium-based kidney stones. Hypercalciuria is thought to both genetic and environmental factors.[179] In this type of stone disease, calcium combines with oxalate or phosphate. Preventing the loss of calcium in the urine is key to reducing the incidence of kidney-stone formation. Acid may contribute to this kind of stone formation. Diets high in animal protein can reduce urinary citrate and increase the acid load, predisposing bones to lose calcium, thus increasing urinary calcium. Some patients who form calcium-based stones and have hypocitraturia have a higher risk of stones because citrate typically increases the solubility of urinary calcium.[185,186] Fruit and vegetable intake plays an integral role in addressing some of the risk factors associated with stone disease. Research indicates that increasing fruit and vegetable intake not only increases potassium intake, an important protective factor, but also increases citrate intake. Additionally, fruits and vegetables confer an alkali load, reducing the risk of acid-related calcium loss and subsequent stone formation.

Sodium increases urinary calcium losses and may lower urinary citrate. It may also interfere with the actions of some medications used to treat hypercalciuria.[185] Interestingly, although excessive calcium intake is not advised, restricting calcium can be detrimental to patients who form kidney stones. Because patients with hypercalciuria lose bone calcium, limiting calcium intake can increase their risk into adulthood for poor bone status and limited bone density. In fact, low bone mineral density is commonly reported in children who form kidney stones.[187] Additionally, many calcium-rich foods are high in potassium. Finally, decreased availability of calcium to bind with oxalate contraindicates limiting calcium because it may increase the presence of the stone-forming factor oxalate in the

urine.[185] In turn, instead of limiting calcium, limiting dietary sodium below the recommended upper limit for age may prevent calcium supersaturation.[184,188] Potassium citrate may be recommended as a medication if compliance with diet is poor. A high magnesium intake may also be a protective. Adequate but not excessive vitamin D is advisable for preventing excessive calcium absorption, but adequacy of bone health.[188]

Reducing protein intake may also be helpful to prevent these type of kidney stones, but it does not seem to be as critical as high fluid and potassium intake and limited dietary sodium intake. Discouraging a particularly high protein intake is a minimal goal.[189] Encouraging plant-based proteins may not only optimize magnesium and potassium intake but may also limit the acid load in patients who form kidney stones. This may be beneficial for all types of kidney stones.[188]

Secondary Hyperoxaluria

Primary hyperoxaluria is a rare disorder and will be discussed later. However, secondary hyperoxaluria may result from fat malabsorption or the idiopathic increased absorption of oxalate. Oxalate intake needs to be restricted in patients who form hyperoxaluric stones.[185] Secondary hyperoxaluria is rare, reported in one pediatric study to be present in only 6% of patients who formed kidney stones. Therefore, limiting oxalate may not prevent this type of stone.[183]

Cystinuria

Cystinuria, an autosomal-recessive disorder, is the cause of about 10% of kidney stones in children. The disorder is related to impaired transport of the amino acids cystine, ornithine, lysine, and arginine. Of these amino acids, cystine is insoluble in the urine; thus, it can cause stone formation. Recurrent stone formation is common without medical management; however, adherence to medication therapy may be poor due to lack of treatment efficacy or side effects, such as GI intolerance. Recurrent stone formation in cystinuria often leads to renal insufficiency, including ESKD. Male patients tend to be more severely affected. In addition to medications, dietary interventions may be beneficial (see Table 22-5). A fluid intake of 3 L/d of neutral or alkali beverages is recommended. Individuals should

ideally drink frequently during the day, prior to bedtime, upon waking once or twice at night, and upon waking in the morning. A 2g sodium intake has been shown to reduce cystine stone formation. Additionally, limiting protein to the DRI also limits the intake of methionine, which is metabolized to cystine. The limitation of protein-rich foods including meat, fish, eggs, soy, and wheat can reduce methionine intake and thus urinary cystine excretion. However, strict protein restriction is not advised in children. Unfortunately, adherence to a low-sodium and lower-protein diet may be poor. High vitamin C intake, sometimes used to reduce cysteine concentration, is controversial in children. Additionally, cystinuric patients often produce other types of kidney stones, and excess ascorbic acid may increase oxalate production. If it is used, natural sources of vitamin C, as opposed to supplements, are recommended.[188] In the absence of other types of stones, 3 g of vitamin C has been recommended for adolescents with cystinuria who require this additional therapy.[190]

Other Kidney Stones

Uric acid stones, found in 2% to 4% of children who form kidney stones, are often a consequence of a high purine load. Limiting animal protein and other high-purine foods should be considered. Meat, including fish, should be reduced to the DRI for protein. Other foods that should be limited include meat extracts such as bouillon, meat gravies, cocoa, mushrooms, high-yeast products, peas, and beans. Organ meat should be avoided.[185,189]

Struvite calculi, often called “infection stones” because they frequently result from urinary tract infections, consist of magnesium ammonium phosphate or a calcium phosphorus mix Unlike other stone diseases, these stones form in an alkali environment. Therefore, increasing urine acidity may help prevent them. Ascorbic acid is suggested as a treatment.[189] Other stones include 2,8-dihydroxyadenine calculi, which should be treated with purine restriction, and xanthine stones, which should be treated with an increased fluid intake.[189]

Renal Tubular Disorders

Renal Tubular Acidosis

Renal tubular acidosis (RTA), which is subtyped as being distal or proximal, can be a secondary condition as a consequence of another condition (eg, posterior urethral values) or a primary condition. Characterized by an inability to acidify urine, RTA commonly leads to growth impairment, nephrolithiasis, and nephrocalcinosis (calcium deposits in the kidney) if untreated. The typical treatment of this condition is alkali therapy.[191] In clinical practice, monitoring for malnutrition and for renal stone disease is imperative. Metabolic bone disease and bone calcium loss may require nutrition monitoring as well.[189]

Bartter Syndrome

Bartter syndrome is an autosomal-recessive disorder with symptoms of poor growth, hypokalemia, and metabolic alkalosis. Gitelman syndrome resembles Bartter syndrome but is a milder disorder. Some mixed forms of Gitelman syndrome and Bartter syndrome may result in hypomagnesemia. Lack of sodium, chloride, and water reabsorption by the kidney causes high urine losses. Chloride loss causes alkalosis and increased potassium wasting. On occasion, calcium absorption is impaired and results in hypercalciuria. Treatment includes replacing sodium, chloride, potassium, and often magnesium. Monitoring for growth failure is important.[189,192]

Nephrogenic Diabetes Insipidus

Nephrogenic diabetes insipidus (NDI) is typically an X-linked or autosomal-recessive disorder in which impaired water reabsorption occurs in the kidney. It manifests as vomiting, anorexia, malnutrition, and constipation in young infants. Hypernatremia is common, and aggressive water supplementation is needed. Infants will often require tube feedings to meet fluid and calorie needs because the amount of fluid needed may inhibit adequacy of oral caloric intake. Poor intake and, possibly, repeated dehydration result in insufficient weight and linear growth.[193] Growth and dietary intake should be carefully monitored in this population.[189] The NDI Foundation recommends limiting sodium intake to 500 mg/d and suggests a

potential benefit from a low-protein diet. The goal of this diet is to reduce solute load on the kidneys and thus the amount of urine the kidneys must excrete.[194] The sodium allowance should be adjusted according to the patients' tolerance, growth, and clinical picture, but should be limited as much as possible. In infants, human milk is ideal because it has a low sodium and protein load and is typically much better tolerated than infant formula.[194]

Other Renal Dysfunction

Oxalosis

Primary hyperoxaluria (type 1) is an autosomal-recessive disorder characterized by a deficiency in glyoxalate aminotransferase. Oxalosis is the final stage of primary hyperoxaluria in which excessive oxalate production leads to calcium oxalate accumulation in the blood and tissues. Oxalate crystal accumulation in the kidneys causes progressive kidney failure. As kidney failure progresses, oxalate accumulates because of continued excessive production and impaired renal excretion. Although frequent HD can help clear oxalate and control oxalate deposition, success is often limited and further buildup in the tissues can occur. Oxalate can deposit in the bones, eyes, heart, vessels, and nerves. Because the defect that results in excessive oxalate production resides in the liver, one treatment option is a combined liver-kidney transplant A kidney transplant alone is not recommended because the liver continues to produce oxalate and can cause kidney failure in the transplanted kidney. Typically, treatment during the immediate posttransplantation period will include hyperhydration of 2–3 L/1.73 m^2/d to keep the concentration of urine crystals at low levels.[195] Hepatic oxalate production is reduced by the pharmacological treatment, Lumasiran, while urinary oxalate may be lowered by pyridoxine supplementation. Overall, a low-oxalate diet is recommended for patients with oxalosis.[195]

As for secondary causes of oxalosis, excessive vitamin C intake may increase the risk of oxalate stone formation and should be avoided. Secondary hyperoxaluria can also occur in the context of fat malabsorption because unabsorbed fat binds with calcium, making it unavailable to bind

oxalate. A low-fat diet with an increased calcium intake is recommended. A high fluid intake is important for urine oxalate removal. Potassium citrate, pyridoxine, magnesium citrate, and other medications may be helpful.[194]

Other Rare Renal Disorders

Many other rare renal disorders exist, including phosphate metabolism disorders, cystinosis, Fanconi's syndrome, Liddle syndrome, Gordon syndrome, and others that are too numerous to discuss in this context. These other disorders may be primary renal disorders or renal disease secondary to a systemic disease. In all cases, the nutrition needs of these patients should routinely be assessed because of the impact it has on growth and development. Close attention to electrolytes and growth are often the primary role of nutrition care in these diseases.

Most causes of kidney disease require monitoring macronutrient and micronutrient intake for growth and normal laboratory parameters. However, some disease processes do not follow the same pattern, therefore it is important to assess these special cases to ensure that appropriate nutrition therapy is provided (Table 22-6 summarizes some of the specific concerns). It is important to remember that as kidney disease progresses or urine output decreases, the patient's needs may change.

TABLE 22-6. Summary of Nutritional Needs for Common Kidney Disorders

Conditions	Energy	Protein	Fluids	Sodium	Potassium	Phosphorus	Other
Obstructive uropathy			High	High; Na wasting common			Proteinuria common
Dysplasia	DRI baseline; high needs likely	High needs likely	High	High; Na wasting common			Proteinuria common
FSGS			Restrict when NS occurs				Proteinuria common
Polycystic disease	Low volume; high concentration needed due to volume intolerance						Volume tolerance improved with nephrectomies
Cystinuria			High; polyuria	High; Na wasting	High; K+ wasting	High	High Mg
Congenital NS	High	High	Maintenance or more fluid + IV albumin				Mineral (Ca, Mg) supplements may be needed
Urinary tract anomalies (posterior urethral valves, prune belly, reflux)			High; polyuria common	High; Na wasting common in infants and young children			
Fanconi's syndrome			High; polyuria common	High; Na wasting	High; K+ wasting	High	Mineral supplements may be needed
Bartter syndrome	High-poor growth common			High; Na wasting	High; K+ wasting		High Mg; high Cl
HUS (post infection)			High	If AKI requiring dialysis, treat per modality			Present with bloody diarrhea
Atypical HUS (hereditary)				Treat per symptoms upon presentation and relapses			

Abbreviations: AKI, acute kidney injury; DRI, dietary reference intake; HUS, hemolytic uremic syndrome; IV, intravenous; NS, nephrotic syndrome.

[a] Open cells indicate no disease-specific guidelines for that specific nutrition parameter.

Conclusion

In summary, nutrition care for pediatric kidney diseases is multifaceted. It is important to understand the condition being treated as this can result in very different nutrition needs. Good nutrition care may help prevent damage to the kidneys or other organs, help prevent progression to ESKD, or maintain transplant organ longevity.

Test Your Knowledge Questions

1. What is the optimal feeding route for children in AKI receiving CKRT who need supplemental nutrition?
   A. Parenteral nutrition
   B. Nasogastric feeding of a "renal" formula

C. Transpyloric feeding of a standard tube-feeding formula
D. Nasogastric feeding of a standard tube-feeding formula

2. Which of the following vitamins or minerals may be beneficial to supplement pediatric patients receiving dialysis treatments?
   A. Vitamin B_6
   B. 25-Hydroxyvitamin D
   C. Folic acid
   D. All of these
3. Which of the following comorbid diseases is responsible for 40% of deaths in patients with CKD?
   A. ESKD
   B. Respiratory arrest
   C. CVD
   D. Diabetes mellitus
4. Which of the following statements regarding nPCR is false?
   A. Studies show that serum albumin is a better nutrition marker than nPCR.
   B. KDIGO guidelines recommend monitoring nPCR in long-term pediatric HD patients.
   C. It is a measure of protein intake in g/kg/d.
   D. nPCR is an algebraic equation.

References

1. Warady BA, Chadha V. Chronic kidney disease in children: the global perspective. *Pediatr Nephrol.* 2007;22(12):1999–2009. https://doi.org/10.1007/s00467-006-0410-1
2. National Kidney Foundation. KDOQI Clinical Practice Guideline for Nutrition in Children with CKD 2008 update Executive summary. *Am J Kidney Dis.* 2009;53(2):S11–104. https://doi.org/10.1053/j.ajkd.2008.11.017
3. Rees L, Shaw V. Nutrition in children with CRF and on dialysis. *Pediatr Nephrol.* 2007;22(10):1689–1702. https://doi.org/10.1007/s00467-006-0279-z

4. Goldstein SL, Baronette S, Gambrell TV, Currier H, Brewer ED. nPCR assessment and IDPN treatment of malnutrition in pediatric hemodialysis patients. *Pediatr Nephrol.* 2002;17(7):531–534. https://doi.org/10.1007/s00467-002-0925-z
5. Krause I, Shamir R, Davidovits M, et al. Intradialytic parenteral nutrition in malnourished children treated with hemodialysis. *J Ren Nutr.* 2002;12(1):55–59. https://doi.org/10.1053/jren.2002.29601
6. Vanderheyden T, Kumar S, Fisk NM. Fetal renal impairment. *Semin Neonatol.* 2003;8(4):279–289. https://doi.org/10.1016/s1084-2756(03)00022-8
7. Bueva A, Guignard JP. Renal function in preterm neonates. *Pediatr Res.* 1994;36(5):572–577. https://doi.org/10.1203/00006450-199411000-00005
8. Ceriotti F, Boyd JC, Klein G, et al. Reference intervals for serum creatinine concentrations: assessment of available data for global application. *Clin Chem.* 2008;54(3):559–566. https://doi.org/10.1373/clinchem.2007.099648
9. Lameire N, Van Biesen W, Vanholder R. Acute renal failure. *Lancet.* 2005;365(9457):417–430. https://doi.org/10.1016/s0140-6736(05)17831-3
10. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002;39(1):S1–266.
11. Wong CS, Pierce CB, Cole SR, et al. Association of proteinuria with race, cause of chronic kidney disease, and glomerular filtration rate in the chronic kidney disease in children study. *Clin J Am Soc Nephrol.* 2009;4(4):812–819. https://doi.org/10.2215/cjn.01780408
12. North American Pediatric Renal Trials and Collaborative Studies. *NAPRTCS 2008 annual report*. Accessed February 25, 2023. https://naprtcs.org/system/files/2008_Annual_CKD_Report.pdf
13. Becherucci F, Roperto RM, Materassi M, Romagnani P. Chronic kidney disease in children. *Clin Kidney J.* 2016;9(4):583–591. https://doi.org/10.1093/ckj/sfw047
14. Fischbach M, Fothergill H, Seuge L, Zaloszyc A. Dialysis strategies to improve growth in children with chronic kidney disease. *J Ren Nutr.* 2011;21(1):43–46. https://doi.org/10.1053/j.jrn.2010.10.022

15. Lacson E, Jr., Wang W, Lester K, Ofsthun N, Lazarus JM, Hakim RM. Outcomes associated with in-center nocturnal hemodialysis from a large multicenter program. *Clin J Am Soc Nephrol.* 2010;5(2):220–226. https://doi.org/10.2215/cjn.06070809
16. Hoppe A, von Puttkamer C, Linke U, et al. A hospital-based intermittent nocturnal hemodialysis program for children and adolescents. *J Pediatr.* 2011;158(1):95–99.e91. https://doi.org/10.1016/j.jpeds.2010.06.036
17. Fischbach M, Zaloszyc A, Schaefer B, Schmitt CP. Optimizing peritoneal dialysis prescription for volume control: the importance of varying dwell time and dwell volume. *Pediatr Nephrol.* 2014;29(8):1321–1327. https://doi.org/10.1007/s00467-013-2573-x
18. Shaw V, Polderman N, Renken-Terhaerdt J, et al. Energy and protein requirements for children with CKD stages 2–5 and on dialysis-clinical practice recommendations from the Pediatric Renal Nutrition Taskforce. *Pediatr Nephrol.* 2020;35(3):519–531. https://doi.org/10.1007/s00467-019-04426-0
19. Silverstein DM. Growth and Nutrition in Pediatric Chronic Kidney Disease. *Front Pediatr.* 2018;6:205. https://doi.org/10.3389/fped.2018.00205
20. Rees L, Jones H. Nutritional management and growth in children with chronic kidney disease. *Pediatr Nephrol.* 2013;28(4):527–536. https://doi.org/10.1007/s00467-012-2258-x
21. Franke D, Alakan H, Pavičić L, et al. Birth parameters and parental height predict growth outcome in children with chronic kidney disease. *Pediatr Nephrol.* 2013;28(12):2335–2341. https://doi.org/10.1007/s00467-013-2604-7
22. Schaefer F, Benner L, Borzych-Dużałka D, et al. Global variation of nutritional status in children undergoing chronic peritoneal dialysis: a longitudinal study of the International Pediatric Peritoneal Dialysis Network. *Sci Rep.* 2019;9(1):4886. https://doi.org/10.1038/s41598-018-36975-z
23. Tom A, McCauley L, Bell L, et al. Growth during maintenance hemodialysis: impact of enhanced nutrition and clearance. *J Pediatr.* 1999;134(4):464–471. https://doi.org/10.1016/s0022-3476(99)70205-2

24. Tönshoff B, Kiepe D, Ciarmatori S. Growth hormone/insulin-like growth factor system in children with chronic renal failure. *Pediatr Nephrol.* 2005;20(3):279–289. https://doi.org/10.1007/s00467-005-1821-0
25. Mahan JD, Warady BA. Assessment and treatment of short stature in pediatric patients with chronic kidney disease: a consensus statement. *Pediatr Nephrol.* 2006;21(7):917–930. https://doi.org/10.1007/s00467-006-0020-y
26. Brown DD, Roem J, Ng DK, et al. Low serum bicarbonate and CKD progression in children. *Clin J Am Soc Nephrol.* 2020;15(6):755–765. https://doi.org/10.2215/cjn.07060619
27. Vimalachandra D, Hodson EM, Willis NS, Craig JC, Cowell C, Knight JF. Growth hormone for children with chronic kidney disease. *Cochrane Database Syst Rev.* 2006(3):Cd003264. https://doi.org/10.1002/14651858.cd003264.pub2
28. Nelms CL, Shaw V, Greenbaum LA, et al. Assessment of nutritional status in children with kidney diseases-clinical practice recommendations from the Pediatric Renal Nutrition Taskforce. *Pediatr Nephrol.* 2021;36(4):995–1010. https://doi.org/10.1007/s00467-020-04852-5
29. Foster BJ, Leonard MB. Measuring nutritional status in children with chronic kidney disease. *Am J Clin Nutr.* 2004;80(4):801–814. https://doi.org/10.1093/ajcn/80.4.801
30. Baumgartner RN, Roche AF, Himes JH. Incremental growth tables: supplementary to previously published charts. *Am J Clin Nutr.* 1986;43(5):711–722. https://doi.org/10.1093/ajcn/43.5.711
31. Wong CS, Gipson DS, Gillen DL, et al. Anthropometric measures and risk of death in children with end-stage renal disease. *Am J Kidney Dis.* 2000;36(4):811–819. https://doi.org/10.1053/ajkd.2000.17674
32. Stephens K, Orlick M, Beattie S, et al. Examining mid-upper arm circumference malnutrition z-Score thresholds. *Nutr Clin Pract.* 2020;35(2):344–352. https://doi.org/10.1002/ncp.10324
33. Wong CS, Hingorani S, Gillen DL, et al. Hypoalbuminemia and risk of death in pediatric patients with end-stage renal disease. *Kidney Int.* 2002;61(2):630–637. https://doi.org/10.1046/j.1523-1755.2002.00169.x

34. Juarez-Congelosi M, Orellana P, Goldstein SL. Normalized protein catabolic rate versus serum albumin as a nutrition status marker in pediatric patients receiving hemodialysis. *J Ren Nutr.* 2007;17(4):269–274. https://doi.org/10.1053/j.jrn.2007.04.002
35. Srivaths PR, Sutherland S, Alexander S, Goldstein SL. Two-point normalized protein catabolic rate overestimates nPCR in pediatric hemodialysis patients. *Pediatr Nephrol.* 2013;28(5):797–801. https://doi.org/10.1007/s00467-012-2371-x
36. Mendley SR, Majkowski NL. Urea and nitrogen excretion in pediatric peritoneal dialysis patients. *Kidney Int.* 2000;58(6):2564–2570. https://doi.org/10.1046/j.1523-1755.2000.00442.x
37. Hogan J, Schneider MF, Pai R, et al. Grip strength in children with chronic kidney disease. *Pediatr Nephrol.* 2020;35(5):891–899. https://doi.org/10.1007/s00467-019-04461-x
38. Sgambat K, Roem J, Mitsnefes M, et al. Waist-to-height ratio, body mass index, and cardiovascular risk profile in children with chronic kidney disease. *Pediatr Nephrol.* 2018;33(9):1577–1583. https://doi.org/10.1007/s00467-018-3987-2
39. Salusky IB, Fine RN, Nelson P, Blumenkrantz MJ, Kopple JD. Nutritional status of children undergoing continuous ambulatory peritoneal dialysis. *Am J Clin Nutr.* 1983;38(4):599–611. https://doi.org/10.1093/ajcn/38.4.599
40. Pontón-Vázquez C, Vásquez-Garibay EM, Hurtado-López EF, de la Torre Serrano A, García GP, Romero-Velarde E. Dietary intake, nutritional status, and body composition in children with end-stage kidney disease on hemodialysis or peritoneal dialysis. *J Ren Nutr.* 2017;27(3):207–215. https://doi.org/10.1053/j.jrn.2016.12.007
41. Paglialonga F, Edefonti A. Nutrition assessment and management in children on peritoneal dialysis. *Pediatr Nephrol.* 2009;24(4):721–730. https://doi.org/10.1007/s00467-007-0719-4
42. Kavey RE, Allada V, Daniels SR, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular

Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation.* 2006;114(24):2710–2738. https://doi.org/10.1161/circulationaha.106.179568

43. American Academy of Pediatrics. Cardiovascular risk reduction in high-risk pediatric populations. *Pediatrics.* 2007;119(3):618–621. https://doi.org/10.1542/peds.2006-3557
44. Quan A, Baum M. Protein losses in children on continuous cycler peritoneal dialysis. *Pediatr Nephrol.* 1996;10(6):728–731. https://doi.org/10.1007/s004670050200
45. Azocar MA, Cano FJ, Marin V, Delucchi MA, Rodriguez EE. Body composition in children on peritoneal dialysis. *Adv Perit Dial.* 2004;20:231–236.
46. Morgans HA, Chadha V, Warady BA. The role of carnitine in maintenance dialysis therapy. *Pediatr Nephrol.* 2021;36(8):2545–2551. https://doi.org/10.1007/s00467-021-05101-z
47. Harshman LA, Lee-Son K, Jetton JG. Vitamin and trace element deficiencies in the pediatric dialysis patient. *Pediatr Nephrol.* 2018;33(7):1133–1143. https://doi.org/10.1007/s00467-017-3751-z
48. Joyce T, Rasmussen P, Melhem N, Clothier J, Booth C, Sinha MD. Vitamin and trace element concentrations in infants and children with chronic kidney disease. *Pediatr Nephrol.* 2020;35(8):1463–1470. https://doi.org/10.1007/s00467-020-04536-0
49. Harris M, Varnell C, Taylor V, Nehus ST, Zhang B, Erkan E. Hypervitaminosis A in pediatric patients with advanced chronic kidney disease. *J Ren Nutr.* 2022;32(3):275–281. https://doi.org/10.1053/j.jrn.2021.03.010
50. Manickavasagar B, McArdle AJ, Yadav P, et al. Hypervitaminosis A is prevalent in children with CKD and contributes to hypercalcemia. *Pediatr Nephrol.* 2015;30(2):317–325. https://doi.org/10.1007/s00467-014-2916-2
51. Portale AA, Booth BE, Tsai HC, Morris RC, Jr. Reduced plasma concentration of 1,25-dihydroxyvitamin D in children with moderate renal insufficiency. *Kidney Int.* 1982;21(4):627–632. https://doi.org/10.1038/ki.1982.70

52. Portale AA, Booth BE, Halloran BP, Morris RC, Jr. Effect of dietary phosphorus on circulating concentrations of 1,25-dihydroxyvitamin D and immunoreactive parathyroid hormone in children with moderate renal insufficiency. *J Clin Invest.* 1984;73(6):1580–1589. https://doi.org/10.1172/jci111365
53. Wagner CL, Greer FR. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics.* 2008;122(5):1142–1152. https://doi.org/10.1542/peds.2008-1862
54. Querfeld U. Vitamin D and inflammation. *Pediatr Nephrol.* 2013;28(4):605–610. https://doi.org/10.1007/s00467-012-2377-4
55. Patange AR, Valentini RP, Du W, Pettersen MD. Vitamin D deficiency and arterial wall stiffness in children with chronic kidney disease. *Pediatr Cardiol.* 2012;33(1):122–128. https://doi.org/10.1007/s00246-011-0101-y
56. Wesseling-Perry K, Salusky IB. Phosphate binders, vitamin D and calcimimetics in the management of chronic kidney disease-mineral bone disorders (CKD-MBD) in children. *Pediatr Nephrol.* 2013;28(4):617–625. https://doi.org/10.1007/s00467-012-2381-8
57. Shroff R, Wan M, Nagler EV, et al. Clinical practice recommendations for native vitamin D therapy in children with chronic kidney disease Stages 2–5 and on dialysis. *Nephrol Dial Transplant.* 2017;32(7):1098–1113. https://doi.org/10.1093/ndt/gfx065
58. Dibas BI, Warady BA. Vitamin D status of children receiving chronic dialysis. *Pediatr Nephrol.* 2012;27(10):1967–1973. https://doi.org/10.1007/s00467-012-2203-z
59. Blumberg A, Hanck A, Sander G. Vitamin nutrition in patients on continuous ambulatory peritoneal dialysis (CAPD). *Clin Nephrol.* 1983;20(5):244–250.
60. Iughetti L, Perugini C, Predieri B, et al. Low-density lipoprotein oxidizability in children with chronic renal failure. *Pediatr Int.* 2008;50(4):447–453. https://doi.org/10.1111/j.1442-200x.2008.02614.x
61. Németh I, Túri S, Haszon I, Bereczki C. Vitamin E alleviates the oxidative stress of erythropoietin in uremic children on hemodialysis. *Pediatr Nephrol.* 2000;14(1):13–17. https://doi.org/10.1007/s004670050003

62. Bhat RV, Deshmukh CT. A study of Vitamin K status in children on prolonged antibiotic therapy. *Indian Pediatr.* 2003;40(1):36–40.
63. Don T, Friedlander S, Wong W. Dietary intakes and biochemical status of B vitamins in a group of children receiving dialysis. *J Ren Nutr.* 2010;20(1):23–28. https://doi.org/10.1053/j.jrn.2009.04.008
64. Descombes E, Hanck AB, Fellay G. Water soluble vitamins in chronic hemodialysis patients and need for supplementation. *Kidney Int.* 1993;43(6):1319–1328. https://doi.org/10.1038/ki.1993.185
65. Canepa A, Carrea A, Caridi G, et al. Homocysteine, folate, vitamin B_{12} levels, and C677T MTHFR mutation in children with renal failure. *Pediatr Nephrol.* 2003;18(3):225–229. https://doi.org/10.1007/s00467-002-1058-0
66. Kang HG, Lee BS, Hahn H, et al. Reduction of plasma homocysteine by folic acid in children with chronic renal failure. *Pediatr Nephrol.* 2002;17(7):511–514. https://doi.org/10.1007/s00467-002-0864-8
67. Sunder-Plassmann G, Winkelmayer WC, Födinger M. Approaching the end of the homocysteine hype? *Am J Kidney Dis.* 2008;51(4):549–553. https://doi.org/10.1053/j.ajkd.2008.01.007
68. Bamgbola OF, Kaskel F. Role of folate deficiency on erythropoietin resistance in pediatric and adolescent patients on chronic dialysis. *Pediatr Nephrol.* 2005;20(11):1622–1629. https://doi.org/10.1007/s00467-005-2021-7
69. Hongsawong N, Chawprang N, Kittisakmontri K, Vittayananan P, Srisuwan K, Chartapisak W. Vitamin C deficiency and impact of vitamin C administration among pediatric patients with advanced chronic kidney disease. *Pediatr Nephrol.* 2021;36(2):397–408. https://doi.org/10.1007/s00467-020-04662-9
70. Kennedy SS, Perilloux A, Pereira RC, Handelman G, Wesseling-Perry K, Salusky IB. Vitamin C overload may contribute to systemic oxalosis in children receiving dialysis. *Pediatr Nephrol.* 2021;36(2):435–441. https://doi.org/10.1007/s00467-020-04702-4
71. Warady BA, Kriley M, Alon U, Hellerstein S. Vitamin status of infants receiving long-term peritoneal dialysis. *Pediatr Nephrol.* 1994;8(3):354–356. https://doi.org/10.1007/bf00866365

72. Tamura T, Vaughn WH, Waldo FB, Kohaut EC. Zinc and copper balance in children on continuous ambulatory peritoneal dialysis. *Pediatr Nephrol.* 1989;3(3):309–313. https://doi.org/10.1007/bf00858539
73. Escobedo-Monge MF, Ayala-Macedo G, Sakihara G, et al. Effects of zinc supplementation on nutritional status in children with chronic kidney disease: arandomized trial. *Nutrients.* 2019;11(11). https://doi.org/10.3390/nu11112671
74. Mazani M, Argani H, Rashtchizadeh N, et al. Effects of zinc supplementation on antioxidant status and lipid peroxidation in hemodialysis patients. *J Ren Nutr.* 2013;23(3):180–184. https://doi.org/10.1053/j.jrn.2012.08.012
75. Warady BA, Nelms C, Jennings J, Johnson S. Copper deficiency: a common cause of erythropoietin (rHuEPO) resistant anemia in children on hemodialysis? *Hemodial Inter.* 2005;9(1):99.
76. Napolitano G, Bonomini M, Bomba G, et al. Thyroid function and plasma selenium in chronic uremic patients on hemodialysis treatment. *Biol Trace Elem Res.* 1996;55(3):221–230. https://doi.org/10.1007/bf02785281
77. National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. *Am J Kidney Dis.* 2006;47(suppl 3):S11–145. https://doi.org/10.1053/j.ajkd.2006.03.010
78. Katsoufis CP, Kertis M, McCullough J, et al. Pica: an important and unrecognized problem in pediatric dialysis patients. *J Ren Nutr.* 2012;22(6):567–571. https://doi.org/10.1053/j.jrn.2011.10.038
79. Pedrozzi NE, Truttmann AC, Faraone R, et al. Circulating ionized and total magnesium in end-stage kidney disease. *Nephron.* 1998;79(3):288–292. https://doi.org/10.1159/000045051
80. Pizzo HP, Perriloux A, Brophy E, Zaritsky JJ. Hypermagnesemia in a peritoneal dialysis patient. Poster presented at the Annual Dialysis Conference 2017, March 8, 2017, Long Beach, CA.
81. Wyskida K, Witkowicz J, Chudek J, Więcek A. Daily magnesium intake and hypermagnesemia in hemodialysis patients with chronic kidney disease. *J Ren Nutr.* 2012;22(1):19–26. https://doi.org/10.1053/j.jrn.2011.03.001

82. Wasana HM, Aluthpatabendi D, Kularatne WM, Wijekoon P, Weerasooriya R, Bandara J. Drinking water quality and chronic kidney disease of unknown etiology (CKDu): synergic effects of fluoride, cadmium and hardness of water. *Environ Geochem Health.* 2016;38(1):157–168. https://doi.org/10.1007/s10653-015-9699-7
83. Hayes W, Paglialonga F. Assessment and management of fluid overload in children on dialysis. *Pediatr Nephrol.* 2019;34(2):233–242. https://doi.org/10.1007/s00467-018-3916-4
84. Wuhl E, Flynn JT. Management of hypertension in pediatric dialysis patients. In: Warady BA,.Alexander SR, Schaefer F, eds. *Pediatric Dialysis.* 3rd ed. Springer; 2021:589–608.
85. Hothi DK, Rees L, Marek J, Burton J, McIntyre CW. Pediatric myocardial stunning underscores the cardiac toxicity of conventional hemodialysis treatments. *Clin J Am Soc Nephrol.* 2009;4(4):790–797.
86. U.S. Department of Agriculture Food and Drug Administration. *Dietary Guidelines for Americans 2020–2025*. Published December 2020. Accessed April 8, 2023. https://www.dietaryguidelines.gov/sites/default/files/2020-12/Dietary_Guidelines_for_Americans_2020-2025.pdf
87. Desloovere A, Renken-Terhaerdt J, Tuokkola J, et al. The dietary management of potassium in children with CKD stages 2–5 and on dialysis-clinical practice recommendations from the Pediatric Renal Nutrition Taskforce. *Pediatr Nephrol.* 2021;36(6):1331–1346. https://doi.org/10.1007/s00467-021-04923-1
88. Shaw V, Anderson C, Desloovere A, et al. Nutritional management of the infant with chronic kidney disease stages 2–5 and on dialysis. *Pediatr Nephrol.* 2023;38(1):87–103. https://doi.org/10.1007/s00467-022-05529-x
89. Parekh RS, Flynn JT, Smoyer WE, et al. Improved growth in young children with severe chronic renal insufficiency who use specified nutritional therapy. *J Am Soc Nephrol.* 2001;12(11):2418–2426. https://doi.org/10.1681/asn.v12112418
90. Rodriguez-Soriano J, Arant BS, Brodehl J, Norman ME. Fluid and electrolyte imbalances in children with chronic renal failure. *Am J Kidney Dis.* 1986;7(4):268–274. https://doi.org/10.1016/s0272-6386(86)80067-1

91. Warady BA, Ng E, Bloss L, Mo M, Schaefer F, Bacchetta J. Cinacalcet studies in pediatric subjects with secondary hyperparathyroidism receiving dialysis. *Pediatr Nephrol.* 2020;35(9):1679–1697. https://doi.org/10.1007/s00467-020-04516-4
92. McAlister L, Pugh P, Greenbaum L, et al. The dietary management of calcium and phosphate in children with CKD stages 2–5 and on dialysis-clinical practice recommendation from the Pediatric Renal Nutrition Taskforce. *Pediatr Nephrol.* 2020;35(3):501–518. https://doi.org/10.1007/s00467-019-04370-z
93. Shinaberger CS, Greenland S, Kopple JD, et al. Is controlling phosphorus by decreasing dietary protein intake beneficial or harmful in persons with chronic kidney disease? *Am J Clin Nutr.* 2008;88(6):1511–1518. https://doi.org/10.3945/ajcn.2008.26665
94. Benini O, D'Alessandro C, Gianfaldoni D, Cupisti A. Extra-phosphate load from food additives in commonly eaten foods: a real and insidious danger for renal patients. *J Ren Nutr.* 2011;21(4):303–308. https://doi.org/10.1053/j.jrn.2010.06.021
95. Sullivan CM, Leon JB, Sehgal AR. Phosphorus-containing food additives and the accuracy of nutrient databases: implications for renal patients. *J Ren Nutr.* 2007;17(5):350–354. https://doi.org/10.1053/j.jrn.2007.05.008
96. Uribarri J, Calvo MS. Hidden sources of phosphorus in the typical American diet: does it matter in nephrology? *Semin Dial.* 2003;16(3):186–188. https://doi.org/10.1046/j.1525-139x.2003.16037.x
97. Abercrombie EL, Greenbaum LA, Baxter DH, Hopkins B. Effect of intensified diet education on serum phosphorus and knowledge of pediatric peritoneal dialysis patients. *J Ren Nutr.* 2010;20(3):193–198. https://doi.org/10.1053/j.jrn.2009.10.011
98. Hanudel MR, Laster M, Ramos G, Gales B, Salusky IB. Clinical experience with the use of ferric citrate as a phosphate binder in pediatric dialysis patients. *Pediatr Nephrol.* 2018;33(11):2137–2142. https://doi.org/10.1007/s00467-018-3999-y
99. National Kidney Foundation. Clinical practice guidelines for bone metabolism and disease in children with chronic kidney disease. *Am J Kidney Dis.* 2003;42:S1-S201.

100. Wallot M, Bonzel KE, Winter A, Geörger B, Lettgen B, Bald M. Calcium acetate versus calcium carbonate as oral phosphate binder in pediatric and adolescent hemodialysis patients. *Pediatr Nephrol.* 1996;10(5):625–630. https://doi.org/10.1007/s004670050175
101. Ahlenstiel T, Pape L, Ehrich JH, Kuhlmann MK. Self-adjustment of phosphate binder dose to meal phosphorus content improves management of hyperphosphataemia in children with chronic kidney disease. *Nephrol Dial Transplant.* 2010;25(10):3241–3249. https://doi.org/10.1093/ndt/gfq161
102. Sedlacek M, Dimaano F, Uribarri J. Relationship between phosphorus and creatinine clearance in peritoneal dialysis: clinical implications. *Am J Kidney Dis.* 2000;36(5):1020–1024. https://doi.org/10.1053/ajkd.2000.19105
103. Kooienga L. Phosphorus balance with daily dialysis. *Semin Dial.* 2007;20(4):342–345. https://doi.org/10.1111/j.1525-139x.2007.00304.x
104. Portale AA, Wolf M, Jüppner H, et al. Disordered FGF23 and mineral metabolism in children with CKD. *Clin J Am Soc Nephrol.* 2014;9(2):344–353. https://doi.org/10.2215/cjn.05840513
105. Srivaths PR, Goldstein SL, Krishnamurthy R, Silverstein DM. High serum phosphorus and FGF 23 levels are associated with progression of coronary calcifications. *Pediatr Nephrol.* 2014;29(1):103–109. https://doi.org/10.1007/s00467-013-2575-8
106. Parekh RS, Carroll CE, Wolfe RA, Port FK. Cardiovascular mortality in children and young adults with end-stage kidney disease. *J Pediatr.* 2002;141(2):191–197. https://doi.org/10.1067/mpd.2002.125910
107. Lilien MR, Groothoff JW. Cardiovascular disease in children with CKD or ESRD. *Nat Rev Nephrol.* 2009;5(4):229–235. https://doi.org/10.1038/nrneph.2009.10
108. Mitsnefes MM. Cardiovascular complications of pediatric chronic kidney disease. *Pediatr Nephrol.* 2008;23(1):27–39. https://doi.org/10.1007/s00467-006-0359-0
109. Saland JM, Pierce CB, Mitsnefes MM, et al. Dyslipidemia in children with chronic kidney disease. *Kidney Int.* 2010;78(11):1154–1163. https://doi.org/10.1038/ki.2010.311

110. Milliner DS, Morgenstern BZ, Murphy M, Gonyea J, Sterioff S. Lipid levels following renal transplantation in pediatric recipients. *Transplant Proc.* 1994;26(1):112–114.
111. Akchurin OM, Kaskel F. Update on inflammation in chronic kidney disease. *Blood Purif.* 2015;39(1–3):84–92. https://doi.org/10.1159/000368940
112. Sylvestre LC, Fonseca KP, Stinghen AE, Pereira AM, Meneses RP, Pecoits-Filho R. The malnutrition and inflammation axis in pediatric patients with chronic kidney disease. *Pediatr Nephrol.* 2007;22(6):864–873. https://doi.org/10.1007/s00467-007-0429-y
113. Srivaths PR, Silverstein DM, Leung J, Krishnamurthy R, Goldstein SL. Malnutrition-inflammation-coronary calcification in pediatric patients receiving chronic hemodialysis. *Hemodial Int.* 2010;14(3):263–269. https://doi.org/10.1111/j.1542-4758.2010.00442.x
114. Asfaw M, Mingle J, Hendricks J, Pharis M, Nucci AM. Nutrition management after pediatric solid organ transplantation. *Nutr Clin Pract.* 2014;29(2):192–200. https://doi.org/10.1177/0884533614521242
115. McPartland KJ, Pomposelli JJ. Update on immunosuppressive drugs used in solid-organ transplantation and their nutrition implications. *Nutr Clin Pract.* 2007;22(5):467–473. https://doi.org/10.1177/0115426507022005467
116. U.S. Department of Agriculture Food and Drug Administration. Food Safety for Transplant Recipients. Accessed April 8, 2023. https://permanent.access.gpo.gov/gpo51931/UCM312793.pdf
117. Phillips S, DeMello S. Nutrition and the kidney donor. *J Ren Nutr.* 2014;24(2):E15–17. https://doi.org/10.1053/j.jrn.2013.12.001
118. Kasiske BL, Zeier MG, Chapman JR, et al. KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. *Kidney Int.* 2010;77(4):299–311. https://doi.org/10.1038/ki.2009.377
119. Wu Y, Cheng W, Yang XD, Xiang B. Growth hormone improves growth in pediatric renal transplant recipients—a systemic review and meta-analysis of randomized controlled trials. *Pediatr Nephrol.* 2013;28(1):129–133. https://doi.org/10.1007/s00467-012-2208-7

120. Litwin M, Niemirska A. Metabolic syndrome in children with chronic kidney disease and after renal transplantation. *Pediatr Nephrol.* 2014;29(2):203–216. https://doi.org/10.1007/s00467-013-2500-1
121. Stabouli S, Polderman N, Nelms CL, et al. Assessment and management of obesity and metabolic syndrome in children with CKD stages 2–5 on dialysis and after kidney transplantation-clinical practice recommendations from the Pediatric Renal Nutrition Taskforce. *Pediatr Nephrol.* 2022;37(1):1–20. https://doi.org/10.1007/s00467-021-05148-y
122. Hoppe B, Schaar B. The impact of nutrition and physical activity on long-term survival after pediatric solid organ transplantation. *Pediatr Transplant.* 2012;16(7):675–677. https://doi.org/10.1111/j.1399-3046.2012.01663.x
123. Filler G, Weiglein G, Gharib MT, Casier S. Ω3 fatty acids may reduce hyperlipidemia in pediatric renal transplant recipients. *Pediatr Transplant.* 2012;16(8):835–839. https://doi.org/10.1111/j.1399-3046.2012.01772.x
124. Guzzo I, Di Zazzo G, Laurenzi C, et al. Parathyroid hormone levels in long-term renal transplant children and adolescents. *Pediatr Nephrol.* 2011;26(11):2051–2057. https://doi.org/10.1007/s00467-011-1896-8
125. Fine RN WS, Olthoff KM, Kelly DA, Harmon WE, eds. *Pediatric Solid Organ Transplantation.* 2nd ed. Blackwell Publishing; 2007.
126. Salvatierra O, Jr., Singh T, Shifrin R, et al. Successful transplantation of adult-sized kidneys into infants requires maintenance of high aortic blood flow. *Transplantation.* 1998;66(7):819–823. https://doi.org/10.1097/00007890-199810150-00001
127. Salvatierra O, Jr., Millan M, Concepcion W. Pediatric renal transplantation with considerations for successful outcomes. *Semin Pediatr Surg.* 2006;15(3):208–217. https://doi.org/10.1053/j.sempedsurg.2006.03.007
128. Vega MRW, Cerminara D, Desloovere A, et al. Nutritional management of children with acute kidney injury-clinical practice recommendations from the Pediatric Renal Nutrition Taskforce. *Pediatr Nephrol.* 2023;38:3559–3580. https://doi.org/10.1007/s00467-023-05884-3

129. Star RA. Treatment of acute renal failure. *Kidney Int.* 1998;54(6):1817–1831. https://doi.org/10.1046/j.1523-1755.1998.00210.x
130. Fiaccadori E, Cremaschi E. Nutritional assessment and support in acute kidney injury. *Curr Opin Crit Care.* 2009;15(6):474–480. https://doi.org/10.1097/mcc.0b013e328332f6b2
131. Kyle UG, Akcan-Arikan A, Orellana RA, Coss-Bu JA. Nutrition support among critically ill children with AKI. *Clin J Am Soc Nephrol.* 2013;8(4):568–574. https://doi.org/10.2215/cjn.05790612
132. Kyle UG, Akcan-Arikan A, Silva JC, Goldsworthy M, Shekerdemian LS, Coss-Bu JA. Protein feeding in pediatric acute kidney injury is not associated with a delay in renal recovery. *J Ren Nutr.* 2017;27(1):8–15. https://doi.org/10.1053/j.jrn.2016.09.009
133. Vega MW, Juarez M, Lee JY, Srivaths P, Williams E, Akcan Arikan A. Quality improvement bedside rounding audits enhance protein provision for pediatric patients receiving continuous renal replacement therapy. *Pediatr Crit Care Med.* 2018;19(11):1054–1058. https://doi.org/10.1097/pcc.0000000000001698
134. Symons JM, Brophy PD, Gregory MJ, et al. Continuous renal replacement therapy in children up to 10 kg. *Am J Kidney Dis.* 2003;41(5):984–989. https://doi.org/10.1016/s0272-6386(03)00195-1
135. Goldstein SL, Vidal E, Ricci Z, et al. Survival of infants treated with CKRT: comparing adapted adult platforms with the Carpediem™. *Pediatr Nephrol.* 2022;37(3):667–675. https://doi.org/10.1007/s00467-021-05180-y
136. Jonckheer J, Vergaelen K, Spapen H, Malbrain M, De Waele E. Modification of nutrition therapy during continuous renal replacement therapy in critically ill pediatric patients: a narrative review and recommendations. *Nutr Clin Pract.* 2019;34(1):37–47. https://doi.org/10.1002/ncp.10231
137. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. *Hum Nutr Clin Nutr.* 1985;39(suppl 1):5–41.
138. López-Herce J, Sánchez C, Carrillo A, et al. Transpyloric enteral nutrition in the critically ill child with renal failure. *Intensive Care Med.* 2006;32(10):1599–1605. https://doi.org/10.1007/s00134-006-0271-x

139. Maxvold NJ, Smoyer WE, Custer JR, Bunchman TE. Amino acid loss and nitrogen balance in critically ill children with acute renal failure: a prospective comparison between classic hemofiltration and hemofiltration with dialysis. *Crit Care Med.* 2000;28(4):1161–1165. https://doi.org/10.1097/00003246-200004000-00041
140. Scheinkestel CD, Adams F, Mahony L, et al. Impact of increasing parenteral protein loads on amino acid levels and balance in critically ill anuric patients on continuous renal replacement therapy. *Nutrition.* 2003;19(9):733–740. https://doi.org/10.1016/s0899-9007(03)00107-2
141. Zappitelli M, Goldstein SL, Symons JM, et al. Protein and calorie prescription for children and young adults receiving continuous renal replacement therapy: a report from the Prospective Pediatric Continuous Renal Replacement Therapy Registry Group. *Crit Care Med.* 2008;36(12):3239–3245. https://doi.org/10.1097/ccm.0b013e31818f3f40
142. Lion RP, Vega MR, Smith EO, et al. The effect of continuous venovenous hemodiafiltration on amino acid delivery, clearance, and removal in children. *Pediatr Nephrol.* 2022;37(2):433–441. https://doi.org/10.1007/s00467-021-05162-0
143. Santiago MJ, López-Herce J, Urbano J, Bellón JM, del Castillo J, Carrillo A. Hypophosphatemia and phosphate supplementation during continuous renal replacement therapy in children. *Kidney Int.* 2009;75(3):312–316. https://doi.org/10.1038/ki.2008.570
144. Assadi F, Sharbaf FG. *Pediatric Continuous Renal Replacement Therapy: Principles and Practice.* Springer; 2016.
145. Nakamura AT, Btaiche IF, Pasko DA, Jain JC, Mueller BA. In vitro clearance of trace elements via continuous renal replacement therapy. *J Ren Nutr.* 2004;14(4):214–219.
146. Berger MM, Shenkin A, Revelly JP, et al. Copper, selenium, zinc, and thiamine balances during continuous venovenous hemodiafiltration in critically ill patients. *Am J Clin Nutr.* 2004;80(2):410–416. https://doi.org/10.1093/ajcn/80.2.410
147. Sgambat K, Moudgil A. Carnitine deficiency in children receiving continuous renal replacement therapy. *Hemodial Int.* 2016;20(1):63–67. https://doi.org/10.1111/hdi.12341

148. Sgambat K, Clauss S, Moudgil A. Effect of levocarnitine supplementation on myocardial strain in children with acute kidney injury receiving continuous kidney replacement therapy: a pilot study. *Pediatr Nephrol.* 2021;36(6):1607–1616. https://doi.org/10.1007/s00467-020-04862-3
149. Chioléro R, Berger MM. Nutritional support during renal replacement therapy. *Contrib Nephrol.* 2007;156:267–274. https://doi.org/10.1159/000102111
150. Moghal NE, Embleton ND. Management of acute renal failure in the newborn. *Semin Fetal Neonatal Med.* 2006;11(3):207–213. https://doi.org/10.1016/j.siny.2006.01.007
151. Abitbol CL, Bauer CR, Montané B, Chandar J, Duara S, Zilleruelo G. Long-term follow-up of extremely low birth weight infants with neonatal renal failure. *Pediatr Nephrol.* 2003;18(9):887–893. https://doi.org/10.1007/s00467-003-1186-1
152. Spinozzi NS NP. Nutrition support in the newborn intensive care unit. *J Ren Nutr.* 1996;6(4):188–197.
153. Wong Vega M, Vuong KT, Chmielewski J, et al. Nutrition for critically ill children and neonates requiring dialysis: Application of clinical practice recommendations. *Nutr Clin Pract.* 2023;38(suppl 2):S139–S157. https://doi.org/10.1002/ncp.11048
154. Groh-Wargo S TM, Hovasi Cox J, eds. *ADA Pocket Guide to Neonatal Nutrition.* American Dietetic Association; 2009.
155. Carmody JB, Charlton JR. Short-term gestation, long-term risk: prematurity and chronic kidney disease. *Pediatrics.* 2013;131(6):1168–1179. https://doi.org/10.1542/peds.2013-0009
156. Nelms CL. Optimizing enteral nutrition for growth in pediatric chronic kidney disease (CKD). *Front Pediatr.* 2018;6:214. https://doi.org/10.3389/fped.2018.00214
157. Rees L, Brandt ML. Tube feeding in children with chronic kidney disease: technical and practical issues. *Pediatr Nephrol.* 2010;25(4):699–704. https://doi.org/10.1007/s00467-009-1309-4
158. Rees L, Shaw V, Qizalbash L, et al. Delivery of a nutritional prescription by enteral tube feeding in children with chronic kidney disease stages 2–5 and on dialysis-clinical practice recommendations

from the Pediatric Renal Nutrition Taskforce. *Pediatr Nephrol.* 2021;36(1):187–204. https://doi.org/10.1007/s00467-020-04623-2
159. Coleman JE, Norman LJ, Watson AR. Provision of dietetic care in children on chronic peritoneal dialysis. *J Ren Nutr.* 1999;9(3):145–148. https://doi.org/10.1016/s1051-2276(99)90054-7
160. Hawkins NM, Coffey S, Lawson MS, Delves HT. Potential aluminium toxicity in infants fed special infant formula. *J Pediatr Gastroenterol Nutr.* 1994;19(4):377–381. https://doi.org/10.1097/00005176-199411000-00002
161. Warady BA, Kriley M, Belden B, Hellerstein S, Alan U. Nutritional and behavioural aspects of nasogastric tube feeding in infants receiving chronic peritoneal dialysis. *Adv Perit Dial.* 1990;6:265–268.
162. Bunchman TE, Wood EG, Schenck MH, Weaver KA, Klein BL, Lynch RE. Pretreatment of formula with sodium polystyrene sulfonate to reduce dietary potassium intake. *Pediatr Nephrol.* 1991;5(1):29–32. https://doi.org/10.1007/bf00852836
163. Le Palma K, Pavlick ER, Copelovitch L. Pretreatment of enteral nutrition with sodium polystyrene sulfonate: effective, but beware the high prevalence of electrolyte derangements in clinical practice. *Clin Kidney J.* 2018;11(2):166–171. https://doi.org/10.1093/ckj/sfx138
164. Raaijmakers R WJ, Houkes B, Heuval CS, Monnens LA. Pretreatment of various dairy products with sevelamer: effective P reduction but also a rise in pH. *Perit Dial Int.* 2008;29:S15A.
165. Ruley EJ, Bock GH, Kerzner B, Abbott AW, Majd M, Chatoor I. Feeding disorders and gastroesophageal reflux in infants with chronic renal failure. *Pediatr Nephrol.* 1989;3(4):424–429. https://doi.org/10.1007/bf00850220
166. Marlais M, Stojanovic J, Jones H, Cleghorn S, Rees L. Catch-up growth in children with chronic kidney disease started on enteral feeding after 2 years of age. *Pediatr Nephrol.* 2020;35(1):113–118. https://doi.org/10.1007/s00467-019-04382-9
167. Brewer ED. Pediatric experience with intradialytic parenteral nutrition and supplemental tube feeding. *Am J Kidney Dis.* 1999;33(1):205–207. https://doi.org/10.1016/s0272-6386(99)70285-4
168. Larson-Nath C, Goday P. Malnutrition in children with chronic disease. *Nutr Clin Pract.* 2019;34(3):349–358.

https://doi.org/10.1002/ncp.10274
169. Juarez MD. Intradialytic parenteral nutrition in pediatrics. *Front Pediatr.* 2018;6:267. https://doi.org/10.3389/fped.2018.00267
170. Council on Renal Nutrition of New England. Intradialytic parenteral nutrition. In: *Renal Nutrition Handbook for Renal Dietitians.* National Kidney Foundation; 1993:86–98.
171. Cherry N, Shalansky K. Efficacy of intradialytic parenteral nutrition in malnourished hemodialysis patients. *Am J Health Syst Pharm.* 2002;59(18):1736–1741. https://doi.org/10.1093/ajhp/59.18.1736
172. Haskin O, Sutherland SM, Wong CJ. The effect of intradialytic intralipid therapy in pediatric hemodialysis patients. *J Ren Nutr.* 2017;27(2):132–137. https://doi.org/10.1053/j.jrn.2016.10.003
173. Group KDIGOKGW. KDIGO clinical practice guidelines for glomerulonephritis. *Kidney Int Suppl.* 2012;2(2):139–274.
174. Nephrotic Syndrome in Children. National Kidney Foundation. Accessed April 8, 2023. https://www.kidney.org/atoz/content/nephrotic-syndrome-children#:~:text=Nephrotic%20syndrome%20is%20a%20kidney,%2C%20called%20glomeruli%2C%20are%20injured
175. Polderman N, Cushing M, McFadyen K, et al. Dietary intakes of children with nephrotic syndrome. *Pediatr Nephrol.* 2021;36(9):2819–2826. https://doi.org/10.1007/s00467-021-05055-2
176. AbuMaziad AS, Abusaleh R, Bhati S. Congenital nephrotic syndrome. *J Perinatol.* 2021;41(12):2704–2712. https://doi.org/10.1038/s41372-021-01279-0
177. Boyer O, Schaefer F, Haffner D, et al. Management of congenital nephrotic syndrome: consensus recommendations of the ERKNet-ESPN Working Group. *Nat Rev Nephrol.* 2021;17(4):277–289. https://doi.org/10.1038/s41581-020-00384-1
178. Hölttä T, Jalanko H. Congenital nephrotic syndrome: is early aggressive treatment needed? Yes. *Pediatr Nephrol.* 2020;35(10):1985–1990. https://doi.org/10.1007/s00467-020-04578-4
179. Ramello A, Vitale C, Marangella M. Epidemiology of nephrolithiasis. *J Nephrol.* 2000;13(suppl 3):S45–50. https://pubmed.ncbi.nlm.nih.gov/11132032/

180. Ayoob R, Wang W, Schwaderer A. Body fat composition and occurrence of kidney stones in hypercalciuric children. *Pediatr Nephrol.* 2011;26(12):2173–2178. https://doi.org/10.1007/s00467-011-1927-5
181. Selimoğlu MA, Meneks¸e E, Tabel Y. Is urolithiasis in children associated with obesity or malnutrition? *J Ren Nutr.* 2013;23(2):119–122. https://doi.org/10.1053/j.jrn.2012.03.004
182. VanDervoort K, Wiesen J, Frank R, et al. Urolithiasis in pediatric patients: a single center study of incidence, clinical presentation and outcome. *J Urol.* 2007;177(6):2300–2305. https://doi.org/10.1016/j.juro.2007.02.002
183. Lande MB, Varade W, Erkan E, Niederbracht Y, Schwartz GJ. Role of urinary supersaturation in the evaluation of children with urolithiasis. *Pediatr Nephrol.* 2005;20(4):491–494. https://doi.org/10.1007/s00467-004-1779-3
184. Carvalho-Salemi J, Moreno L, Michael M. Medical nutrition therapy for pediatric kidney stone prevention, part one. *J Ren Nutr.* 2017;27(1):e5–e8. https://doi.org/10.1053/j.jrn.2016.09.004
185. Pak CY. Medical management of urinary stone disease. *Nephron Clin Pract.* 2004;98(2):c49–53. https://doi.org/10.1159/000080252
186. Meschi T, Maggiore U, Fiaccadori E, et al. The effect of fruits and vegetables on urinary stone risk factors. *Kidney Int.* 2004;66(6):2402–2410. https://doi.org/10.1111/j.1523-1755.2004.66029.x
187. Schwaderer AL, Kusumi K, Ayoob RM. Pediatric nephrolithiasis and the link to bone metabolism. *Curr Opin Pediatr.* 2014;26(2):207–214. https://doi.org/10.1097/mop.0000000000000069
188. Carvalho-Salemi J, Moreno L, Michael M. Medical nutrition therapy for pediatric kidney stone prevention, part two. *J Ren Nutr.* 2017;27(2):e11–e14. https://doi.org/10.1053/j.jrn.2016.12.001
189. Kher KK, Schnaper HW, Makker SP, eds. *Clinical Pediatric Nephrology.* 2nd ed. Informa Healthcare; 2007.
190. Knoll T, Zöllner A, Wendt-Nordahl G, Michel MS, Alken P. Cystinuria in childhood and adolescence: recommendations for diagnosis, treatment, and follow-up. *Pediatr Nephrol.* 2005;20(1):19–24. https://doi.org/10.1007/s00467-004-1663-1

191. Caldas A, Broyer M, Dechaux M, Kleinknecht C. Primary distal tubular acidosis in childhood: clinical study and long-term follow-up of 28 patients. *J Pediatr.* 1992;121(2):233–241. https://doi.org/10.1016/s0022-3476(05)81194-1
192. Fulchiero R, Seo-Mayer P. Bartter Syndrome and Gitelman Syndrome. *Pediatr Clin North Am.* 2019;66(1):121–134. https://doi.org/10.1016/j.pcl.2018.08.010
193. Wesche D, Deen PM, Knoers NV. Congenital nephrogenic diabetes insipidus: the current state of affairs. *Pediatr Nephrol.* 2012;27(12):2183–2204. https://doi.org/10.1007/s00467-012-2118-8
194. Diagnosis and Treatment. NDI Foundation. Accessed April 7, 2023. https://ndif.org/ndi-facts/diagnosis-treatment/
195. Gupta A, Somers MJG, Baum MA. Treatment of primary hyperoxaluria type 1. *Clin Kidney J.* 2022;15(Suppl 1):i9–i13. https://doi.org/10.1093/ckj/sfab232

Test Your Knowledge Answers

1. The correct answer is **C**. The use of CKRT provides greater solute clearance, and thus electrolytes typically do not need to be limited and are often supplemented. Therefore, using a regular formula as opposed to a low-electrolyte renal formula is appropriate. Additionally, enteral products designed for renal patients often are more concentrated, which can cause GI discomfort. GI side effects are common in this population, and the use of transpyloric feeding improves tolerance. PN should be considered only if continued tolerance problems or poor gut perfusion/function is suspected.
2. The correct answer is **D**. Although dialysis losses may be minimal, vitamin B6 intake is often inadequate, likely due to the restriction of high-protein foods to limit excess intake of phosphorus and potassium. Studies indicate that 25-hydroxyvitamin D, in addition to the well-known 1,25-$(OH)_2$D, may have a role in bone metabolism and the prevention of hyperparathyroidism. Supplementation of 1,25-$(OH)_2$D is recommended to keep serum levels in the appropriate reference range. Although controversial in its role with homocysteine reduction and

cardiovascular implications, folic acid plays a part in anemia management.

3. The correct answer is **C**. CVD is the major cause of mortality in patients with CKD. Not only do patients with CKD typically have traditional risk factors, including HTN, dyslipidemia, and LVH, but they also have nontraditional markers or uremic factors that can contribute to CVD. These factors include inflammation, anemia, fluid overload, proteinuria, abnormal calcium and phosphorus levels, dyslipidemia, and vascular injury.
4. The correct answer is **A**. Studies indicate nPCR is a superior marker of nutrition status in adolescent children on maintenance HD. In these studies, serum albumin was a poor indicator of nutrition status. An nPCR of <1 g/kg/d was a strong predictor of weight loss in adolescent patients. However, an increased risk of mortality has also been associated with hypoalbuminemia. Therefore, serum albumin may be used as a nutrition status marker as well, with recognition of its limitations in the setting of inflammation or hypervolemia when low values of albumin may result.

23

Gastrointestinal Disease

Jill Dorsey, MD, MS; Donald George, MD; and Elizabeth Bobo, MS, RD, LDN, CNSC, FAND

Learning Objectives

1. Explain the mechanisms leading to nutrition deficiency in gastrointestinal diseases.
2. Know the pathophysiology of the common gastrointestinal diseases in children and how it alters the corresponding nutrition support.
3. Use nutrition support as a therapy in the treatment of inflammatory bowel disease, celiac disease, and functional gastrointestinal disorders.

Introduction

The gastrointestinal (GI) tract is the original biologic route for transforming food into nutrition. The GI tract can take the wide variety of foods that humans ingest and break them down into the basic nutrients that humans require. The tasks of ingesting, processing, digesting, and absorbing nutrients are coordinated through a complex network of cellular, neural, and hormonal factors that help direct the function of the GI tract. GI diseases may cause malnutrition by affecting nutrient intake, digestion, or absorption or by altering nutrient requirements. When dealing with a patient who has a

GI disease, the clinician must determine if the patient is malnourished, whether nutrition deficiencies are likely to occur, and whether the patient would benefit from nutrition therapy. This chapter reviews common GI diseases and their impact on the ability of the GI tract to function as the primary source of nutrition.

Mechanisms of Nutrition Deficiency

Mechanisms responsible for nutrition deficiency are summarized in Table 23-1 and described in the following sections.

TABLE 23-1. Mechanisms of Nutrition Deficiency

Mechanism	Examples
Disordered ingestion	Anorexia Dental disease Dysphagia of any cause Esophagitis Inadequate access to food
Failure of digestion	Pancreatic enzyme deficiency Sucrase-isomaltase deficiency Cholestasis with failure of bile salt secretion
Failure of absorption	Short bowel syndrome due to surgery Celiac disease Inflammatory bowel disease Liver disease Motility disorders
Increased needs	Fever Work of breathing Certain medications

Disordered Ingestion

Disordered ingestion may result from refusal to feed, difficulty swallowing, or from being presented with an inadequate diet. Refusal to feed may be related to pain with swallowing, abdominal pain with eating, or failure to protect the airway during feeding.

Difficulty swallowing can be related to oral, neurological, or esophageal diseases. The inability to chew or produce saliva also interferes with the ability to swallow. In addition, many behavioral problems (eg, food aversion, depression, autism, eating disorders) influence the ability to ingest

nutrients. GI inflammation or vomiting of any cause will limit the ability to eat.

Failure of Digestion

Failure of digestion occurs in diseases that affect the production of digestive enzymes secreted from the stomach (pepsin), pancreas (lipase, amylase, proteases), or the surface of the GI tract (lactase or sucrase-isomaltase). In addition, bile acids are important in the solubilization of fat, and patients with cholestasis of any cause will have impaired digestion.

Failure of Absorption

Failure of absorption occurs if an inadequate surface area is available due to mucosal injury or surgical shortening of the GI tract, or a system failure may be involved in specific nutrient absorption (eg, pernicious anemia, glucose-galactose malabsorption). Lack of luminal factors such as biliary secretions impairs absorption, especially of lipids. Deficiency of luminal bile salts occurs in liver disease, gallbladder disease, or disease of the biliary ducts.

Additionally, absorption may not occur despite an adequate surface area. Congenital disorders such as microvillus inclusion disease preclude normal absorption, while disorders of motility of the bowel, such as achalasia, gastroparesis, or pseudo-obstruction, may interfere with absorption by inhibiting the movement of the food bolus and chyme through the intestine.

Increased Needs

A hypermetabolic state resulting in increased energy needs can occur in diseases with fever, increased breathing effort, or because of certain medications needed for treatment.

Nutrition deficiency usually involves multiple mechanisms. For example, a patient with Crohn’s disease may have a poor appetite or be unable to eat because of pain or oral ulcers. In addition, there may be small bowel inflammation or intestinal resection that affects absorption (eg, vitamin B12 in the terminal ileum). Some patients with Crohn’s disease have lactose deficiency and may benefit from lactose restriction.

Furthermore, the presence of fever or underlying inflammation may increase energy and protein needs.

Nutrition Assessment

Nutrition assessment is an essential component of the evaluation of all children. It cannot be assumed that all children eat normally, and a detailed diet history is important. Monitoring of growth should be part of each routine well-child examination. Assessment of both linear and ponderal growth of the child or adolescent is central to the evaluation of nutrition status. Alterations in linear growth patterns and weight gain may be the earliest manifestation of disease.

Malnutrition is commonly diagnosed in hospitalized patients and is also a common comorbidity in patients with GI diseases.[1,2] Malnutrition during illness may complicate the response to therapies or impair recovery (see Table 23-2). Nutrition assessment is thus an integral part of both the initial and ongoing evaluation of all children with acute and/or chronic disease and is of crucial importance when evaluating children with GI disease.[3,4]

TABLE 23-2. Gastrointestinal Nutrient Deficiencies

Nutrient	Signs/Symptoms of Deficiency	Laboratory Markers
Iron	Fatigue Microcytic anemia	↓ Hemoglobin ↓ Hematocrit ↓ MCV ↑ RDW ↓ % TIBC ↓ Ferritin ↓ Serum iron
Folate	Megaloblastic anemia Glossitis Diarrhea Forgetfulness	↓ Serum folate ↓ Red blood cell folate ↑ MCV
Vitamin B12	Megaloblastic anemia Ataxia Diarrhea Mental status changes Paresthesias Glossitis	↑ MCV ↓ Hemoglobin ↓ Serum vitamin B12
Calcium	Osteopenia Osteoporosis Tetany	↓ Serum total calcium ↓ Serum ionized calcium
Vitamin D	Bone pain Muscle weakness Tetany Osteomalacia Rickets	↑ Serum alkaline phosphatase ↓ 25-Hydroxyvitamin D ↑ PTH
Vitamin A	Night blindness Decreased appetite Decreased immune function Hyperkeratosis	↓ Plasma vitamin A
Vitamin K	Bleeding Bruising	↑ PT
Vitamin E	Hemolytic anemia Truncal ataxia Hyporeflexia or areflexia	↓ Serum creatinine; creatinuria ↓ Serum vitamin E to total serum lipid ratio
Zinc	Diarrhea Dry skin Skin sloughing on palms	↓ Serum alkaline phosphatase ↓ Serum zinc[a]

Nutrient	Signs/Symptoms of Deficiency	Laboratory Markers
	Mental status changes Hair loss Growth stunting Anorexia	↓ Urinary zinc[b]
Magnesium	Muscle cramps Bone pain Nausea Seizures	↓ Serum magnesium

Abbreviations: MCV, mean corpuscular volume; PT, prothrombin time; PTH, parathyroid hormone; RDW, red cell distribution width; TIBC, total iron-binding capacity.

[a] Zinc binds to serum proteins, which can make levels appear low if protein levels are depleted.

[b] Associated with disease status.

Information derived from Groleau et al4 and Green Corkins and Teague.[5]

A thorough nutrition assessment includes 6 key focus areas:

(1) food/nutrition-related history
(2) anthropometrics
(3) biochemical information
(4) medical tests/procedures
(5) nutrition-focused physical findings
(6) client/patient history[5]

When obtaining a nutrition-focused history, it is important to inquire about social circumstances that may affect the client's ability to consume an appropriate diet. Asking what vitamin/mineral/herbal products the client is taking, if there are any recent changes to weight or dietary intake, any gastrointestinal symptoms that have developed, or any difficulties with chewing and/or swallowing are also informative.[5]

Objective assessment includes information from clinical, anthropometric, and laboratory evaluations. Clinical data include the diagnosis, current medical or surgical problems, allergies, and medications that may affect nutrition support options. Measures of nutrition status

include growth indices (both previous and current), current weight, mid-upper arm circumference, and skinfold thickness. It is standard practice to measure these parameters in patients at risk for chronic malnutrition, such as those with pancreatic insufficiency, inflammatory bowel disease, celiac disease, or short bowel syndrome, in which maldigestion or malabsorption may be prominent. It is rare to find many specific findings of severe malnutrition in children. Wasting is observed most often, sometimes accompanied by edema. The determination of body mass index (BMI) for children ≥2 years of age provides important information regarding proportionality. In children <2 years of age, weight for length is used. For more detailed information on nutrition assessment, refer to Chapter 30, "Assessment of Nutrition Status by Age and Determining Nutrient Needs."

Examination of the abdomen requires specific attention. Abdominal tenderness, abdominal distention, and the presence of bowel sounds not only provide helpful clues to the nature of the disease process but also influence treatment decisions. There may be other findings that suggest nutrient deficiency; thus, a nutrition-focused physical exam is an essential part of the overall nutrition assessment. For example, examining the hair, noting both texture and distribution may suggest a specific deficiency of nutrients such as protein or biotin.[6] Angular stomatitis and dermatitis may suggest riboflavin deficiency. Dermatitis may represent a variety of nutrient deficiencies, such as essential fatty acids, zinc, or niacin.[6] Dystrophic nails, spooning of the nails, or pallor of the conjunctiva or skin may suggest iron deficiency. Peripheral neuropathy may be observed with numerous vitamin deficiencies, including thiamin, B6, B12, and niacin. Zinc deficiency is often manifested by alopecia and perioral or perianal rash. Bowing of the legs, tetany, or rickets suggests vitamin D deficiency. Petechiae, bruising of the skin, or bleeding gums may indicate vitamin K deficiency, as apparent in liver disease. For additional information, refer to Chapter 24, "Hepatic Disease."

Gastroesophageal Reflux

Gastroesophageal reflux (GER) is the passage of gastric contents into the esophagus with or without regurgitation. It is a common occurrence in

healthy infants, children, and adults.[7–9] Regurgitation occurs daily in 40% of healthy infants and usually resolves spontaneously by 12 to 24 months of age.[10–12] Regurgitation occurs at least weekly in 12% to 15% of children ages 3 to 17 years.[8] Gastroesophageal reflux disease (GERD) refers to reflux-associated tissue damage (eg, esophagitis) or symptoms severe enough to impair health and quality of life.[13]

The genesis of reflux-related injury and reflux symptoms is not the same. Each relates to a combination of factors that lead to an excessive number of reflux events, impaired clearance of material from the esophagus, increased acidity, decreased buffering of the refluxed material, or impaired protection of the esophageal or supraesophageal mucosa.[14] The most important mechanism causing GER is transient lower esophageal sphincter relaxations.[15] Delayed gastric emptying, increased intra-abdominal pressure, and chronically reduced lower esophageal sphincter resting pressure have also been implicated.[16] Studies of stomach function have demonstrated that gastric emptying is related to both the composition and caloric density of the feedings. Diets higher in fat or caloric density will slow the emptying and thereby promote reflux.[17]

GER and GERD have a variety of presentations that vary with age. Regurgitation associated with poor growth, irritability, or airway compromise are common reasons for evaluation in infancy. Heartburn and epigastric abdominal pain are more common complaints in older children and adolescents. Abnormal posturing (Sandifer's syndrome) and acute life-threatening events are often manifestations in infants with GERD but are rarely seen in older children or adults.

Regurgitation in infancy is rarely serious. Most instances of infantile GER resolve spontaneously. However, a minority of infants may have severe or prolonged problems that lead to caloric insufficiency and malnutrition. Some severe cases result in malnutrition, possibly from persistent vomiting, difficulty feeding (coughing or gagging), and/or feeding aversion with a subsequent lack of intake. In these cases, specialized nutrition support is needed. Specialized support may be accomplished orally with the use of certain formulas or supplements. However, some patients with complicated GER or GERD benefit from alternate enteral access. Factors that influence this decision include

aspiration risk, degree of malnutrition, child's age, associated anatomic or neurological problems, and expected duration of treatment.

Disordered ingestion and nutrient losses because of vomiting or regurgitation dominate the clinical picture. In children with poor weight gain or weight loss, the focus should be on modalities to increase calories. Insufficient oral intake can be related to pain associated with eating, food aversion because of vomiting, or dysphagia associated with esophagitis.

Treatments to reduce emesis in infants with regurgitation include smaller feedings, thickening the formula with cereal, commercial thickeners or pre-thickened formula, and positioning. Smaller, more frequent feeds are often suggested but are sometimes impractical and poorly tolerated by babies and parents.[18] In neonates with dysphagia, the frequency of GER events is reduced if feeds are given over a longer duration.[19] Feeding in an upright position and maintaining the infant with the head elevated for a period after eating is often recommended, although data demonstrating effectiveness are sparse. Because of the risk of sudden infant death syndrome, prone positioning is acceptable only if the infant is awake and carefully observed.[18,20]

Thickening of feedings has been shown to reduce symptomatic GER. Agents commonly used to thicken formula include rice cereal, guar gum, carob bean gum, locust bean gum, pectin, pregelatinized waxy rice starch, and soy polysaccharides.[21,22] Of note, for infants who are receiving human milk instead of formula, rice cereal is not recommended because the mammary amylase degrades cereal. Instead, xanthum gum or a carob bean thickener is recommended.[20] Thickened formulas lessen the frequency of emesis but may contribute to some side effects.

Despite a reduced number of episodes of obvious reflux and emesis, pH probe studies do not indicate a reduction in exposure to acid in the esophagus.[23,24] Thickening of feeds does not reduce apnea events in preterm infants.[25] Furthermore, studies found increased postprandial coughing in infants fed thickened formula, suggesting continued reflux despite improvement in emesis.[26] Reports have indicated necrotizing enterocolitis in some preterm infants given specific thickening agents.[27] Because of this concern, carob bean thickeners should not be used for

infants who are <42 weeks gestation and xanthum gum thickeners should not be used for children who are <1 year of age.[20]

The effect of thickened formulas on the macronutrient content and micronutrient absorption is also a concern. Thickening formulas with rice cereal alters the macronutrient composition of the formula, resulting in additional calories and protein. Importantly, indigestible carbohydrate thickening agents, such as locust bean gum, have been linked with decreased bioavailability of calcium, zinc, and iron. Conversely, digestible carbohydrate thickening agents, such as pregelatinized waxy rice starch, have not been linked with decreased nutrient absorption.[28] Because of the lack of definite data regarding the efficacy of thickened formulas, it is recommended that they only be used under medical supervision.[20]

Milk-protein intolerance may have a clinical presentation that mimics GERD. A 2-to-4-week trial of an extensively hydrolyzed protein or an amino-acid-based formula may be beneficial. For infants receiving human milk, a 2-to-4-week trial of a maternal exclusion diet that restricts dairy and possibly egg protein is recommended.[20,29]

In older children with GER, nutrition therapy is dependent on individual tolerance to various foods. Obesity and exposure to alcohol and tobacco smoke may worsen GER. Sparse evidence supports the avoidance of caffeine (coffee in particular), peppermint, spearmint, chocolate, and spicy foods.[30–32] The fat content of a meal does not affect esophageal reflux except in the presence of delayed gastric emptying.[33,17] Nutritional rehabilitation can improve symptoms of GER. Data suggest that GER improves in children who are malnourished and neurologically hindered when they are nutritionally repleted.[34]

Medications used to treat GERD include antacids, proton pump inhibitors (PPIs), and H2 histamine receptor antagonists. These medications are associated with various nutrition-related side effects (see Table 23-3). There is concern about decreased absorption of supplemental iron along with possible infection risks associated with long-term PPI usage.[35,36] Prokinetic medications are suggested to improve gastric emptying. Metoclopramide is often prescribed, although there is limited evidence supporting its effectiveness. It reduces symptoms, but it is also associated with side effects, therefore it is now rarely used in children.[20,37]

Erythromycin also has prokinetic activity and improves gastric emptying, however, it has not been shown to improve GER symptoms. These medications are used mostly in patients with weight loss or failure to gain weight related to GERD.

TABLE 23-3. Potential Effects of Medications Used for Gastroesophageal Reflux Disease

Side Effect	Proton Pump Inhibitor	H2 Histamine Receptor Antagonist
Diarrhea	X	X
Constipation	X	X
Abdominal pain	X	X
Nausea/vomiting	X	X
Anorexia	X	
Anemia	X	
Weight gain/loss	X	
Hepatotoxicity		X

Information derived from Rosen et al.[20]

Clinical outcomes of GERD can be measured in various ways. Lower esophageal pH recording is accepted as a valid measure of GER; however, serial recordings are rarely used in clinical practice. Symptom reduction (frequency of vomiting in infants or episodes of heartburn in older children and adolescents) can be monitored by recall or the use of diaries with symptom severity and frequency estimates. For GERD causing poor weight gain, improved weight gain over time is the accepted measure.

Celiac Disease

Celiac disease is a chronic T-cell–mediated autoimmune inflammatory disorder, characterized by damage to the small intestinal mucosa in genetically susceptible individuals, due to abnormal reactions to the gliadin fraction of wheat gluten and similar peptides present in barley and rye. A

specific peptide fragment of gliadin, comprising 33 amino acids, is resistant to degradation by pancreatic, gastric, or small intestinal enzymes. This peptide can pass through the epithelial barrier and interact with immune cells of the intestine. Immune responses affecting both adaptive and innate immunity promote an inflammatory reaction in the lamina propria of the intestinal wall leading to villus atrophy.

The genetic factors for celiac disease are linked to the human leukocyte antigen system (HLA), specifically HLA-DQ2/DQ8, which regulates the immune response. It is diagnosed by a combination of symptoms, positive celiac antibodies, and duodenal histology.

The prevalence of celiac disease has increased significantly in the last 30 years because of increased knowledge and awareness as well as the widespread use of highly sensitive and specific diagnostic tests for celiac disease. The European Society for Paediatric Gastroenterology Hepatology and 2020 Nutrition guidelines recommend a tissue tTG-IgA test, which is highly sensitive and specific and less costly compared to an EMA-IgA antibody test, as an initial screening test for suspected celiac disease and the total IgA test to rule out selective IgA deficiency.[38] The analysis of a deamidated gliadin peptide IgA (DGP-IgA) test is recommended for children under 2 years of age. If there is IgA deficiency, the tTG-IgG test, the EMA-IgG test, or the DGP-IgG test should be performed.[38–40]

If serological tests are negative for tTG-IgA and the total IgA level is normal, celiac disease is unlikely. In this situation, possible reasons leading to the false negative tTG result should be considered, including low gluten intake, protein-losing enteropathy, immunosuppressive drug use, and patients being under 2 years of age.[38,40]

In the past, celiac disease was thought to be uncommon and was diagnosed mainly in patients who had typical symptoms (see Table 23-4). However, population studies using serologic markers now suggest that celiac disease occurs in 1.4% of the population.[40] Little difference exists in the rates in Europe (0.8%) compared with South America (0.4%), North America (0.5%), Africa (0.5%), and Asia (0.6%).[39,40] The duration of breastfeeding and the timing of the infant's introduction to gluten seem to have no impact on the risk of developing celiac disease, even in those at high risk.

TABLE 23-4. Presentation of Celiac Disease

Type of Presentation	Signs and Symptoms
Typical (usually young)	Weight loss Failure to grow Vomiting Diarrhea Bloating Anorexia Abdominal pain
Atypical (adolescent or young adult)	Constipation Short stature Dermatitis Herpetiformis Osteopenia Elevated liver enzymes Arthritis Iron deficiency Anemia Dental enamel defects
Silent (any age)	No obvious signs or symptoms; patient identified when tested because of risk factors and, on biopsy, has typical enteropathy
Latent (any age)	Mild or nonspecific symptoms identified by screening; positive serology but normal biopsy; may develop typical disease at a later time

Since the development and implementation of screening of patients "at risk," it is now clear that some patients with celiac disease are asymptomatic, even despite significant intestinal mucosal injury. Patients may also have symptoms that do not immediately call to mind intestinal disease. The typical presentation of celiac disease usually occurs in the first few years of life and manifests as diarrhea with growth failure and anemia. It is now recognized that celiac disease can present at any age following the inclusion of gluten in the diet and has a variety of manifestations, many of which are extraintestinal in nature. Older children and adolescents may present with constitutional symptoms such as fatigue or lassitude. Nonspecific GI symptoms may be mild or even absent. Patients with celiac

disease often have derangements of bone and mineral metabolism, and idiopathic osteopenia may be the sole clinical feature.[41,42]

Because of the recognition of atypical presentations of celiac disease, screening with serology is offered to patients with growth failure or short stature, recurrent abdominal pain, irritable bowel syndrome (IBS), unexplained diarrhea or iron deficiency, or delayed puberty. In addition, serologic testing is indicated in children with type 1 diabetes mellitus, Down syndrome, Turner syndrome, Williams syndrome, or autoimmune thyroid or liver disease. First-degree relatives of patients with celiac disease should also be screened.[42]

The effects of celiac disease on nutrition status can be profound. A patient may have linear and/or ponderal growth failure. Diarrhea and weight loss may also be present. In addition, vitamin and mineral deficiencies may be noted at the time of diagnosis. A thorough physical assessment of the patient and an assessment of laboratory values when indicated are necessary to identify such deficiencies. In particular, either microcytic or macrocytic anemia may be present due to the impaired absorption of iron or folic acid in the proximal intestine[43] or of B12 in the distal small bowel. Other nutrients of concern include but are not limited to fat-soluble vitamins (A, D, E, and K), zinc, and calcium. Special attention is paid to vitamin D status. Inadequate calcium may be due to malabsorption or poor dietary intake. Calcium supplementation may be needed. Lactose intolerance is common in untreated patients due to damage to the villi. Most often this improves with treatment; however, “adult-type” lactase deficiency not associated with intestinal injury may complicate the clinical picture.

The management of celiac disease includes the complete avoidance of all gluten and correction of any vitamin or mineral deficiencies. The fundamental basis of the gluten-free (GF) diet includes avoidance of wheat, barley, and rye.[44] Oats that are specifically labeled as being GF may be consumed in the diet; however, general commercial oats should not be consumed secondary to cross-contamination with wheat, rye, or barley in processing.[45] It is recommended that patients introducing pure, uncontaminated oats into their diet be monitored for clinical symptoms such as abdominal discomfort (often a product of increased dietary fiber) or an allergy that can develop. The consumption of a moderate amount (¼ cup

dry rolled pure oats per day) is generally thought to be appropriate for children following a GF diet.[46] For a list of gluten-containing grains and GF grains, see Table 23-5.

TABLE 23-5. Grains and Gluten[a]

Gluten Containing	Gluten Free
Barley	Amaranth
Bulgur	Arrowroot
Couscous	Buckwheat
Dinkle (spelt)	Corn
Durum	Flaxseed
Einkorn	Rice
Emmer	Millet
Farina	Milo
Fu	Potato flour
Graham flour	Quinoa
Kamut	Sorghum
Seitan	Soy
Semolina	Tapioca
Rye	Tef
Wheat	Taro flour
Triticale	Urd

[a] This is not an all-inclusive list.

The GF diet is more cumbersome than simply avoiding the grains listed as containing gluten. There are many secondary hidden sources of gluten in processed foods in the form of additives, fillers, and texture stabilizers. Detailed patient instruction on label reading and avoiding cross-contamination is crucial for proper adherence to the GF diet. When replenishing vitamin and mineral stores with dietary supplements, it is important to read labels for the presence of gluten.

GF diets are sometimes recommended for the treatment of other conditions that are not celiac disease. Because a GF diet has a profound effect on serologic testing, the GF diet should be considered only after a thorough evaluation of the possibility of celiac disease. Placing a patient on a GF diet before celiac disease is excluded or confirmed is detrimental because this can interfere with the ability to make a clear-cut diagnosis, which is crucial because the GF diet for celiac disease is strict, expensive, and lifelong.[38]

In patients with celiac disease, the removal of gluten from the diet usually results in clinical and histological recovery. Specialized oral feedings or enteral nutrition (EN) are rarely necessary in a patient with celiac disease. Parenteral nutrition (PN) is not used unless some other indication exists deeming it necessary.

Because of difficulties encountered with the GF diet, medications have been tried in the treatment of celiac disease. Medications that promote the digestion of gluten or improve mucosal integrity are being studied. However, currently, there is no alternative to the GF diet in the treatment of celiac disease.[41,42]

When the diagnosis of celiac disease is confirmed, routine nutrition follow-up of the child is necessary to monitor growth parameters, promote adherence to the diet, and ensure proper nutrition, particularly because many of the GF products are not fortified. The ongoing monitoring of vitamins (especially A, D, B12, and folate), as well as the assessment of anemia and markers of bone health, is suggested.[47] Fortunately, with proper nutrition and adherence to the GF diet, bone density in children returns to normal 1 year after initiating the diet.[48]

Clinical outcome is measured by resumption of normal growth and weight gain and by monitoring serologic markers, especially tTG-IgA. Failure of tTG-IgG and IgA levels to return to normal values after adherence to a GF diet for 6 to 12 months warrants further inspection of the child's diet for inadvertent gluten consumption.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) refers to chronic inflammation anywhere along the GI tract. The term includes Crohn's disease, ulcerative colitis, and indeterminate colitis (ie, IBD with features that do not allow clear distinction between Crohn's disease and ulcerative colitis). The incidence and prevalence of pediatric IBD has been increasing.[49] IBD may present at any age. Peak age of onset of Crohn's disease in children is in the second decade of life. The most important risk factor for developing IBD in pediatrics is a positive family history.

Inflammation of the bowel leads to a number of derangements that culminate in diarrhea, GI bleeding, and abdominal pain. Other symptoms depend on the location of inflammation within the GI tract. For example, vomiting is more prominent in patients with gastric or small bowel disease. The most common presentation is a patient with abdominal pain and diarrhea. Stools may be bloody. Weight loss is common, especially in patients with Crohn's disease. However, nonspecific manifestations of the disease are often the initial presentation, and failure to recognize their importance may lead to delay in the diagnosis. Joint pain and swelling, skin rashes, muscle pain, elevated liver enzymes, or eye changes (uveitis, iritis, or episcleritis) may be present prior to any specific GI manifestation. Oral ulcerations can range from painless to severe pain with bleeding. It is well recognized that the deterioration of linear and ponderal growth may precede the development of more specific symptoms.

The effect of IBD on nutrition status is multifaceted. Growth, bone health, and macronutrient and micronutrient stores are commonly affected, and malnutrition is common.[50] Nutrition assessment of children with IBD includes measurements of weight, height, and calculation of BMI. These values should be plotted and followed serially on appropriate growth charts.[51] The importance of tracking these measurements is emphasized by the fact that upon diagnosis the majority of children with IBD will have growth failure.[52] In fact, reduced linear growth velocity may precede GI manifestations of IBD by months or even years.[53–55] Criteria for defining growth failure include a height z-score ≤ -1.9 (adjusted for low midparental height), a height velocity z- score ≤ -2 or a decline in height z-score of $\geq$

2.[56] Males may be more susceptible to growth failure, but all children with IBD are at risk.[57] Factors affecting risk include malnutrition, treatment modality, and the extent and severity of intestinal inflammation.

Malnutrition in IBD patients is multifactorial and includes energy losses, increased requirements, malabsorption, and decreased energy intake due to diarrhea, abdominal pain, and other disease-related side effects.[58] Appetite-related cytokine activity in the inflammatory process further contributes to malnutrition.[59] Inflammatory cytokines have also been shown to reduce insulinlike growth factor 1 (IGF-1).[60] Children with active Crohn's disease often have lower serum IGF-1 levels than controls. In addition, chronic usage of corticosteroids as treatment can suppress IGF-1 and also decrease osteoblast activity.[61] Data indicates that nutrition therapy in comparison to corticosteroid usage is beneficial in the treatment of Crohn's disease and spares linear growth.[62–64]

Assessment of nutrition status includes sufficiency of vitamin and mineral stores. Analyses of dietary records and/or 24-hour food recall, as well as laboratory values, help assess micronutrient status. Commonly deficient nutrients include iron, folate, vitamin B12, vitamin D, calcium, zinc, and magnesium.[65] For information regarding deficiency signs/symptoms and laboratory markers, see Table 23-2. Reduced iron stores occur because of decreased intake, reduced absorption, and increased losses (ie, blood loss).[65] Often, iron supplementation is required along with a diet rich in iron and vitamin C to correct the deficiency. Laboratory values to monitor iron status (other than iron) include hemoglobin, reticulocyte count, mean corpuscular volume, red blood cell distribution width, ferritin, transferrin saturation.[56,59] However, one should use caution in interpreting the ferritin since it is an acute-phase reactant and can be elevated during episodes of acute inflammation.

Folate stores may be affected by insufficient intake because many good sources of folate (eg, leafy green vegetables) are often not tolerated by children with active inflammation. In addition, medications used in disease treatment, such as methotrexate and sulfasalazine, have direct and deleterious effects on folate metabolism. Children on these medications require folate supplementation.[51]

Vitamin B12 deficiency may occur in children with surgical resection of the stomach or involvement of the terminal ileum, as well as in cases of bacterial overgrowth. Notably, deficiency may be masked by folate supplementation. Deficiency is corrected by intramuscular injection, oral supplementation, or nasal gel.[65]

Maintenance of adequate calcium and vitamin D stores is imperative in children with IBD, particularly in those receiving steroid therapy because of the relationship between steroid usage and decreased bone mineral density. Lactose intolerance often limits the consumption of milk and dairy products rich in these nutrients.[65] Supplementation may be required to obtain values within normal limits. Research suggests that supplementation of vitamin D above the standard recommendation may be necessary to achieve an appropriate 25-hydroxyvitamin D level.[66] Children with Crohn's disease of the upper intestine and children with darker complexions may have an increased need for vitamin D supplementation.[67] The winter season may also dictate increased need. Vitamin D replacement recommendations for children with IBD suggest a cumulative dose at least 400,000 IU if the 25-hydroxy vitamin D level is <20 ng/mL (= 50,000 IU/wk for 8 wk) and a minimum of 250,000 IU if the level is between 20 and 31 ng/mL.[68]

Zinc and magnesium deficiencies are associated with increased stool output and may require supplementation. Treatment is usually given empirically as the interpretation of serum zinc levels is sometimes difficult. Oral magnesium supplementation is important, but it can worsen diarrhea if it is administered at increased doses over a short time frame.

The energy and protein needs of the child with IBD are based on collected anthropometric data as well as disease status. In the adequately nourished child with IBD, resting energy expenditure is no different than in healthy children.[51] However, in children with insufficient energy stores and increased inflammation, energy needs may be elevated 5% to 35% above estimated needs. Protein supplementation has no guidelines. However, it may be prudent to increase protein delivery in a child with inflammation or infection, as well as postoperatively.[65] When nutrient needs cannot be met with oral intake alone, the preferred route of nutrition support is EN.

PN may be indicated if the enteral route is not feasible or if it is insufficient to completely meet nutrient needs. Furthermore, PN may be

indicated preoperatively and/or postoperatively or for patients with fistulas. For more information regarding PN and surgery, see chapter 29 (Surgery).

There are 3 primary nutrition interventions used in the treatment of pediatric Crohn's disease: (1) exclusive enteral nutrition (EEN), (2) the Specific Carbohydrate Diet (SCD), and (3) the Crohn's Disease Exclusion Diet (CDED). Evidence suggests that EEN is as effective in inducing disease remission as corticosteroid usage in children with active Crohn's disease.[69,70] This method of treatment may be particularly beneficial in children with ileal or ileocolonic Crohn's disease. With EEN as primary therapy, 100% of the child's nutritional needs are met with a nutrition supplement drink, either orally or with tube feedings, for approximately 8 to 12 weeks.[62] The caloric provision is initially based on the child's estimated energy requirement if indirect calorimetry is not available. Weight gain and reports of hunger should be monitored to indicate if an increase in the calorie goal is indicated. Additional fluid sources will likely be needed to meet maintenance fluid requirements. Outcomes are not significantly different for patients receiving a polymeric, semi-elemental, or elemental formula.[71,72] If a child is significantly malnourished, it is prudent to monitor for refeeding syndrome when initiating therapy. If an improvement in clinical status is not seen within 3 to 4 weeks of starting nutrition therapy, a different course of treatment may need to be considered. After the initial phase of treatment, solids are gradually reintroduced as the formula is concurrently reduced. No definitive guidelines exist on the most effective way to introduce solids. Research indicates that individuals who incorporate EN therapy along with a regular diet are less likely to relapse than those who follow a regular diet alone after remission of Crohn's has been achieved.[73] However, standardized guidelines on how to continue EN therapy after achieving disease remission have not been established.

The CDED is a diet designed to modulate the gut microbiome by the avoidance of foods that stimulate gut dysbiosis or contribute to reduced gut barrier function. In general, the diet is a whole food diet high in protein, low in fat, and devoid of food additives.[74,75] Gluten, dairy, and red and processed meats are initially avoided and then judiciously allowed as the diet progresses.[74] The diet consists of an induction phase followed by a maintenance phase during which foods are gradually introduced based on

disease response. The induction phase is 12 weeks in total with two, 6-week phases.[74] In each phase, there are mandatory foods (eg, chicken breast, potato, banana, apple, and egg) that must be consumed daily, as well as allowed foods with guidelines on maximum portion sizes and disallowed foods. The maintenance phase continues to promote the basic diet principles but does allow for more flexibility and some unrestricted meals. Research has shown that this diet in combination with partial EN is as effective as EEN in inducing remission in children with mild to moderate Crohn's disease.[76,77] Because this diet does allow food ingestion and has a definitive maintenance phase, it may be better suited for sustained remission than EEN.[76]

An alternative diet to EEN or CDED is the SCD. The SCD was developed in the 1920s initially as a treatment for celiac disease.[78] This diet focuses on restricting certain types of carbohydrates that may contribute to gut dysbiosis. Specifically, this diet allows simple carbohydrates but prohibits complex carbohydrates under the assumption that simple carbohydrates are easily absorbed and, therefore, do not support bacterial growth.[79] On SCD, all grains are thus eliminated, as well as sugars (except honey), and most dairy products are avoided. This diet provides a list of "legal" and "illegal" foods that serves as a diet reference guide. Secondary to the restrictiveness of this diet, most of the foods are prepared in the home, which may be a limiting factor for some clients. The limited research on this diet is not clear regarding its effectiveness. Some research indicates a possible benefit of this diet clinically and regarding mucosal healing.[80,81] However, other research suggests that benefits are negligible.[82] Given the restrictiveness of this diet, it is important that clients be monitored for dietary deficiencies, particularly that of calcium and vitamin D.[83] If supplementation is required, only supplements within the diet guidelines may be used (ie, no sugar additives). With all the mentioned diet therapies for the treatment of Chron's disease, the specific diet nuances must be clearly explained and discussed with the child and family. For example, some families may be strongly against taking away solids as is done with EEN, whereas other families may struggle to commit to the long-term restrictiveness of the SCD. Shared decision making is essential to assure commitment to the treatment and to foster open communication.

Decreased bone mineral density, as determined by dual energy x-ray absorptiometry scan, is an unfortunate side effect of IBD. Osteopenia may result from malnutrition, inadequate calcium intake or malabsorption, vitamin D deficiency, physical inactivity, or corticosteroid use or it may be related to cytokines released as part of the inflammatory disease. Children receiving 7.5 mg per day of steroids, receiving a lifetime dose of 5 g, or with 12 months of exposure are particularly at increased risk and should be monitored closely.[84]

Diarrhea

Despite improvements in sanitation, the aggressive use of oral rehydration therapy, and early refeeding, diarrheal diseases continue to be a major cause of morbidity and mortality in children. It remains a significant cause of undernutrition and malnutrition in both developed and developing countries.[85]

Diarrhea is defined as the excessive loss of fluid and electrolytes in the stool. This loss may also be associated with nutrient loss. Acute diarrhea (ie, diarrhea of sudden onset) is most often related to infection or specific food intolerance. Chronic diarrhea (diarrhea that lasts more than 2 weeks without obvious cause) has a number of possible etiologies. It is beyond the scope of this chapter to discuss in detail the many different causes of diarrhea. Emphasis here is on the general principles guiding nutrition therapy in patients with the symptoms.

The basis for diarrhea is impaired transport of intestinal content, including nutrients, electrolytes, and other solutes. Water movement across the intestinal mucosa depends on the active and passive fluxes of solutes. Diarrhea encompasses 4 mechanisms that often overlap. Each mechanism may present a unique nutrition challenge. In addition, patients with diarrhea often do not ingest adequate amounts of nutrients due to associated nausea and vomiting or discomfort.[86]

Osmotic diarrhea occurs when a nonabsorbed solute, often a carbohydrate, creates an osmotic load in the distal bowel and produces increased fluid losses. This can be due to either congenital or acquired disease. A common example is diarrhea associated with lactose intolerance.

Excessive sugar intake by children, either juices or sodas, may contribute to osmotic diarrhea. Ingestion of nonabsorbable materials such as sorbitol or xylitol, used in some candies, will cause diarrhea as well. This type of diarrhea will stop with fasting or with the removal of the offending solute.

Secretory diarrhea occurs when the intestinal surface cells secrete fluid into the lumen of the bowel. This may be due to congenital disorders, such as congenital chloridorrhea, or acquired. Toxins may induce fluid and electrolyte secretion. This is seen with cholera and some other infections. Also, some tumors may produce hormones that induce secretion. Secretory diarrhea does not stop with fasting.

Children with motility-type diarrhea often have normal absorption and digestion; however, they have rapid transit with resultant looseness and fluidity of stools. This mechanism predominates in toddlers' diarrhea or IBS.

Intestinal inflammation is associated with diarrhea. It often involves elements of the other 3 mechanisms. In addition, there may be an increased loss of blood and protein. Infectious enteritis, celiac disease, IBD, eosinophilic disease of the GI tract, and certain medications can cause intestinal inflammation.

Diarrhea can affect nutrition status in numerous ways. Reduced and/or altered dietary intake, fecal loses of macronutrients and micronutrients, fluid losses, and malabsorption of ingested nutrients are all factors that can compromise the child with diarrhea.[77,78] Malnutrition is an independent risk factor for the development of diarrhea. Thus, correction of diarrhea-associated malnutrition is not only crucial for assuring proper growth of the child but also for prevention of future diarrheal episodes.[79,80]

Guidelines for treatment for acute diarrhea have been established.[87,88] Acute diarrhea is often related to infection. A common occurrence during infectious diarrhea is the development of dehydration. Subsequently, acidosis may occur. Central to the treatment of acute diarrhea is the use of reduced-osmolarity oral rehydration solution (ORS) with a sodium concentration of 50 to 60 nmol/L. Many products are available and efficacious comparable with intravenous (IV) rehydration. In most situations, the use of ORS will eliminate the need for IV therapy. Oral fluids may be given using an ORS at a dosage of 50 to 120 mL/kg over 4 to 6

hours, followed by maintenance fluids. Fluids with a high osmotic load, such as sodas or fruit juices, should not be given because they may worsen the diarrhea.[86,89] Human milk feeding should be continued during rehydration.

After initial rehydration, rapid reintroduction of feeding is recommended. In the absence of vomiting, feeding of a regular diet (ie, human milk, infant formula, and/or solids) should begin after rehydration commences to reduce or prevent malnutrition and subsequent growth stunting.[88,89] Caloric intake enhances recovery.[87] Some evidence indicates that the use of lactose-free foods can decrease the duration of diarrhea, but if they are not available, then lactose-containing foods and formulas can be used. Diluted formulas do not reduce the duration of diarrhea. The BRAT diet (banana, rice, apple, and toast) is often recommended; however, the efficacy of the diet has not been proven, and it carries a risk of inadequate nutrient intake if used for more than a few days.

Chronic Diarrhea

Chronic diarrhea has many causes, and a detailed evaluation is necessary. The approach to the management of chronic diarrhea depends on the etiology of the condition.

Congenital sucrase-isomaltase deficiency is the most common of the congenital disaccharidase deficiencies. This condition usually presents when juices, formula, or solids containing sucrose, such as baby food fruits, are introduced to the infant's diet.[90] The absence of enzymes prevents the breakdown and absorption of the sucrose disaccharide, which in turn results in osmotic diarrhea.[91] Other symptoms include but are not limited to malnutrition, colic, abdominal distention, gassiness, and diaper rash.[92] Congenital sucrase-isomaltase deficiency is identified by the analysis of disaccharidases obtained from an intestinal biopsy. The management strategy is avoidance or significant limitation of dietary sucrose, maltose, and starch due to a reduction or absence of the enzymes needed to break down these disaccharides on the intestinal surface.[92] Initially, foods and beverages containing sucrose and starch are removed from the diet, while nutrition needs to support growth and development are provided. Once symptoms have abated and the child is stable, foods and beverages

containing low amounts (≤ 2%) of sucrose are introduced. Foods are gradually introduced over time, and the amount of sucrose allowed is increased as tolerated as per the direction of the medical team. In some instances, the usage of an oral enzyme preparation (sacrosidase) may be beneficial to improve dietary sucrose tolerance. Once the tolerance level for sucrose has been established, starch can be introduced into the diet. Tolerance to starch is variable and dependent on the child's enzyme levels.[93] A registered dietitian or nutritionist should counsel caregivers regarding label reading and provide resources regarding sucrose and starch presence in foods and beverages to achieve optimal results.

Similarly, individuals with chronic lactose intolerance also may present with abdominal distention, gassiness, and diarrhea. Lactose intolerance is a result of the absence of the lactase enzyme to break down the dairy carbohydrate lactose. The management of this condition involves the avoidance or limited consumption of lactose-containing foods and beverages depending on the lactase level. Lactose-free formula and milk substitutes are available. Older children with lactose intolerance can supplement with lactase pills prior to the ingestion of lactose-containing foods.

Fructose intolerance is yet another source of chronic diarrhea and abdominal pain observed in children.[94] Fructose is found in the diet as a monosaccharide, as a component of the disaccharide sucrose, and in a polymeric form (fructans). Free fructose has limited absorption in the small intestine. Fructose is absorbed by passive diffusion; it is not actively transported. Fructans are neither digested nor absorbed. Fructose malabsorption contributes to osmotic load. In addition, it provides a substrate for bacterial fermentation and may affect GI motility, all leading to diarrhea. Malabsorption may contribute to abdominal pain. Fructose intolerance can be evaluated using a breath hydrogen test. Treatment is the dietary restriction of foods rich in fructose, foods with a high fructose-to-glucose ratio, and foods high in sorbitol.

In both acute and chronic diarrhea, various micronutrients may be compromised either due to the failure of absorption or increased losses in the stool. Losses commonly associated with diarrhea include zinc, copper, folate, magnesium, vitamin A, vitamin B12, and selenium.[95,96] The

clinician should be mindful of signs of deficiency of these nutrients and conduct laboratory screening as appropriate.

The supplementation of probiotics, particularly of *Lactobacillus GG* and *Saccharomyces boulardii*, may be beneficial in the management of diarrhea.[97,98] In controlled studies, the duration of diarrhea was reduced by about 1 day. The effects are strain-specific, and the safety and efficacy of each should be established. Currently, no standard guidelines exist for using probiotics in the management of pediatric diarrhea. In areas where zinc deficiency is common, zinc supplementation has been beneficial in reducing the duration of diarrhea.

Pancreatic Insufficiency

The pancreas plays an integral role in the digestion of complex carbohydrates, proteins, and fats. This organ is composed of endocrine cells that secrete hormones, exocrine cells that make digestive enzymes, and duct cells that secrete bicarbonate and water. The endocrine pancreas only makes up approximately 2% of the pancreatic cell mass. It is primarily in the form of an islet of Langerhans cells that produce and secrete the hormones insulin and glucagon, which are central to glucose homeostasis. The exocrine pancreas, on the other hand, consists of cells organized into acini and a ductal system that provides a pathway to the small intestine. The pancreas secretes approximately 1.5 L of an enzyme-rich alkaline fluid each day. Pancreatic juice is clear, colorless, and isotonic. Even though this juice is continuously secreted, the composition changes depending on hormonal and neuronal mechanisms. For example, in response to acid in the duodenum from a meal, the duodenal endocrine cells release secretin into the bloodstream. Secretin stimulates the pancreatic duct cells to release bicarbonate and water to neutralize the acid, thus achieving the optimal environment for the digestion of gastric chyme.

Furthermore, in response to the presence of proteins and fats in the proximal intestine, cholecystokinin is released from gut endocrine cells. This regulatory hormone stimulates pancreatic acinar cells to release digestive proenzymes through vagal afferents. These acinar cells secrete inactivated forms (zymogens) of the proteolytic digestive enzymes (trypsin,

chymotrypsin, elastase, etc) to prevent autodigestion of the pancreas. Other pancreatic enzymes are secreted in their active forms. After transportation to the duodenum via the ductal system, the inactivated trypsin is converted to its active form by enterokinase, which is produced from the duodenal mucosa. The activated trypsin then activates other zymogens. Autodigestion of the pancreas is further prevented by trypsin inhibitors (eg, SPINK1) that are produced by the exocrine pancreas. Furthermore, trypsin can cleave and thus inactivate itself, which limits the amount of active trypsin.

When the normal mechanisms are disrupted, then pancreatic exocrine dysfunction results in the malabsorption of nutrients. Pancreatic insufficiency exists when the amount of digestive enzymes delivered to the intestine is inadequate for nutrient digestion. Overt steatorrhea, the presence of excess fat in the stool, occurs when ~90% of the glandular function has been lost. Children may present with growth failure, weight loss, foul-smelling stools, edema, or diarrhea. Parents of children who are toilet-trained may report that stools appear to be floating (due to the high-fat content of the stool). It is possible that with mild pancreatic insufficiency, stools appear normal. Pancreatic insufficiency may result from congenital or acquired disease. Evaluation of pancreatic insufficiency is typically made by direct or indirect testing. Direct testing requires stimulation of the pancreas (with secretin, cholecystokinin, or both) and the collection of pancreatic fluid to analyze the pancreatic enzyme content. However, these tests are invasive given that they require tube placement or an endoscopic procedure to accomplish the testing. In children who require long-term follow-up for their pancreatic insufficiency, repetitive testing is not feasible. Indirect tests are noninvasive and less expensive. However, in mild pancreatic exocrine dysfunction, indirect testing is less sensitive and specific.[99] In contrast, direct stimulation of the pancreas with secretin has high sensitivity and specificity in identifying pancreatic insufficiency in general, as well as isolated pancreatic enzyme deficiencies.[100]

The most widely used of the indirect tests is fecal elastase-1. This test is the most specific for the human pancreas and is resistant to intestinal breakdown.[101] Children do not have to stop pancreatic enzyme supplementation to complete this test. However, false positives can be found in children with villous atrophy (as in celiac disease) or acute

episodes of diarrhea.[102,103] The ordering clinician should be aware of the limitations of indirect testing and consider direct pancreatic exocrine testing if clinical suspicion remains high for pancreatic insufficiency.

Cystic fibrosis (see Chapter 26, "Pulmonary Disorders") is the most common cause of pancreatic insufficiency in childhood; approximately 90% of children with cystic fibrosis will develop pancreatic insufficiency by 1 year of age.[104] Other causes of pancreatic insufficiency in childhood are uncommon.

Shwachman-Diamond syndrome (SDS) is the second most common cause of pancreatic insufficiency in children. It is estimated to occur in 1 in 77000 live births. In the majority of patients with SDS, a mutation on the Shwachman-Bodian-Diamond syndrome (*SBDS*) gene, located on chromosome 7, can be found.[105] Children will classically present with pancreatic insufficiency, hematologic abnormalities (especially variable neutropenia), and bone abnormalities (especially metaphyseal dysostosis). The pancreatic insufficiency found in children with SDS results from the severe depletion of acinar cells. The normal tissue is replaced with fat.[106,107] Interestingly, the ductal tissue remains intact.

Noninvasive tests to identify pancreatic dysfunction in SDS are serum trypsinogen, pancreatic isoamylase, and fecal elastase.[108] The response to pancreatic enzyme supplementation for pancreatic insufficiency is usually excellent in this population. However, children should be monitored intermittently for the need for enzyme replacement; approximately 50% of children with SDS can stop their replacement therapy by 4 years of age.[109] Clinical consensus guidelines for the diagnosis and treatment of SDS have been published.[110]

Johanson-Blizzard syndrome is a rare disorder first described in 1971.[111] This autosomal recessive disorder is the result of mutations in the *UBR1* gene, located on chromosome 15.[112] A history of parental consanguinity can often be found. No gender-based differences have been noted. The most consistent features of this syndrome are a small beaklike nose due to aplasia of the alae nasi and exocrine pancreatic insufficiency. However, other possible clinical features include dental anomalies, congenital scalp defects,

sensorineural hearing loss, hypothyroidism, imperforate anus, and genitourinary anomalies.[113]

Even more rare than Johanson-Blizzard syndrome is Pearson syndrome, which is exocrine pancreatic insufficiency associated with sideroblastic anemia.[114] It results from defects in mitochondrial DNA.[115] Because it is a mitochondrial disease, multiple organs can be involved.

Isolated congenital deficiencies of the exocrine pancreas (lipase, colipase, amylase, and trypsinogen) have been described but are exceedingly rare. Enterokinase deficiency has also been described. Enterokinase is produced by the intestinal mucosa and activates trypsin. These deficiencies are treated with enzyme replacement therapy. Chronic pancreatitis can also cause pancreatic insufficiency over time due to chronic inflammation leading to fibrosis and the destruction of exocrine and endocrine tissue. Unfortunately, this damage is irreversible.

Pancreatic insufficiency can lead to poor growth and nutritional deficiencies. Children with pancreatic insufficiency can develop deficiencies in fat-soluble vitamins (A, D, E, and K).

Symptoms may include impaired night vision, metabolic bone disease, sensory or motor neuropathy, hemolysis, and easy bleeding or bruising. Children with documented pancreatic insufficiency should be screened for serum vitamin A, 25-hydroxyvitamin D, α-tocopherol, and prothrombin time (PT). (If total lipids are increased, then further evaluation of α-tocopherol will be needed; see Chapter 8, “Fat-Soluble Vitamins”). Based on the results, individual supplementation can be prescribed. A deficiency of B12 is thought to be due to the decreased intestinal pH interfering with the transfer of vitamin B12 from R protein to intrinsic factor.[116]

In the past, a low-fat diet was suggested to help control symptoms. However, current recommendations are to optimize pancreatic enzyme supplementation and not to restrict fat to promote weight gain and growth.[117] Research indicates that individuals with pancreatic insufficiency have a higher resting energy requirement than individuals with pancreatic sufficiency.[118] Therefore, calories will likely need to be provided at >100% of estimated needs.[119] The U.S. Food and Drug Administration mandates that all pancreatic enzymes must be approved. Currently, 5 approved products are available (Zenpep, Creon, Pancreaze, Viokace, and Pertzye).

Viokace is the only pancreatic enzyme preparation that is not enteric-coated, and it is only approved for adults. The remaining pancreatic enzymes are approved for children. Dosing is based on the lipase component. Enzyme dosage should not exceed 2500 lipase units/kg per meal or 4000 lipase units/g fat per day to avoid fibrosing colonopathy.[120]

Pancreatitis

Pancreatitis is an inflammatory process of the pancreas with variable involvement of other organs and tissues. Exposure to a causal factor initiates a cascade of events in which trypsinogen is converted to trypsin in quantities that overwhelm the innate protective mechanisms. Causes of pancreatitis include trauma, infection, drugs or toxins, multisystem disease, and congenital abnormalities of the pancreatic or biliary ductal system. Many cases do not have a clear trigger identified. In children, most cases are either acute and isolated or recurrent acute attacks. Chronic pancreatitis is seen more commonly in adults. In children, it is most often related to structural malformation or a specific gene defect as seen in hereditary pancreatitis. The incidence of acute pancreatitis in childhood is uncertain. Though not rare, it accounts for a small proportion of pediatric admissions.[121,122] Likewise, the incidence of chronic pancreatitis in children is not clear.

Pancreatitis is diagnosed by the combination of abdominal pain with an elevation of the levels of amylase and lipase in the serum. The levels of the enzymes do not predict the severity of pancreatitis. No scoring systems apply to children, in contrast to adults. However, guidelines for the diagnosis and management of acute pancreatitis in pediatric patients have been published.[123] Clinical features suggestive of more severe disease include hypotension, renal failure, altered sensorium, and hemorrhage.

The initial management of children with acute pancreatitis includes analgesia and IV fluids. If vomiting is present, a nasogastric tube may be used to decompress the stomach. In patients with mild disease, feedings are sometimes restricted for a short period. Re-initiation of feedings is based on the resolution of abdominal pain, ileus, and vomiting. If nausea and

vomiting are well controlled, a return to a regular diet is encouraged. Most patients with mild disease recover quickly without complications.

Patients with severe pancreatitis often show signs of hemodynamic instability and are at risk for multiple complications including severe nutrition depletion. Nutrition support is important in these patients once they are hemodynamically stable and is considered an active therapeutic intervention.[124] Patients can be fed enterally by nasogastric or nasojejunal tube. There are fewer adverse outcomes in patients who receive EN as opposed to PN.[125] There does not seem to be a difference in feedings of polymeric versus semi-elemental or "immunity-enhancing" formulas.[126] It is encouraged to institute enteral feedings as soon as possible in this patient population.[123]

Chronic pancreatitis is a condition in which continued inflammation of the pancreas produces irreversible changes in the gland. In some cases, it is related to continued recurrent injury from acute attacks. Often the etiology is not clear even when risk factors are present. In adults, repeated exposure to toxins (eg, alcohol) is often implicated. In children, hereditary factors such as the mutation of the trypsinogen molecule, of the cystic fibrosis transmembrane regulator (*CFTR*) gene, or of the trypsin inhibitor genes are often sought. Autoimmune disorders, both isolated autoimmune pancreatitis and systemic autoimmune diseases, are seen. Patients with recurrent acute pancreatitis are at risk for developing chronic pancreatitis.[127]

Treatment of chronic pancreatitis revolves around several concerns: chronic pain, the development of diabetes due to islet cell destruction, and pancreatic insufficiency due to acinar cell destruction. Pain impacts the ability to ingest nutrients. The treatment of chronic pain is beyond the scope of this chapter. The treatment of diabetes mellitus, however, is discussed in Chapter 19, "Diabetes Mellitus and Other Endocrine Disorders."

Digestive enzyme insufficiency is a late complication of chronic pancreatitis. The treatment for pancreatic digestive enzyme insufficiency is enzyme replacement. The goal is to provide enzyme supplements enough to restore digestive function. The dose of pancreatic enzyme is calculated according to the lipase content. A usual dose of enzyme is 1000 to 2500 U of lipase per kilogram of body weight per meal. This is often altered based on the estimated fat content of the meal. This is discussed in more detail in

Chapter 26, “Pulmonary Disorders.” Both polymeric and elemental dietary supplements have been used for nutrition support, and scant data have evaluated the effectiveness in children. It deserves to be restated that a major goal of nutrition support in these patients is the maintenance of normal growth.

Disorders of Chyle Loss

Chyle is a creamy fluid consisting of fat, protein, electrolytes, and lymphocytes, and it is an important aspect of the metabolism of fat. Triglycerides are broken down in the intestinal lumen into fatty acids and monoacylglycerols, which are then absorbed into the intestinal epithelial cells. This process is aided by the action of bile salts mixing with the fatty acids, forming micelles that enhance the transport of the molecules. Within the enterocytes, the absorbed fatty acids are re-esterified to glycerol, and the resultant lipid is complexed with proteins (forming chylomicrons) and transported through the lymphatic system of the GI tract and abdomen, ultimately into the thoracic duct and then into the bloodstream.

Disorders of chyle loss are rare, with the most common disorders being chylothorax or chylous ascites. Chylothorax is defined by the pooling of lymphatic fluid, chyle, in mediastinal or pleural cavities. Chylous ascites occur when lymphatic disruption is present in the abdominal cavity with resultant pooling of chyle in the abdomen. This condition is usually seen as a complication of surgery,[128] although congenital defects of lymph flow are also described. For more detailed information, see Chapter 21, “Cardiac Disease.”

A less common disorder of chyle is intestinal lymphangiectasia. This condition results from the failure of lymph flow often related to inflammation, causing the enlargement of intestinal lymph vessels, which causes breakage of the lacteals and spillage of chyle into the intestinal lumen.[129] As a result, protein-losing enteropathy leading to hypoalbuminemia and edema may result. Hypogammaglobulinemia is often present. Edema of the intestinal mucosa causes malabsorption. Steatorrhea is typically seen.[130] Even more rare are the disorders of chylomicron formation, such as abetalipoproteinemia, in which a defect exists in the

ability to complex the lipids with carrier proteins, and the lipid is therefore not carried into the lymphatic system.

Regardless of the specific disorder of chyle processing, the nutrition approach is similar. The initial treatment is the restriction of dietary fat. A low-fat, high-protein diet is recommended because of the associated protein loss that usually occurs in the GI tract. Because medium-chain-length triglycerides can be metabolized without entry into the lymphatic system, dietary fats should be primarily from medium-chain triglycerides (MCTs), often by using a specialized formula that is high in MCTs but low in long-chain triglycerides (LCTs).[129] The rationale for this diet is twofold. One, the decreased amount of fat lowers the amount of circulating chyle. This reduction lowers the risk of lacteals becoming dilated and releasing chyle. Two, MCTs are directly transported via the portal system, which reduces lymphatic circulation.[130] Most often, this diet is needed for 4 to 8 weeks[128] If an infant or child is on formula, one should be cautious about supplying sufficient amounts of essential fatty acids, linoleic (LA) and α-linolenic acids (ALA), to prevent deficiency; not all high-MCT oil-containing formulas contain sufficient quantities of these nutrients. It is recommended that 2% to 4% of the daily caloric intake be derived from LA and 0.25% to 0.5% be derived from ALA.[131] Also, depending on which formula is used, chromium, molybdenum, and selenium need to be supplemented if the child is on formula for an extended period. PN may be initiated in instances when EN is not adequate to meet nutrient needs or is not indicated for other reasons. Lipids in PN are not absorbed via the lymphatic system and have no effect on the condition, so they can be used without modification.

Disorders of Gut-Brain Interaction

Disorders of gut-brain interaction, formerly known as functional disorders, are a diverse group of conditions in which symptoms persist for a prolonged period and no specific tissue damage nor pathogen is identified.[132] These include recurrent and/or chronic abdominal pain, chronic nonspecific diarrhea, gastroparesis, functional dyspepsia, cyclic vomiting syndrome, constipation, and IBS. Because the underlying pathophysiology is unclear, both the evaluation and treatment are related to the predominant symptom.

Malnutrition is rare in these patients and, if present, suggests an alternative diagnosis. Frequently, dietary interventions are suggested for symptom control. These include increasing fiber, reducing fermentable carbohydrates, and altering the fat content of the diet. These interventions are often recommended and frequently reported to be helpful, though data documenting effectiveness are lacking.[133]

Chronic abdominal pain is a common symptom in children and adolescents, and it is estimated to affect 10% to 15% of the population at some time.[132] The etiology and pathogenesis are unknown, and no specific diagnostic markers have been identified to help in diagnosis. The clinical presentation, careful history and physical examination will often suggest that the diagnosis is functional abdominal pain. A few laboratory or x-ray studies may assist in the evaluation and are remarkable for their normality.

The role of dietary modifications in the management of functional abdominal pain disorders is not established. If symptoms are mainly postprandial or include the sensation of bloating, a low-fat diet is sometimes recommended. If diarrhea or constipation is prominently associated with the pain, an increase in the amount of fiber in the diet is considered. Poor absorption of ingested carbohydrates may trigger symptoms in susceptible individuals. Therefore, restrictions of lactose (milk), fructose (eg, carbonated beverages and certain fruits), or dietary starches (eg, corn, wheat, oat, potato) are sometimes tried. Restriction of nonabsorbable sugar alcohols, often used as artificial sweeteners (eg, sorbitol, xylitol), is advised. It is important to avoid multiple restrictive diets because they may lead to nutrition insufficiency. GF diets should be instituted only after an appropriate evaluation for celiac disease.

Gastroparesis

Gastroparesis is the delay of emptying of the stomach in the absence of a mechanical obstruction. It is considered a disorder of gastric motility. Multiple causes exist. Disorders of the intestinal musculature (myopathic) and the intestinal nervous system (neuropathic), both congenital and acquired, are described. Common causes are immaturity (especially in preterm infants), viral infections, systemic diseases, and drugs.

Gastroparesis often complicates the management of type 1 diabetes mellitus. Evaluation should include the assessment of gastric anatomy and function (eg, upper GI series x-ray and gastric emptying study) as well as a search for and treatment of any underlying condition and bacterial overgrowth. Importantly, malnutrition may be both a cause and a result of gastroparesis.

Gastroparesis has many symptoms, including nausea, vomiting, bloating, upper abdominal discomfort, early satiety, heartburn, esophageal reflux, and decreased appetite. These symptoms are similar to those experienced by patients with functional dyspepsia.[134] These symptoms may lead to malnutrition and the need for nutrition support. Initial treatment of gastroparesis should include maximizing the therapy of treatable systemic illness (eg, optimizing glycemic control in the diabetic patient) and eliminating causes such as medications.

The nutrition assessment of a child with suspected gastroparesis should include a dietary recall and/or dietary record, an evaluation of changes in weight over time, laboratory studies, a description of symptoms, and a listing of medications as well as nutrition supplements.[135] The dietary recall and record provide important information regarding both symptoms and intake. Factors to consider are meal volume tolerance, preference of liquids over solids, and fiber and fat tolerance. Because early satiety is commonly seen in gastroparesis, small frequent meals may be better tolerated than 3 large meals. Liquids are often better tolerated than solids, except for carbonated beverages, which may worsen symptoms.[136] A diet of liquids and/or purees may thus be more effective in delivering ample nutrition than a conventional solid-based diet. Avoidance of high-fiber and high-fat diets, with the exception of fat in liquid nutrition, is also often beneficial because both of these nutrients delay gastric emptying. Dietary osmolality is less of an issue in managing gastroparesis.[135] If diet modification is not successful in managing the symptoms of gastroparesis and adequate oral nutrition is not possible, post pyloric EN may be necessary. More studies are needed in this area to further define the role of nutrition support.[137]

Laboratory markers that are commonly monitored include ferritin, glucose, and hemoglobin A1C. Iron-deficiency anemia is common in this cohort of patients, in part due to symptom management. Usage of acid-

reducing medications to manage reflux and heartburn decreases the gastric acid needed to convert dietary iron to its more absorbable form. Furthermore, the use of nasojejunal tube feedings in the setting of chronic vomiting to promote weight gain by bypassing the stomach can increase the risk of iron-deficiency anemia because the duodenum is the main area of iron absorption. Ferritin is a more appropriate marker to screen for iron-deficiency anemia than hemoglobin and hematocrit. However, it is important to remember that ferritin is an acute-phase reactant and will not be accurate during acute inflammation.[138] Other laboratory markers may require monitoring if indicated by the nutrition assessment (see Chapter 30, "Assessment of Nutrition Status by Age and Determining Nutrient Needs").

Constipation is a common symptom among humans of all ages and is especially troubling in infants and young children. It is most often both self-limited and short-lived. However, a substantial number of patients have symptoms that persist for 6 months or more. Constipation may be related to an inadequate intake of fluid or fiber, side effects of medication, inactivity, or disordered bowel motility. Most cases are idiopathic and fulfill the definition of functional constipation. Although most recognize a role for diet in both the etiology and the treatment of constipation, little data identify specific foods as either causal or beneficial in pediatrics. In the adult population, there is evidence to recommend increasing soluble fiber (ie, psyllium and ispaghula husk) slowly to a goal of 25 to 30 g/d; increasing the daily fiber intake quickly may aggravate abdominal pain and bloating.[139]

It has long been suggested that the consumption of cow's milk contributes to constipation.[140] Evidence suggests a role of sensitivity to cow's milk- protein in constipation.[141,142] In addition, it is known that the fat content of milk may also be associated with harder or more difficult-to-pass stools.

Few studies have documented the benefit of a high-fiber diet for the management of constipation in children.[143,144] Additionally, no conclusive evidence exists that fiber supplements or a lactose-free diet are beneficial in alleviating recurrent abdominal pain in children. Age-based recommendations for fiber intake can be found in the Dietary Guidelines for

Americans 2020–2025. In general, it is recommended to provide 14 g of fiber per 1000 calories in children 2 years of age and older.[145]

Cyclic Vomiting Syndrome

Although increasingly recognized in children, the pathogenesis of cyclic vomiting syndrome remains unknown. The clinical features overlap with those of abdominal migraine. The distinguishing characteristic is a repeated pattern of stereotypical episodes of severe vomiting often associated with pallor, lethargy, and abdominal pain. The episodes are similar in onset and usually duration. A prodrome of variable duration often occurs. An important feature is that the children return to baseline health in between episodes.

In cyclic vomiting syndrome, the primary nutrition concern is the management of any fluid and electrolyte disturbances that may arise because dietary interventions to prevent onset or reduce duration of the condition are unknown.[132] Diets used to prevent migraines have been tried. It is recommended to avoid prolonged fasting because that may trigger vomiting.

Irritable Bowel Syndrome

In IBS, no clear evidence exists to suggest that diet causes the condition; however, diet modification is frequently recommended.[146] It may be prudent to undergo an elimination trial of foods containing lactose, fructose, and/or sorbitol because intolerance to these foods manifests as abdominal pain.[147] Specifically, the low FODMAP (fermentable, oligosaccharides, disaccharides, monosaccharides, and polyols) diet has been beneficial in managing abdominal pain in adults with IBS (see Table 23-6).[148–150] This diet eliminates and/or restricts the consumption of certain fermentable short-chain carbohydrates, which can exacerbate GI symptoms such as gas production. The diet consists of an elimination phase of FODMAP and then a gradual introduction of 1 category at a time, while monitoring for disease symptoms. It may be prudent to have a breath hydrogen test before starting the diet to determine if lactose or fructose malabsorption is present.

Depending on the results, foods and beverages within these groups may or may not need to be restricted as part of the diet.[151]

TABLE 23-6. Low FODMAP Diet[148,150]

Fermentable Short-Chain Carbohydrates	Examples
Oligosaccharides	Fructans (eg, wheat products, inulins, some vegetables, fructo-oligosaccharides) and galacto-oligosaccharides (eg, beans, chickpeas, lentils)
Disaccharides	Lactose (eg, cow, sheep, goat milk)
Monosaccharides	Fructose (eg, fruits, high-fructose corn syrup, honey, certain vegetables, grains)
Polyols	Mannitol, maltitol, xylitol, sorbitol, polydextrose, isomalt, certain fruits (eg, blackberries, prunes, peaches), certain vegetables (eg, snow peas, mushrooms, cauliflower)

Abbreviation: FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides and polyols.

The role of dietary fiber, particularly soluble fiber, in symptom management is debatable. Soluble fiber is found in fruits, vegetables, and whole grains. When ingested, fiber helps to give the stool a gel-like consistency and serves as a fuel source for colonic bacteria. The result is a reduction in gut transit time and a subsequent reduction in constipation and intracolonic pressure.[127,152] However, increased fiber consumption can also exacerbate bloating and flatulence, which are undesirable side effects and can limit adherence to a high-fiber diet.[153] To date, no definitive conclusions exist as to the benefit of fiber in the management of IBS symptoms in pediatrics.[154] Similarly, there is little evidence for the usage of probiotics in the management of IBS in pediatrics and the American College of Gastroenterology recommends against its use in adults.[155]

More research is needed regarding which strains or combinations of strains are most beneficial before guidelines can be established.[149] Nutrition counseling should be individualized based on the patient's reported food–

symptom correlations.[156] The suspected offending food should be removed from the diet for 2 to 3 weeks. If no relief in symptoms is observed, the food may be added back to the diet.

Eosinophilic Conditions of the GI Tract

Eosinophilic gastroenteritis is a condition characterized by either patchy or diffuse infiltration of eosinophils anywhere in the GI tract. Damage to the GI tract is due to both the infiltration and degranulation of eosinophils. The triggering process is not clear. Both IgE-mediated and non-IgE-mediated sensitivities are described. Many patients (especially older patients) have conditions such as a high eosinophil count, asthma, allergic rhinitis, or eczema suggesting underlying atopy. Allergies to food or inhalants are sometimes implicated. In addition, atopy often appears in family history. It may affect children of any age.[157]

The signs and symptoms of eosinophilic gastroenteritis are nonspecific, and the presentation varies by location, depth, and extent of the eosinophilic infiltration. There may be involvement of the mucosal, muscular, or serosal layers. Mucosal disease presents as nausea and vomiting, diarrhea (often bloody), malabsorption, and weight loss. When the muscular layers are involved, signs and symptoms of obstruction are present. If serosal involvement occurs, there may be ascites. The most common symptom is colicky abdominal pain.

The most frequently seen form of eosinophilic disease in infants is proctitis, often referred to as allergic colitis. The disorder is characterized by bloody diarrhea in an infant <2 months of age. Cases of food-induced eosinophilic proctocolitis are reported regardless of whether the infant is being fed human milk or formula. Infants presenting with this condition usually have normal linear and ponderal growth. The infants will have diarrhea, usually accompanied by mucous and/or blood and often with pain or straining at the time of bowel motion. A biopsy of the rectal mucosa will show eosinophilic infiltration of the mucosa. Frequently, the diagnosis is made on clinical presentation alone. The dietary management of this condition involves the elimination of the offending protein until approximately 9 to 12 months of age. If an infant is fed human milk, the

offending protein should be removed from the parent's diet. Earlier reintroduction of the protein will usually result in a recurrence of bleeding.[157,158]

Eosinophilic esophagitis (EOE) affects children and adults. Symptoms include but are not limited to vomiting, abdominal pain, poor growth or weight gain, and iron-deficiency anemia.[159] EOE is diagnosed by the combination of symptoms of esophageal dysfunction, such as vomiting, dysphagia, or feeding difficulties, in a patient with esophageal biopsies demonstrating at least 15 eosinophils per high powered field in the absence of other conditions associated with esophageal eosinophilia, such as gastroesophageal reflux disease, achalasia, vasculitis, hypereosinophilic syndrome, Crohn's disease, Ehler's Danlos syndrome, graft versus host disease, infections, and drug hypersensitivity. A trial of a proton pump inhibitor (PPI) to exclude a diagnosis of gastroesophageal reflux disease is no longer considered appropriate in diagnosing eosinophilic esophagitis.[159]

The recommended dietary treatment is avoidance of the offending allergens. An elemental diet, as well as empiric food elimination of commonly implicated dietary antigens (eg, 6 food or 4 food eliminations) and allergy-directed food elimination are suggested. Dairy, eggs, and wheat are the most commonly implicated foods.[160] Particular attention should be paid to the quality of the diet as malnutrition may develop if numerous foods are eliminated. For more information regarding eosinophilic conditions of the gut please refer to Chapter 18, "Food Allergies."

Conclusion

Because of the central role of the digestive system in maintaining normal nutrition, disease of the GI tract, liver, or pancreas has a profound influence on the growth and development of children. Provision of adequate nutrition support can not only improve nutrition parameters and growth but also in many cases can treat the underlying disease. Careful evaluation of the child including assessment of nutrition needs, is crucial to effective management. The clinical examination and judiciously applied laboratory investigation will identify nutrition deficiencies. With an understanding of the underlying

disease process, appropriate nutrition management can improve growth, quality of life, and outcomes of patients.

Test Your Knowledge Questions

1. A 15-year-old boy is admitted to the hospital because of diarrhea and abdominal pain. He has had unintentional weight loss of 15 lb in the last 3 months. Laboratory evaluation reveals the following:
   - Albumin, 3.1 gm/dL
   - Total protein, 6.2 gm/dL
   - Hemoglobin/hematocrit, 9.3gm/dL/27%
   - MCV, 71 fL (normal >79 fL)
   - WBC, 11,500 K/microL

   Radiology studies demonstrated inflammation of the ileum and cecum. Which of the following should diet therapy include?

   A. A polymeric defined formula diet
   B. A semi-elemental defined formula diet
   C. An elemental defined formula diet
   D. Any of A, B, or C
   E. A clear liquid diet
2. His medical therapy includes methotrexate and sulfasalazine. Which of the following should supplementation include?

   A. Folate, B12, and iron
   B. Pyridoxine, thiamin, and magnesium
   C. B12, vitamin C, and manganese
   D. Folate, vitamin C, and copper
3. In a patient with celiac disease, how long should a GF diet be maintained?

   A. Until diarrhea subsides
   B. Until normal linear growth is established
   C. Until new and as yet undiscovered treatments are available
   D. Until bone mineral density has returned to normal
   E. A GF diet is not necessary
4. Your patient has just been diagnosed with pancreatic insufficiency. Which lab tests are appropriate?

A. Vitamin A, 25-hydroxyvitamin D, iron panel
B. 25-hydroxyvitamin D, folate, iron panel
C. Vitamin A, folate, PT
D. Vitamin A, 25-hydroxyvitamin D, α-tocopherol/total lipids, PT

5. Which of the following recommendations is not appropriate to make for this patient with pancreatic insufficiency?
   A. Start pancreatic enzymes at a dose <2500 lipase units/kg per meal.
   B. Your patient should start a low-fat diet.
   C. Your patient's actual caloric needs will likely be >100% of their estimated needs.
   D. Your patient should take the prescribed pancreatic enzymes before all meals and snacks.

References

1. Carvalho-Salemi J, Phillips W, et al. Malnutrition among hospitalized children in the United States: a 2012–2019 update of annual trends. *J AcadNutr Diet*. 2023;123(1):109–116. https://doi.org/10.1016/j.jand.2022.05.021
2. Samela K, Vance K, Goodwin S. Nutritional assessment. In Wylie R, Hyams J, and Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*. Elvesier; 2021:963–972.
3. Pacheco-Acosta JC, Gomez-Correa AC, Flores ID, et al. Incidence of nutrition deterioration in nonseriously ill hospitalized children younger than 5. *Nutr Clin Pract.* 2014;29(5):692–697. https://doi.org/10.1177/0884533614533122
4. Groleau V, Thibault M, Doyon M, et al. Malnutrition in hospitalized children: prevalence, impact and management. *Can J Diet Pract Res.* 2014;75(1):29–34. https://doi.org/10.3148/75.1.2014.29
5. Green Corkins K, Teague E. Pediatric nutrition assessment: anthropometrics to zinc. *Nutr Clin Pract.* 2017;32:40–51. https://doi.org/10.1177/0884533616679639
6. Green Corkins K. Nutrition-focused physical examination in pediatric patients. *Nutr Clin Pract.* 2015;30(2):203–9. https://doi.org/10.1177/0884533615572654

7. Shay S, Tutian R, Sifrim D, et al. Twenty-four hour ambulatory simultaneous impedance and pH monitoring: a multicenter report of normal values from 60 healthy volunteers. *Am J Gastroenterol.* 2004;99:1037–1043. https://doi.org/10.1111/j.1572-0241.2004.04172.x
8. Nelson SP, Chen EH, Syniar GM, et al. Prevalence of symptoms of gastroesophageal reflux during childhood: a pediatric practice-based survey. *Arch Pediatric Adol Med.* 2000;154:150–154. https://doi.org/10.1001/archpedi.154.2.150
9. Vandenplas Y, Goyvaerts H, Helven R, Sacre L. Gastroesophageal reflux, as measured by 24-hour pH monitoring, in 509 healthy infants screened for risk of sudden infant death syndrome. *Pediatrics.* 1991;88:834–890. https://doi.org/10.1542/peds.88.4.834
10. Martin AJ, Pratt N, Kennedy JD, et al. Natural history and familial relationships of infant spilling to 9 years of age. *Pediatrics.* 2002;109:1061–1067. https://doi.org/10.1542/peds.109.6.1061
11. Nelson SP, Chen EH, Syniar GM, et al. Prevalence of symptoms of gastroesophageal reflux during infancy: a pediatric practice-based survey. *Arch Pediatr Adolesc Med*. 1997;151:569–572. https://doi.org/10.1001/archpedi.1997.02170430035007
12. Nelson SP, Chen EH, Syniar GM, Christoffel KK. One year follow up of symptoms of gastroesophageal reflux during infancy: Pediatric Practice Research Group. *Pediatrics.* 1998;102:e67. https://doi.org/10.1542/peds.102.6.e67
13. Vandenplas Y. Gastroesophageal reflux. In: Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*. 6th ed. Saunders Elsevier; 2021:Chapter 21.
14. Pandolfino JE, Kwiatek MA, Kahrilas PJ. The pathophysiologic basis for epidemiologic trends in gastroesophageal reflux disease. *Gastroenterol Clin North Am*. 2008;37:827–843. https://doi.org/10.1016/j.gtc.2008.09.009
15. Vandenplas Y, Hassall E. Mechanics of gastroesophageal reflux and gastroesophageal reflux disease. *J Pediatr Gastroenterol Nutr.* 2002;35:119–136. https://doi.org/10.1097/00005176-200208000-00005

16. Kawahara H, Dent J, Davidson G. Mechanics responsible for gastroesophageal reflux in children. *Gastroenterology*. 1997;113:399–408. https://doi.org/10.1053/gast.1997.v113.pm9247456
17. Penagini R, Mangano M, Bianchi PA. Effect of increasing the fat content but not the energy load of a meal on gastro-oesophageal reflux and lower oesophageal sphincter motor function. *Gut*. 1998;42:330–333. https://doi.org/10.1136/gut.42.3.330
18. Lightdale JR, Gremse DA; Section on gastroenterology, hepatology, and nutrition: gastroesophageal reflux, management guidance for the pediatrician. *Pediatrics*. 2013;131:e1684–e1695. https://doi.org/10.1542/peds.2013-0421
19. Jadcherla SR, Chan CY, Moore R, et al. Impact of feeding strategies on the frequency and clearance of acid and nonacid gastroesophageal reflux events in dysphagic neonates. *J Parenter Enter Nutr*. 2012;36(4):449–455. https://doi.org/10.1177/0148607111415980
20. Rosen R, Vandenplas Y, Singendonk M, Cabana M, DiLorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: Joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2018; 66:516–534. https://doi.org/10.1097/mpg.0000000000001889
21. Vanderhoof JA, Moran JR, Harris CL, Merkel KL, Orenstein SR. Efficacy of a pre-thickened infant formula: a multicenter, double-blind, randomized, placebo-controlled parallel group trial in 104 infants with symptomatic gastroesophageal reflux. *Clin Pediatr*. 2003;42:483–495. https://doi.org/10.1177/000992280304200602
22. Aggett PJ, Agostoni C, Axelsson I, et al. Antireflux or antiregurgitation milk products for infants and young children: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr*. 2002;394:496–498. https://doi.org/10.1097/00005176-200205000-00003
23. Vandenplas Y, De Wolf D, Sacre L. Influence of xanthines on gastroesophageal reflux in infants at risk for sudden infant death syndrome. *Pediatrics*. 1986;77:807–810. https://doi.org/10.1542/peds.77.6.807

24. Wenzl TG, Schneider S, Scheele F, Silny J, Heimann G, Skopnik H. Effects of thickened feeding on gastroesophageal reflux in infants: a placebo-controlled crossover study using intraluminal impedance. *Pediatrics.* 2003;111(4 Pt 1):e355–e359. https://doi.org/10.1542/peds.111.4.e355
25. Corvaglia l, Spizzichino M, Aceti A, et al. A thickened formula does not reduce apneas related to gastroesophageal reflux in preterm infants. *Neonatology.* 2013;103:98–102.22. https://doi.org/10.1159/000342703
26. Orenstein SR, Shalaby TM, Putnam PE. Thickened feedings as a cause of increased coughing when used as therapy for gastroesophageal reflux in infants. *J Pediatr.* 1992;121:913–915. https://doi.org/10.1016/s0022-3476(05)80339-7
27. Woods CW, Lewis OT, Yang Q. Development of necrotizing enterocolitis in premature infants receiving thickened feeds using SimplyThick. *J Perinatol.* 2012;322:150–152. https://doi.org/10.1038/jp.2011.105
28. Bosscher D, Van Caillie-Bertrand M, Van Dyck K, Robberecht H, Van Cauwenbergh R, Deelstra H. Thickening infant formula with digestible and indigestible carbohydrate: availability of calcium, iron, and zinc in vitro. *J Pediatr Gastroenterol Nutr.* 2000;30:373–378. https://doi.org/10.1097/00005176-200004000-00005
29. Corvaglia L, Mariani E, Aceti A, et al. Extensively hydrolysed protein formula reduces acid gastro-esophageal reflux in symptomatic preterm infants. *Early Hum Dev.* 2013;89(7):453–455. https://doi.org/10.1016/j.earlhumdev.2013.04.003
30. Hills JM, Aaronson PI. The mechanism of action of peppermint oil on gastrointestinal smooth muscle. *Gastroenterology.* 1991;101:55–65. https://doi.org/10.1016/0016-5085(91)90459-x
31. Wendl B, Pfeiffer A, Pehl C, Schmidt T, Kaess H. Effect of decaffeination of coffee or tea on gastro-oesophageal reflux. *Aliment Pharmacol Ther*. 1994;8:283–287. https://doi.org/10.1111/j.1365-2036.1994.tb00289.x
32. Pehl C, Pfeiffer A, Wendl B, Kaess H. The effect of decaffeination of coffee on gastroesophageal reflux in patients with reflux disease.

Aliment Pharmacol Ther. 1997;11:483486. https://doi.org/10.1046/j.1365-2036.1997.00161.x
33. Bulat R, Fachnie E, Chauhan U, Chen Y, Tougas G. Lack of effect of spearmint on lower esophageal sphincter function and acid reflux in healthy volunteers. *Aliment Pharmacol Ther.* 1999;13:805–812. https://doi.org/10.1046/j.1365-2036.1999.00528.x
34. Lewis D, Khoshoo V, Pencharz PB, Golladay ES. Impact of nutritional rehabilitation on gastroesophageal reflux in neurologically impaired children. *J Pediatr Surg.* 1994;29:167–169. https://doi.org/10.1016/0022-3468(94)90312-3
35. Herzig SJ, Howell MD, Ngo LH, Marcantonio GR. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. *JAMA.* 2009;301(20):2120–2188. https://doi.org/10.1001/jama.2009.722
36. Canani RB, Cirillo P, Roggero P, et al; Working Group on Intestinal Infections of the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP). Therapy with gastric acid inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. *Pediatrics.* 2006;117(5):e817–e820. https://doi.org/10.1542/peds.2005-1655
37. Tighe M, Afzal NA, Bevan A, Hayen A, Munro A, Beatie RM Pharmacological treatment of children with gastro-oesopheal reflux *Cochrane Database Syst Rev.* 2014;(11):CD008550. https://doi.org/10.1002/14651858.cd008550.pub2
38. Husby SS, Koletzko S, Korponay-Szabó I, et al. European Society for Paediatric Gastroenterology, Hepatology and Nutrition guidelines for diagnosing coeliac disease 2020. *J Pediatr Gastroenterol and Nutr*. 2020;70(1):141–156. https://doi.org/10.1097/MPG.0000000000002497
39. Singh P, Arora A, Strand TA, et al. Global prevalence of celiac disease: systematic review and meta-analysis. *Clinical Gastroenterology and Hepatology*. 2018;16(6):823–836. https://doi.org/10.1016/j.cgh.2017.06.037
40. Green PHR, Collier C. Celiac disease. *N Engl J Med.* 2007;357:1731–1743. https://doi.org/10.1056/nejmra071600
41. D'Amico MA, Holmes J, Stavropoulos SN, et al. Presentation of celiac disease in the United States: prominent effect of breast feeding.

Clin Pediatr (Phila). 2005;44:249–258. https://doi.org/10.1177/000992280504400309
42. Caio G, Volta U, Sapone A, et al. Celiac disease: a comprehensive current review. *BMC Med.* 2019; 17:142. https://doi.org/10.1186/s12916-019-1380-z
43. Haapalahti M, Kulmala P, Karttunen TJ, et al. Nutritional status in adolescents and young adults with screen-detected celiac disease. *J Pediatr Gastroenterol Nutr.* 2005;40:566–570.4. https://doi.org/10.1097/01.mpg.0000154658.16618.f9
44. See J, Murray JA. Gluten-free diet: the medical and nutrition management of celiac disease. *Nutr Clin Pract.* 2006;21:1–15. https://doi.org/10.1177/011542650602100101
45. Gatti S, Caporelli N, Galeazzi T, et al. Oats in the diet of children with celiac disease: preliminary results of a double-blind, randomized, placebo-controlled multicenter Italian study. *Nutrients*. 2013;5:4653–4664. https://doi.org/10.3390/nu5114653
46. Butzner J. Pure oats and the gluten-free diet: are they safe? *JPEN J Parenter Enteral Nutr*. 2011;35:447–448. https://doi.org/10.1177/0148607111408107
47. Hallert C, Grant C, Grehn S, et al. Evidence of poor vitamin status in celiac patients on a gluten-free diet for 10 years. *Aliment Pharmacol Ther.* 2002;16:1333–1339. https://doi.org/10.1046/j.1365-2036.2002.01283.x
48. Mora S, Barera G, Beccio S, et al. A prospective, longitudinal study of the long-term effect of treatment on bone density in children with celiac disease. *J Pediatr.* 2001;139(4):473–475. https://doi.org/10.1067/mpd.2001.116298
49. Kuenzig ME, Fung SG, Marderfeld L, et al. Twenty-first century trends in the global epidemiology of pediatric-onset inflammatory bowel disease: systematic review. *Gastroenterol*. 2022;162(4)1147–1159. https://doi.org/10.1053/j.gastro.2021.12.282
50. Picorano J, Akabas S, Leleiko N Harmonizing nutritional therapies for pediatric inflammatory bowel disease. *J Pediatr Gasterol and Nutr* 2020;70(3):285–288. https://doi.org/10.1097/mpg.0000000000002602
51. Kleinman RE, Baldassano RN, Caplan A, et al. Nutrition support for pediatric patients with inflammatory bowel disease: a clinical report

of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr*. 2004;39:15–27. https://doi.org/10.1097/00005176-200407000-00005

52. Seidman E, LeLeiko N, Ament M, et al. Nutritional issues in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 1991;12:424–438. https://doi.org/10.1097/00005176-199105000-00004
53. Kanof ME, Lake AM, Bayless TM. Decreased height velocity in children and adolescents before the diagnosis of Crohn's disease. *Gastroenterology*. 1988;95:1523–1527. https://doi.org/10.1016/s0016-5085(88)80072-6
54. Saha MT, Ruuska T, Laippala P, Lenko HL. Growth of prepubertal children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 1998;26:310–314. https://doi.org/10.1097/00005176-199803000-00013
55. Markowitz J, Grancher K, Rosa J, Aiges H, Daum F. Growth failure in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* 1993;16:373–380. https://doi.org/10.1097/00005176-199305000-00005
56. Becker P, Carney LN, Corkins MR, et al. Consensus statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: indicators recommended for the identification and documentation of pediatric malnutrition (undernutrition). *Nutr Clin Pract*. 2015;30(1):147–161. https://doi.org/10.1177/0884533614557642
57. Sentongo TA, Semeao EJ, Piccoli DA, Stallings VA, Zemel BS. Growth, body composition and nutritional status in children and adolescents with Crohn's disease. *J Pediatr Gastroenterol Nutr*. 2000;31:33–40. https://doi.org/10.1097/00005176-200007000-00009
58. Mamula P, Markowitz JE, Baldassano RN. Inflammatory bowel disease in early childhood and adolescence: special considerations. *Gastroenterol Clin North Am*. 2003;32:967–995. https://doi.org/10.1016/s0889-8553(03)00046-3
59. Wiskin AE, Wootton SA, Beattie RM. Nutrition issues in pediatric Crohn's disease. *Nutr Clin Pract*. 2007;22:214–222. https://doi.org/10.1177/0115426507022002214

60. Motil KJ, Grand RJ, Davis-Kraft L, et al. Growth failure in children with inflammatory bowel disease: a prospective study. *Gastroenterology*. 1993;105:681–691. https://doi.org/10.1016/0016-5085(93)90883-e
61. Navarro FA, Hanauer SB, Kirschner BS. Effect of long-term low-dose prednisone on height velocity and disease activity in pediatric and adolescent patients with Crohn disease. *J Pediatr Gastroenterol Nutr*. 2007;45:312–318. https://doi.org/10.1097/mpg.0b013e31805b82c6
62. Critch J, Day A, Otley A, et al. Use of enteral nutrition for the control of intestinal inflammation in pediatric Crohn disease. *J Pediatr Gastroenterol Nutr.* 2012;54:298–305. https://doi.org/10.1097/mpg.0b013e318235b397
63. Sanderson IR, Udeen S, Davies PS, Savage MO, Walker-Smith JA. Remission induced by an elemental diet in small bowel Crohn's disease. *Arch Dis Child.* 1987;61:123–127. https://doi.org/10.1136/adc.62.2.123
64. Borrelli O, Cordischi L, Cirulli M, et al. Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial. *Clin Gastroenterol Hepatol.* 2006;4:744–753. https://doi.org/10.1016/j.cgh.2006.03.010
65. Eiden KA. Nutritional considerations in inflammatory bowel disease. *Practical Gastroenterol*. 2003;27:33–54.
66. Sentongo TA, Semaeo EJ, Stettler N, Piccoli DA, Stallings VA, Zemel BS. Vitamin D status in children, adolescents and young adults with Crohn disease. *Am J Clin Nutr*. 2002;76:1077–1081. https://doi.org/10.1093/ajcn/76.5.1077
67. Pappa HM, Gordon CM, Saslowsky TM, et al. Vitamin D status in children and young adults with inflammatory bowel disease. *Pediatrics.* 2006;118:1950–1961. https://doi.org/10.1542/peds.2006-0841
68. Pappa H, Thayu S, Leonard F, et al. Skeletal health of children and adolescents with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* 2011;53:11–25. https://doi.org/10.1097/mpg.0b013e31821988a3
69. Canani RB, Terrin G, Borrelli O, et al. Short- and long-term therapeutic efficacy of nutritional therapy and corticosteroids in

pediatric Crohn's disease. *Dig Liver Dis*. 2006;38:381–387. https://doi.org/10.1016/j.dld.2005.10.005
70. Lochs H, Dejong C, Hammarqvist F, et al; ESPEN (European Society for Parenteral and Enteral Nutrition). ESPEN Guidelines on Enteral Nutrition: Gastroenterology. *Clin Nutr*. 2006;25:260–274. https://doi.org/10.1016/j.clnu.2006.01.007
71. Zachos M, Tondeur M, Griffiths AM. Enteral nutritional therapy for induction of remission in Crohn's disease. *Cochrane Database Syst Rev.* 2007;(1):CD000542. https://doi.org/10.1002/14651858.cd000542.pub2
72. Griffiths AM, Ohlsson A, Sherman PM, Sutherland LR. Meta-analysis of enteral nutrition as a primary treatment of active Crohn's disease. *Gastroenterology.* 1995;108:1056–1067. https://doi.org/10.1016/0016-5085(95)90203-1
73. Verma S, Kirkwood B, Brown S. Oral nutritional supplementation is effective in the maintenance of remission in Crohn's disease. *Digest Liver Dis.* 2000;32:769–774. https://doi.org/10.1016/s1590-8658(00)80353-9
74. Levine A, El-Matary W, Van Limbergen J. A case-based approach to new directions in dietary therapy of Crohn's disease: food for thought. *Nutrients*. 2020;12,880:1–8. https://doi.org/10.3390/nu12030880
75. Boneh RS, Van Limbergen J, Wine E, et al. Dietary therapies induce rapid response and remission in pediatric patients with active Crohn's disease. *Clinical Gastroenterology and Hepatology*. 2021;19:752–759. https://doi.org/10.1016/j.cgh.2020.04.006
76. Levine A, Wine E, Assa A, et al. Crohn's disease exclusion diet plus partial enteral nutrition induces sustained remission in a randomized controlled trial. *Gastroenterology*. 2019;157:440–450. https://doi.org/10.1053/j.gastro.2019.04.021
77. Niseteo T, Sila S, Trivic I, et al. Modified Crohn's disease exclusion diet is equally effective as exclusive enteral nutrition: real-world data. *Nutr Clin Pract.* 2022;37:435–441. https://doi.org/10.1002/ncp.10752
78. Suskind DL, Lee D, Kim YM, et al. The specific carbohydrate diet and diet modification as induction therapy for pediatric Crohn's disease: a randomized diet controlled trial. *Nutrients*. 2020;12,3749:1–22. https://doi.org/10.3390/nu12123749

79. Kakodkar S, Mutlu EA. Diet as a therapeutic option for adult inflammatory bowel disease. *Gastroenterol Clin N Am.* 2017;46:745–767. https://doi:10.1016/j.gtc.2017.08.016
80. Cohen SA, Gold BD, Oliva S, et al. Clinical and mucosal improvement with specific carbohydrate diet in pediatric Crohn disease. *J Pediatr Gastroenterol Nutr*. 2014;59:516–521. https://doi:10.1097/MPG.0000000000000449
81. Suskin DL, Wahbeh G, Gregory N, et al. Nutritional therapy in pediatric Crohn disease: the specific carbohydrate diet. *J Pediatr Gastroenterol Nutr*. 2014;58:87–91. https://doi:10.1097/MPG.0000000000000103
82. Kaplan HC, Opipari-Arrigan L, Yang J, et al. Personalized research on diet in ulcerative colitis and Crohn's disease: a series of N-of-1 diet trials. *Am J Gastroenterol*. 2022;117(6):902–917. https://doi.org/10.14309/ajg.0000000000001800
83. Braly K, Williamson N, Shaffer M, et al. Nutritional adequacy of the specific carbohydrate diet in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2017;65(5): 533–538. https://doi.org/10.1097/mpg.0000000000001613
84. Levine A, Milo T, Buller H, Markowitz J. Consensus and controversy in the management of pediatric Crohn's disease: an international survey. *J Pediatr Gastroenterol Nutr*. 2003;36:464–469. https://doi.org/10.1097/00005176-200304000-00008
85. Lanata CF, Fischer-Walker CL, Olascoaga AC, et al. Global causes of diarrheal disease mortality in children <5 years of age: a systematic review. *PLoS One.* 2013;8:e72788. https://doi.org/10.1371/journal.pone.0072788
86. Gracey M. Nutritional effects and management of diarrhea in infancy. *Acta Paediatr Suppl.* 1999;430:110–126. https://doi.org/10.1111/j.1651-2227.1999.tb01310.x
87. Islam M, Roy SK, Begum M, Chisti MJ. Dietary intake and clinical response of hospitalized patients with acute diarrhea. *Food Nutr Bull.* 2008;29:25–31. https://doi.org/10.1177/156482650802900103
88. Guarino A, Winter H, Sandhu B, et al. Acute gastroenteritis disease: report of the FISPGHAN Working Group. *J Pediatr Gastroenterol*

Nutr. 2012;55:621–626. https://doi.org/10.1097/mpg.0b013e318272b5e2
89. Guarino A, Ashkenazi S, Gendrel D, Lo Vecchio A, Shamir R, Szajewska H. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Pediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: update 2014. *J Pediatr Gastroenterol Nutr.* 2014;59:132–152. https://doi.org/10.1097/mpg.0000000000000375
90. Treem W. Clinical aspects and treatment of congenital sucrase-isomaltase deficiency. *J Pediatr Gastroenterol Nutr.* 2012;55(suppl 2):S7–S13. https://doi.org/10.1097/01.mpg.0000421401.57633.90
91. Belmont JW, Reid B, Taylor W, et al. Congenital sucrase-isomaltase deficiency presenting with failure to thrive, hypercalcemia and nephrocalcinosis. *BMC Pediatr.* 2002;2:4. https://doi.org/10.1186/1471-2431-2-4
92. Treem WR, McAdams L, Stanford L, Kastoff G, Justinich C, Hyams J. Sacrosidase therapy for congenital sucrase-isomaltase deficiency. *J Pediatr Gastroenterol Nutr.* 1999;28:137–142. https://doi.org/10.1097/00005176-199902000-00008
93. McMeans A. Congenital sucrase-isomaltase deficiency: diet assessment and education guidelines. *J Pediatr Gastroenterol Nutr.* 2012;55(suppl 2):S37–S39. https://doi.org/10.1097/01.mpg.0000421410.72880.ae
94. Escobar MA Jr, Lustig D, Pflugeisen B, et al. Fructose intolerance/malabsorption and recurrent abdominal pain in children. *J Pediatr Gastroenterol Nutr.* 2014;58:498–501. https://doi.org/10.1097/mpg.0000000000000232
95. Castillo-Duran C, Vial P, Uauy R. Trace mineral balance during acute diarrhea in infants. *J Pediatr.* 1988;113:452–457. https://doi.org/10.1016/s0022-3476(88)80627-9
96. Matoth Y, Zamir R, Bar-Shani S, Grossowicz N. Studies in folic acid in infancy: II. folic and folinic acid blood levels in infants with diarrhea, malnutrition, and infection. *Pediatrics.* 1964;33:694–699. https://doi.org/10.1542/peds.33.5.694

97. Guandalini S. Probiotics for children with diarrhea. *J Clin Gasteroenterol.* 2008;42:S53–S57.
98. Wallace B. Clinical use of probiotics in the pediatric population. *Nutr Clin Pract.* 2009;24:50–59. https://doi.org/10.1177/0884533608329298
99. Walkowiak J, Cichy WK, Herzig KH. Comparison of fecal elastase-1 determination with the secretin-cholecystokinin test in patients with cystic fibrosis. *Scand J Gastroenterol*. 1999;34:202–207. https://doi.org/10.1080/00365529950173104
100. Wali PD, Loveridge-Lenza B, He Z, Horvath K. Comparison of fecal elastase-1 and pancreatic function testing in children. *J Pediatr Gastroenterol Nutr.* 2012;54(2):277–280. https://doi.org/10.1097/mpg.0b013e31820b0227
101. Sziegoleit A, Krause E, Klör HU, Kanacher L, Linder D. Elastase 1 and chymotrypsin B in pancreatic juice and feces. *Clin Biochem*. 1989;22:85–89. https://doi.org/10.1016/s0009-9120(89)80003-7
102. Walkowiak J, Herzig KH. Fecal elastase-1 is decreased in villous atrophy regardless of the underlying disease. *Eur J Clin Invest*. 2001;31:425–430. https://doi.org/10.1046/j.1365-2362.2001.00822.x
103. Salvatore S, Finazzi S, Barassi A, et al. Low fecal elastase: potentially related to transient small bowel damage resulting from enteric pathogens. *J Pediatr Gastroenterol Nutr*. 2003;36:392–396. https://doi.org/10.1097/00005176-200303000-00018
104. Bronstein MN, Sokol RJ, Abman SH, et al. Pancreatic insufficiency, growth, and nutrition in infants identified by newborn screening as having cystic fibrosis. *J Pediatr*. 1992;120(4 Pt 1):533–540. https://doi.org/10.1016/s0022-3476(05)82478-3
105. Boocock GR, Morrison JA, Popovic M, et al. Mutations in SBDS are associated with Shwachman-Diamond syndrome. *Nat Genet*. 2003;33:97–101. https://doi.org/10.1038/ng1062
106. Bodian M, Sheldon W, Lightwood R. Congenital hypoplasia of the exocrine pancreas. *Acta Pediatr.* 1964;53:282–293. https://doi.org/10.1111/j.1651-2227.1964.tb07237.x
107. Shwachman H, Diamond LK, Oski FA, Khan KT. The syndrome of pancreatic insufficiency and bone marrow dysfunction. *J Pediatr.* 1964;65:645–663. https://doi.org/10.1016/s0022-3476(64)80150-5

108. Myers KC, Davies SM, Shimamura A. Clinical and molecular pathophysiology of Shwachman-Diamond Syndrome. *Hematol Oncol Clin North Am*. 2013; 27(1):117–128. https://doi.org/10.1016/j.hoc.2012.10.003
109. Mack DR, Forstner GG, Wilschanski M, Freedman MH, Durie PR. Shwachman syndrome: exocrine pancreatic dysfunction and variable phenotypic expression. *Gastroenterology.* 1996;111:1593–1602. https://doi.org/10.1016/s0016-5085(96)70022-7
110. Dror Y, Donadieu, J, Koglmeier J, et al. Draft consensus guidelines for diagnosis and treatment of Shwachman-Diamond syndrome. *Ann NY Acad Sci.* 2011;1242:40–55. https://doi.org/10.1111/j.1749-6632.2011.06349.x
111. Johanson AJ, Blizzard RM. A syndrome of congenital hypoplasia of the alae nasi, deafness, hypothyroidism, dwarfism, absent permanent teeth and malabsorption. *J Pediatr.* 1971;79:982–987. https://doi.org/10.1016/s0022-3476(71)80194-4
112. Zenker M, Mayerle J, Lerch MM, et al. Deficiency of UBR1, a ubiquitin ligase of the N-end rule pathway, causes pancreatic dysfunction, malformations and mental retardation (Johanson-Blizzard syndrome). *Nat Genet*. 2005;37:1345–1350. https://doi.org/10.1038/ng1681
113. Almshraki N, Abdulnabee MZ, Sukalo M, et al. Johanson-Blizzard syndrome. *World J Gastroenterol*. 2011;17(37):4247–4250. https://doi.org/10.3748/wjg.v17.i37.4247
114. Pearson HA, Lobel JS, Kochshis SA, et al. A new syndrome of refractory sideroblastic anemia with vacuolization of marrow precursors and exocrine pancreatic dysfunction. *J Pediatr.* 1979;95:976–984. https://doi.org/10.1016/s0022-3476(79)80286-3
115. Rotig A, Cormier V, Knoll F, et al. Site-specific deletions of the mitochondrial genome in the Pearson marrow-pancreas syndrome. *Genomics.* 1991;10:502–504. https://doi.org/10.1016/0888-7543(91)90342-c
116. Chen WL, Morishita R, Eguchi T, et al. Clinical usefulness of dual-label Schilling test for pancreatic exocrine function. *Gastroenterology*. 1989;96(5 Pt 1):1337–1345. https://doi.org/10.1016/s0016-5085(89)80021-6

117. Lindkvist B. Diagnosis and treatment of pancreatic exocrine insufficiency. *World J Gastroenterol*. 2013;19(42):7258–7266. https://doi.org/10.3748/wjg.v19.i42.7258
118. Moudiou T, Galli-Tsinopoulou A, Nousia-Arvanitakis S. Effect of exocrine pancreatic function on resting energy expenditure in cystic fibrosis. *Acta Paediatr.* 2007;96:1521–1525. https://doi.org/10.1111/j.1651-2227.2007.00478.x
119. Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. *J Am Diet Assoc.* 2008;108:832–839. https://doi.org/10.1016/j.jada.2008.02.020
120. Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr.* 2002;35:246–259. https://doi.org/10.1097/00005176-200209000-00004
121. Uc, A and Hussain SZ. Pancreatitis in Children. *Gastroenterology*. 2019;156:1969–1978. https://doi.org/10.1053/j.gastro.2018.12.043
122. Park A, Latif SU, Shah AU, et al. Changing referral trends of acute pancreatitis in children: a 12-year single center analysis. *J Pediatr Gastroenterol Nutr.* 2009;49:316–322. https://doi.org/10.1097/mpg.0b013e31818d7db3
123. Abu-El-Haija M, Kumar S, Quiros JA, et al. Management of acute pancreatitis in the pediatric population: a clinical report from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Pancreas Committee. *J Pediatr Gastroenterol Nutr.* 2018;66(1):159–176. https://doi.org/10.1097/mpg.0000000000001715
124. March PC. What is the best way to feed patients with pancreatitis. *Curr Opin Crit Care*. 2009;15:131–138. https://doi.org/10.1097/mcc.0b013e328319910a
125. Lakananurak N, Gramlicj L Nutrition management in acute pancreatitis: clinical practice consideration. *World J Clin Cases.* 2020;8(9):1561–1573. https://doi.org/10.12998/wjcc.v8.i9.1561
126. Petrov MS, Loveday BP, Pylypchuk RD, McIlroy K, Phillips AR, Windsor JA. Systematic review and meta-analysis of enteral nutrition

formulations in acute pancreatitis. *Br J Surg*. 2009;96:1243–1252. https://doi.org/10.1002/bjs.6862
127. Theodoridis X, Grammatikpoulpu MG, Petalidou A et. al. Nutritional interventions in pediatric pancreatitis: guidelines we can trust. *J Pediatr Gastroenterol and Nutr*. 2019;69(1):120–125. https://doi.org/10.1097/mpg.0000000000002364
128. Suddaby EC, Schiller S. Management of chylothorax in children. *Pediatr Nurs.* 2004;30:290–295.
129. McDonald KQ , Bears CM. A preterm infant with intestinal lymphangiectasia: a diagnostic dilemma. *Neonatal Netw.* 2009;28:29–36. https://doi.org/10.1891/0730-0832.28.1.29
130. Bliss CM, Schroy PC. Primary intestinal lymphangiectasia. *Curr Treat Options Gastroenterol.* 2004;7:3–6. https://doi.org/10.1007/s11938-004-0019-z
131. Gramlich L, Ireton-Jones C, Miles JM, et al. Essential fatty acid requirements and intravenous lipid emulsions. *J Pediatr Gastroenterol Nutr*. 2019;43:697–707. https://doi.org/10.1002/jpen.1537
132. Hyams JS, DiLorenzo C, Saps M et al. Functional disorders: children and adolescents. Gastroenterology. 2016;150:1456–1466. https://doi.org/10.1053/j.gastro.2016.02.015
133. de Bruijn CM, Rexwinkel R, Gordon M, Sinopoulou V, Benninga MA, Tabbers MM. Dietary interventions for functional abdominal pain disorders in children: a systematic review and meta-analysis. *Expert Rev Gastroenterol Hepatol*. 2022;16(4):359–371. https://doi.org/10.1080/17474124.2022.2055547
134. Parkman HP, Hasler WL, Fisher RD. American Gastroenterological Association technical review on the diagnosis and treatment of gastroparesis. *Gastroenterology*. 2004;127:1592–1622. https://doi.org/10.1053/j.gastro.2004.09.055
135. Parrish CR, Yoshida CM. Nutrition intervention for the patient with gastroparesis: an update. *Pract Gastroenterol.* 2005;30:29–66. https://www.researchgate.net/publication/281421254_Nutrition_intervention_for_the_patient_with_gastroparesis_An_update
136. Bouras E, Vazquez Roque M, Aranda-Michel J. Gastroparesis: from concepts to management. *Nutr Clin Pract.* 2013;28:437–447. https://doi.org/10.1177/0884533613491982

137. Lehmann S, Ferrie S, Carey S. Nutrition management in patients with chronic gastrointestinal motility disorders: a systematic literature review. *Nutr Clin Pract.* 2020;35:219–230. https://doi.org/10.1002/ncp.10273
138. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *New Engl J Med.* 1999;320:448–454. https://doi.org/10.1056/nejm199902113400607
139. Aziz I, Whitehead WE, Palsson OS, et al. An approach to the diagnosis and management of Rome IV functional disorders of chronic constipation. *Expert Rev Gastroenterol Hepatol*. 2020;14(1):39–46. https://doi.org/10.1080/17474124.2020.1708718
140. Clein NW. Cow's milk allergy in infants. *Pediatr Clin North Am.* 1954;25:949–962. https://doi.org/10.1016/S0031-3955(16)30159-6
141. Iacono G, Cavataio F, Montalto G, et al. Intolerance of cow's milk and chronic constipation in children. *N Engl J Med.* 1998;339:1100–1104. https://doi.org/10.1056/nejm199810153391602
142. Dahr S, Tahan S, Sole D, et al. Cow's milk protein intolerance and chronic constipation in children. *Pediatr Allergy Immunol.* 2001;12:339–342. https://doi.org/10.1034/j.1399-3038.2001.0o057.x
143. Guimães EV, Goulart EM, Penna FJ. Dietary fiber intake, stool frequency and colonic transit time in chronic functional constipation in children. *Braz J Med Biol Res*. 2001;34:1147–1153. https://doi.org/10.1590/s0100-879x2001000900007
144. Pipers MA, Tabbers MM, Benninga MA, et al. Currently recommended treatments of childhood constipation are not evidence based: a systematic literature review on the effect of laxative treatment and dietary measures. *Arch Dis Child.* 2009;94:117–131. https://doi.org/10.1136/adc.2007.127233
145. U.S. Department of Agriculture and U.S. Department of Health and Human Services. *Dietary Guidelines for Americans, 2020–2025. 9th Edition*. Accessed November 14, 2022. https://www.dietaryguidelines.gov/sites/default/files/2021-03/Dietary_Guidelines_for_Americans-2020-2025.pdf.
146. Huertas-Ceballos AA, Logan S, Bennett C, Macarthur C. Dietary interventions for recurrent abdominal pain (RAP) and irritable bowel

syndrome (IBS) in childhood. *Cochrane Database Syst Rev.* 2009; (1):CD003019.134. https://doi.org/10.1002/14651858.cd003019.pub3
147. Sood MR. Treatment approaches to irritable bowel syndrome. *Pediatr Ann.* 2009;38:272– 276. https://pubmed.ncbi.nlm.nih.gov/19476300/
148. Halmos E, Power V, Shepherd S. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. *Gastroenterology.* 2014;146:67–75. https://doi.org/10.1053/j.gastro.2013.09.046
149. Vanuytsel T, Tack J, Boeckxstaens G. Treatment of abdominal pain in irritable bowel syndrome. *J Gastroenterol.* 2014;49:1193–1205. https://doi.org/10.1007/s00535-014-0966-7
150. Shepherd S, Gibson P. *The Complete Low-FODMAP Diet.* The Experiment; 2013.
151. Fernández-Bañares F, Esteve-Pardo M, de Leon R, et al. Sugar malabsorption in functional bowel disease: clinical implications. *Am J Gastroenterol.* 1993;88:2044–2050.
152. Shen YA, Nahas R. Complementary and alternative Medicine for treatment of irritable bowel syndrome. *Can Fam Physician.* 2009;55:143–148. https://www.cfp.ca/content/cfp/55/2/143.full.pdf
153. Bijkerk CJ, Muris JWM, Knottnerus JA, Hoes AW, de Wit NJ. Systematic review: the role of different types of fibre in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther*. 2004;19:245–251. https://doi.org/10.1111/j.0269-2813.2004.01862.x
154. Newlove-Delgado TV, Martin AE, et al. Dietary interventions for recurrent abdominal pain in childhood. Cochrane Database Syst Rev. 2017;3(3):CD010972. https://doi.org/10.1002/14651858.cd010972.pub2
155. Lacy BE, Pimentel M, Brenner DM. ACG clinical guideline: management of irritable bowel syndrome. *Am J Gastroenterol*. 2021. 116(1):17–44. https://doi.org/10.14309/ajg.0000000000001036
156. Torii A, Toda G. Management of irritable bowel syndrome. *Intern Med.* 2004;43:353–358. https://doi.org/10.2169/internalmedicine.43.353
157. Zhang M, Li Y. Eosinophilic gastroenteritis: a state-of-the-art review. *J Gastroetnerol Hepatol.* 2017;31(1):64–72. https://doi.org/10.1111/jgh.13463

158. Muir A, Falk GW. Eosinophilic esophagitis: a review. JAMA. 2021;326(13):1310–1318. https://doi.org/10.1001/jama.2021.14920
159. Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated international consensus diagnostic criteria for eosinophilic sophagitis: proceedings of the AGREE Conference. *Gastroenterology*. 2018,155:1022–1033.e10. https://doi.org/10.1053/j.gastro.2018.07.009
160. Lucendo AJ, Molina-Infante J. Treatment of eosinophilic esophagitis with diets. *Minerva Gastroenterol Dietol*. 2020;66(2):124–135. https://doi.org/10.23736/s1121-421x.19.02634-5

Test Your Knowledge Answers

1. The correct answer is **D**. This patient has Crohn's disease. Diet therapy is effective in the treatment of Crohn's disease. No difference exists in the effectiveness of the polymeric versus elemental diets. A clear liquid diet is inadequate.
2. The correct answer is **A**. Patients with IBD often have deficits of several nutrients. This patient has disease of the ileum and is therefore at greater risk of B12 malabsorption. The combination of anemia and low MCV are suggestive of iron deficiency. Both sulfasalazine and methotrexate interfere with folate metabolism; therefore, routine supplementation with folate is recommended. It should be mentioned that patients with inflammatory bowel disease are also at risk for bone disease, and vitamin D and calcium may also be considered.
3. The correct answer is **C**. Currently, a strictly GF diet is the sole recommended treatment for celiac disease and it should be maintained lifelong.[147] Research is ongoing to discover alternative treatments, including enzyme therapy and immune agents, but none are recommended yet.[148] It should be emphasized that the GF diet should be continued even after all symptoms have abated.
4. The correct answer is **D**. Pancreatic insufficiency can lead to the malabsorption of fat-soluble vitamins if not adequately treated. The direct measurement of Vitamin A, D, E, and K is therefore recommended.

5. The correct answer is **B**. Individuals with pancreatic insufficiency have a higher resting energy requirement than individuals with pancreatic sufficiency. Rather than a low-fat diet, pancreatic enzyme replacement therapy should be optimized. Folate and iron absorption are not directly affected by pancreatic insufficiency.

24

Hepatic Disease

Julie Bonn, MD; Samuel A. Kocoshis, MD

Learning Objectives

1. Outline the underlying mechanisms associated with pediatric liver disease and the risk factors for nutrition deficiencies.
2. Describe supplementation with fat and fat-soluble vitamins in cholestatic liver disease.
3. Understand the macronutrient and micronutrient requirements for infants and children with liver disease.
4. Identify common nutrition problems after liver transplantation.

Introduction

In this chapter, we delve into the topic of nutrition management for infants and children with liver diseases. The liver is responsible for the synthesis, storage, and metabolism of carbohydrates, protein, and fat. It also plays a crucial role in maintaining homeostasis. Thus, pediatric patients with liver diseases face nutritional impediments beyond the direct challenges of their diagnosis.

The liver synthesizes major growth factors such as insulin-like growth factor-1 (IGF-1) and its binding proteins; therefore, pediatric patients with severe liver dysfunction become growth hormone-resistant.[1] The

malfunctioning liver has reduced glycogen stores leading to a risk for hypoglycemia in pediatric patients with chronic liver disease. The reduced glycogen stores lead to amino acids being metabolized for energy rather than protein synthesis.[2] The detoxification of ammonia and synthesis of clotting proteins may also be impeded.[2] Finally, the synthesis of cholesterol and high-density lipoproteins may be faulty, as may the uptake, hydrolysis, and transport of triglycerides.[3] These changes frequently result in hypertriglyceridemia and hypocholesterolemia under conditions of severe hepatic dysfunction.

The significance of a multidisciplinary approach becomes evident when considering the management of pediatric liver disease. A team composed of hepatologists, nurses, dietitians, pharmacists, social workers, speech therapists, occupational therapists, and physical therapists will provide patients with the most comprehensive care and interventions.

The spectrum of liver dysfunction varies from acute viral hepatitis to chronic metabolic disorders. Acute diseases such as viral or toxin-induced hepatitis typically require supportive therapy alone, whereas some metabolic disorders use nutrition therapy as the definitive treatment. Distinctive nutrition demands correspond to the specific liver disease, its progression, and even the possibility that liver transplantation may eventually be required.

Causes of Malnutrition

Malnutrition is common in pediatric liver disease and adversely affects survival both before and after liver transplantation.[4-9] Beyond the impaired intermediate metabolism of carbohydrates, protein, and fat, a variety of factors account for malnutrition in the context of primary hepatic disease. Most studies exploring the mechanisms of malnutrition in liver disease have been performed in adults, but it is known that malnutrition can occur both before and after liver transplantation in children.[7,8] Even though the mechanisms of malnutrition in liver disease as shown in Table 24-1 have not been as fully investigated in pediatric patients, it is quite likely that they are identical.[4-6]

TABLE 24-1. Etiology and Pathophysiology of Malnutrition in Chronic Liver Disease

Etiology	Pathophysiology
Inadequate intake	Inappropriate restriction of diet, anorexia, diminished gastric capacity, abdominal distension, ascites, organomegaly
Iatrogenic factors	Excessive sodium or protein restriction, medication side effects, diuretics
Abnormal hormonal metabolism	Insulin resistance, growth hormone resistance, altered insulinlike growth factor 1 release
Malabsorption	Intraluminal bile acid deficiency, pancreatic insufficiency, portal hypertension-related enteropathy, medications
Increased energy expenditure	Hypermetabolism, recurrent infections, medications

Inadequate Intake

A foremost concern among both adult and pediatric liver patients is inadequate dietary intake. A simple reason that intake might be inadequate is that these patients are frequently offered low-protein, low-sodium diets that are unappetizing and unappealing. This practice may result not only in suboptimal oral intake but also in a diet of poor caloric quality. Many forms of liver disease result in anorexia, and one potential mechanism is the elevation of both serum and tissue leptin levels.[10,11]

Leptin, an appetite-suppressing hormone, is probably cleared via enterohepatic circulation, and serum levels are elevated in patients with hepatic fibrosis and other forms of liver disease. However, the role of leptin in producing anorexia among patients with liver disease remains controversial, specifically because leptin levels are consistently normal in some forms of liver disease (eg, primary biliary cirrhosis) and are consistently elevated in other forms (eg, Laennec's, or alcoholic, cirrhosis).[10,11]

Another factor accounting for anorexia is hepatic encephalopathy. Anorexia has long been recognized as a major symptom of encephalopathy, and it is remarkably difficult to treat without successfully treating the underlying cause of the liver disease. Among children with inflammatory hepatitides, proinflammatory cytokines are released, predictably resulting in

anorexia.[12] Although the phenomenon of hyperinsulinemia and insulin resistance has not been established in children with chronic liver disease, it has been confirmed in adults and may also contribute to anorexia.[13]

Yet another factor potentially contributing to anorexia is zinc deficiency, which is known to be quite common among patients with chronic liver disease.[14] Furthermore, the gastric capacity of children with either massive hepatosplenomegaly or ascites may be so restricted (because of gastric compression by viscera or ascitic fluid) that adequate oral intake becomes impossible.

Iatrogenic Factors

The effect of iatrogenic factors on the nutrition state of pediatric liver patients should not be minimized. Excessive sodium restriction in the absence of hyperaldosteronism will result in salt depletion syndrome and may induce secondary hyperaldosteronism that would not have been present otherwise. This factor can lead to both malnutrition and growth failure. Unwarranted protein restriction can also result in deficiencies of both somatic and visceral proteins, with subsequent malnutrition. Therefore, clinicians caring for children with liver dysfunction should not restrict salt and should exercise judicious caution in restricting protein in the absence of encephalopathy refractory to pharmacotherapy.

Known to be relatively safe, large-volume paracentesis has been a popular therapy for adults with ascites, but it has been relatively unpopular in the pediatric setting because of concerns about large, rapid fluid shifts.[15] This potential complication notwithstanding, the practice now has advocates in the pediatric hepatology community. If large-volume paracentesis is used in pediatric patients, the loss of plasma proteins can be prodigious, rendering the patient deficient in both visceral and somatic proteins. Therefore, for patients undergoing paracentesis, albumin infusions are advisable during paracentesis to maintain adequate circulating blood volume. Adequate protein intake should be maintained in the absence of medically refractory encephalopathy.

Many of the medications administered to children with hepatic disease may also negatively impact their nutrition state. Diuretics, if administered overzealously, may deplete the child's salt supply. Broad-spectrum systemic

or enteral antibiotics may eliminate vitamin K–synthesizing enteric flora, resulting in vitamin K deficiency among cholestatic patients. Additionally, neomycin, commonly administered for hepatic encephalopathy, is believed to produce villous atrophy, reduced intestinal surface area, and malabsorption of multiple nutrients. Administration of lactulose for encephalopathy may speed intestinal transit enough to result in malabsorption as well. Additionally, cholestyramine, an anion exchange resin used to treat the pruritus of cholestasis by binding bile acids, may be so efficient that the intraluminal bile acid concentration may fall below the critical micellar concentration, resulting in malabsorption of fat and fat-soluble vitamins.[16] Because cholestyramine exchanges organic anions for chloride, hyperchloremic metabolic acidosis with resultant growth failure and malnutrition may occur in children on this medication.

Malabsorption

Pediatric patients with liver disease are more likely to have cholestatic disease than their adult counterparts. In cholestatic patients, bile acids are retained in the liver and excreted very poorly into bile. Therefore, intraduodenal primary bile acid concentrations customarily fall below the critical micellar concentration necessary for the efficient solubilization and transport of fat and fat-soluble vitamins across the unstirred water layer and into the enterocyte. Malabsorption is very common and requires enteral administration of large quantities of fat-soluble vitamins, as well as an enteral “cocktail” of medium-chain triglycerides (MCTs) and long-chain triglycerides (LCTs) in food or formula. Patients must receive enough long-chain fat to prevent essential fatty acid deficiency, and they must receive enough medium-chain fat to optimize their enteric fat balance. Arachidonic, linoleic, and linolenic acids, all essential fatty acids, are long-chain fats that can only be derived from dietary LCTs. MCT formulas that were designed during the late 1960s for cholestatic patients were deficient in LCTs, commonly resulting in essential fatty acid deficiency among this population.[17]

Malabsorption may occur in select cases of pediatric cholestasis, not only from intraluminal bile acid deficiency but also from exocrine pancreatic insufficiency. Both cystic fibrosis and Shwachman-Diamond

syndrome, systemic disorders characterized by exocrine pancreatic insufficiency, may present during the neonatal period with cholestasis. Exocrine pancreatic insufficiency is also a less recognized feature of 2 childhood disorders characterized by severe cholestasis: progressive familial intrahepatic cholestasis type 1 (PFIC 1) and Alagille syndrome.

PFIC 1, previously known as Byler disease, occurs because of a mutation in the *ATP8B1* gene, previously known as the FIC1 gene. *ATP8B1* mutations result in reduced activity of the Farnesoid X nuclear receptor (FXR), which maintains intrahepatocyte bile acid homeostasis as well as reduced activity of the cystic fibrosis transporter. As a result, patients with PFIC 1 frequently experience diarrhea, malabsorption, recurrent pancreatitis, and pancreatic fibrosis, leading to exocrine pancreatic insufficiency.[18,19]

Alagille syndrome arises from mutations in the Jagged1 chromosome, which participates in the notch signaling pathway.[18,19] These mutations result in bile duct malformations, leading to intrahepatic bile duct paucity. The syndrome is also characterized by butterfly vertebrae; right-sided cardiac disease, such as pulmonary artery atresia or tetralogy of Fallot; posterior embryotoxon of the eye; and facies typified by a long nose, deep-set eyes, prominent frontal ridge, and pointed chin. People with Alagille syndrome frequently have steatorrhea disproportionate to their degree of cholestasis.[20] Studies in humans have documented pancreatic insufficiency in Alagille syndrome due to pancreatic ductal and acinar malformations. Similar pancreatic histology is seen in Jagged1 knockout animals, whose pancreatic ductules and acini are malformed like the malformation of the bile ductules.[21]

It is notable that any form of chronic liver disease, whether cholestatic or noncholestatic, may be associated with exocrine pancreatic insufficiency. Longstanding cirrhosis and portal hypertension occasionally result in exocrine pancreatic insufficiency due to either pancreatic fibrosis because of venous congestion or the absence of hepatic regulatory mechanisms for satisfactory pancreatic enzyme secretion in response to dietary stimulus.[22] Patients suspected of having pancreatic insufficiency because of fatty stools or poor weight gain should undergo testing of pancreatic function, either by formal pancreozymin-secretin testing or by fecal elastase measurement.

Documentation of exocrine pancreatic insufficiency mandates treatment with pancreatic enzymes.

Intestinal function itself may become impaired in children with chronic liver disease. Portal hypertension with or without cholestasis may be so severe as to result in protein-losing enteropathy. In addition, the elevated serum bile acid concentrations observed in cholestasis may have a deleterious effect on small intestine function. In studies performed among dogs with surgically created Thiry-Villa loops, exposure of the mesenteric artery to bile acids at concentrations of 8 to 22 μmol results in impaired transport of water and electrolytes.[23]

Hypermetabolism

The prevalence of hypermetabolism is unknown in children with liver disease, but at least 30% of cirrhotic adults are hypermetabolic.[6] Even though some cirrhotic adults are normometabolic and a few are hypometabolic, those who are hypermetabolic display a measured resting energy expenditure of 20% or more above predicted levels. Hypermetabolism in cirrhotic adults is closely associated with suboptimal total body mass and total body protein.

One documented mechanism for this phenomenon is increased adrenal tone, presumably because of reduced hepatic catecholamine metabolism. Patients with documented hypermetabolism express a starvation pattern when their respiratory quotient is measured: they have respiratory quotients approaching 0.6, documenting that they begin using fat for energy quite early after a fast and suggesting a reduction in glycogen stores. Under these conditions, gluconeogenesis is increased, and protein catabolism is accelerated. Thus, hypermetabolic patients with cirrhosis are best served by taking 4 or 5 meals per day and receiving adequate dietary protein, even in the face of encephalopathy. For this reason, pharmacologic management of encephalopathy should be attempted before reducing protein.

Specific Pediatric Liver Disorders

Neonatal Cholestasis

Infantile liver disease is quite commonly cholestatic in nature.[24,25] Extrahepatic biliary atresia is responsible for approximately half of the cases among infants with cholestasis; the rest result from various infectious and metabolic disorders. As molecular medicine has advanced, disorders previously lumped into the "wastebasket" diagnosis of "neonatal hepatitis" are now being recognized as discrete entities. The following are some of the many infantile disorders characterized by cholestasis at the time of presentation:

- Alagille syndrome
- Gestational alloimmune liver disease of neonates
- Progressive familial intrahepatic cholestasis disorders
- Citrin deficiency
- Niemann-Pick type C
- Type I tyrosinemia
- Galactosemia
- Hereditary fructose intolerance
- Type IV glycogenosis

In addition, although cholestasis is far from universally present in α-1-antitrypsin deficiency or cystic fibrosis, it may be the dominant symptom for certain patients with these disorders.

Nutrition strategies may be the definitive therapy for some of these disorders; for example, the elimination of dietary galactose for galactosemia and fructose for hereditary fructose intolerance is curative. For other disorders, such as tyrosinemia, reduction of dietary tyrosine is helpful but not curative. Because the block in tyrosine metabolism results in an overabundance of toxic intermediates, such as succinylacetone, succinylacetoacetate, fumarylacetoacetate, and maleylacetoacetate, upstream inhibition of tyrosine metabolism with 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) has been lifesaving insofar as metabolism is shunted to nontoxic intermediates, such as parahydroxy-phenylpyruvate.[26]

Neonatal hemochromatosis is now attributable to gestational alloimmune liver disease (GALD) in nearly all cases.[27] GALD is an alloimmune disorder, with maternal immunoglobulin G (IgG) antibodies affecting the fetal liver.[27,28] The result is a complement-mediated hepatocyte injury causing marked loss of hepatocytes with surviving hepatocytes showing iron storage. Unlike therapy for adult-onset hemochromatosis associated with mutations in the *HFE* gene, treatment of GALD should not include chelation but rather double-volume exchange transfusion to remove existing reactive antibodies followed immediately by high-dose intravenous immunoglobulin to block antibody-induced complement activation.[27,28]

Whatever the cause of neonatal cholestasis, the basic nutrition strategy should be to provide ample quantities of fat-soluble vitamins (vitamins A, D, K, and E) and to monitor vitamin levels and/or coagulation studies frequently to prevent fat-soluble vitamin deficiency. Because some element of fat malabsorption nearly always occurs during cholestatic periods, a substantial percentage of fat calories should be given in the form of MCTs, which do not require micellar solubilization before absorption into the portal circulation. However, infants should not be overloaded with MCTs, because MCTs cannot be stored and must be immediately oxidized, putting infants at risk for metabolic acidosis from short-chain fatty acid oxidation products.[29] Furthermore, MCTs are less calorically dense than LCTs because of the reduced number of carbon atoms in their skeleton. Overenthusiastic efforts to provide MCTs to cholestatic infants resulted in diets that were inadequate in essential fatty acids, leading to essential fatty acid deficiency.[17] At worst, with complete biliary diversion, about 50% of long-chain fats can be absorbed without full solubilization. Therefore, infants with cholestasis should receive a mixture of MCTs and LCTs.[4] Formulas with a 1:1 mix of the 2 types of fat tend to result in optimal fat balance for infants with cholestasis.

Noncholestatic Liver Disease

Some pediatric liver disorders infrequently result in cholestasis, including viral hepatidities, autoimmune hepatitis, α-1-antitrypsin deficiency, glycogenoses, mitochondrial hepatopathies, Wilson disease, and nonalcoholic steatohepatitis. When the patient is not cholestatic, absorption

is customarily normal and specialized formulas may be unnecessary, but it is imperative to provide adequate calorie and protein intake. It is also important to recognize the underlying metabolic abnormalities that impede the adequate assimilation of calories and design nutrition regimens that maximize energy availability. Providing 150% of the estimated caloric and protein requirement to cirrhotic patients is quite reasonable based on adult data suggesting hypermetabolism.[4-6] Additionally, patients with primary mitochondrial disorders or glycogenoses should be advised to avoid prolonged fasting because incomplete beta oxidation in mitochondrial disease and absent glycogenolysis result in hypoglycemia and/or the production of toxins, such as ketoacids.

Nutrition as Primary Therapy for Select Liver Disorders

Glycogen Storage Diseases

The glycogen storage diseases, also known as glycogenoses, are a group of disorders whereby enzyme deficiencies adversely affect glycogen degradation or glycogen synthesis. There are at least 10 of these disorders, affecting the liver, muscle, or both. Dietary therapy is variably effective for these disorders.[30-34] For example, the only effective therapy for type IV glycogen storage disease is liver transplantation. Among those for which dietary therapy is beneficial, types II and VI have shown only modest responses to high-protein diets; the only definitive therapy for type II is enzyme replacement. The greatest dietary advances have been made for type I. This disorder, caused by impaired movement of glucose-6-phosphatase into or out of the endoplasmic reticulum, is characterized by fasting hypoglycemia, hyperuricemia, lactic acidosis, and hyperlipidemia.[30-34] Type IB is also characterized by neutrophil dysfunction, and frequently, inflammatory bowel disease. Late complications include hepatic adenomas, pulmonary hypertension, and renal hyperfiltration. Initial trials in the 1980s of continuous enteral glucose or polycose infusions to prevent hypoglycemia had the unexpected benefit of totally or partially reversing lactic acidosis, hyperuricemia, and hyperlipidemia. Glucose infusion rates of 8 mg/kg/min for infants, 6

mg/kg/min for children, and 4 mg/kg/min for adults were empirically noted to be beneficial. Raw cornstarch has been used in preference to glucose polymers because of its longer duration of action, obviating the need for a nasogastric tube or gastrostomy tube. The cornstarch must be uncooked because cooking partially hydrolyzes it and produces a glucose tolerance curve similar to when glucose is administered. A cornstarch dose of 1.75 to 2.75 g/kg will deliver about 5 to 7 mg/kg/min of glucose for approximately 6 hours.[31,34]

Wilson Disease

Wilson disease is caused by a mutation in a p-type adenosine triphosphatase (ATPase), which is responsible for transporting copper across membranes to permit the formation of metallothionein and biliary excretion of copper.[34,35] Defective copper excretion results in excessive hepatic copper stores, leading to hepatic dysfunction. Excessive brain and renal copper stores are responsible for central nervous system and renal manifestations.

Wilson disease can be treated with copper chelators if it doesn't progress too far. Hepatic manifestations vary from mild transaminase elevation to fulminant hepatic failure. Typically, when the total body copper level is elevated, there is a reciprocal deficiency in zinc because copper and zinc share a common intestinal transporter. Excessive copper absorption results in inadequate zinc absorption. Zinc is a cofactor for alkaline phosphatase synthesis, so in Wilson disease, the alkaline phosphatase level is disproportionally low in the face of severe liver dysfunction. Chelation is employed to increase copper excretion or to decrease copper absorption. D-penicillamine has been used for years, but trientene is just as effective, with a lower risk of complications. Zinc can also be used to prevent copper absorption by competitive inhibition of intestinal transporters.[36] A newer agent, tetrathiomolybdate, shows great promise insofar as it complexes with copper in the intestinal lumen, rendering copper unabsorbable, and it is absorbed itself, complexing with serum copper and albumin, preventing cellular uptake of copper.[37]

Beyond chelation, dietary therapy is important (especially in the early phases of treatment). Foods high in copper, such as shellfish, nuts, gelatin, mushrooms, liver, and soy products, should be avoided. In addition, the

copper content of the patient's major water supply should be analyzed if well water is consumed.

Metabolic Dysfunction-Associated Steatotic Liver Disease

Ironically, overnutrition should be the etiology of a liver disease that is seen in pandemic proportions throughout the world. Obesity is present in more than 40% of the adult population and 25% of the pediatric population in the United States[38], and 25% to 30% of adults have some degree of fatty liver.[39] What was formerly known as nonalcoholic fatty liver disease has recently been renamed metabolic dysfunction-associated steatotic liver disease and may range in severity from simple fatty infiltrate to steatohepatitis and cirrhosis.[40]

Steatohepatitis is characterized by both fat and inflammation, and its prognosis is far worse than steatotic liver disease alone. Natural progression or a second hepatic insult of any sort may result in fibrosis and eventually cirrhosis. The factors governing the progression of steatotic liver disease to steatohepatitis are not fully understood, but oxidative stress seems to play a role. Therapy should target comorbid conditions such as type 2 diabetes mellitus and hypertriglyceridemia and should emphasize weight reduction. In addition, treatment with betaine, n-acetylcysteine, vitamin E, or ursodeoxycholic acid may lower liver enzyme levels.[39] Oral hypoglycemics such as gemfibrozil or metformin may decrease hepatic steatosis and improve enzymes, but clofibrate seems to be ineffective.[39] Ultimately, the most reliable therapy is a sensible weight loss regimen in which losing 3% to 5% improves steatosis, and losing >10% improves steatohepatitis and fibrosis. The optimal rate of loss should be <0.9 kg/wk because losing too rapidly may result in excessive lipid peroxidation and more rapid progression to fibrosis.[39]

Assessment of Nutrition State

Protein-energy malnutrition is the most common comorbidity associated with chronic liver disease in children. Because malnutrition is directly linked to unsatisfactory patient and graft survival following pediatric liver

transplantation, optimization of nutrition status is of paramount importance.[7,8]

An initial comprehensive nutrition assessment should be conducted when patients first present with liver insufficiency. Evaluating formula selection, feeding frequency, daily intakes, vitamin and mineral supplementation, and anthropometric status—including the assessment of lean body mass (LBM)—is essential to initiate early interventions that will optimize nutrition status and minimize complications. The usual markers of nutrition status, such as weight and body mass index, are very unreliable in the face of advanced liver disease because body weight is significantly impacted by ascites, edema, and organomegaly. LBM assessment is best evaluated by serial upper-arm measurement of mid-arm-muscle circumference and triceps skinfolds. These measurements are a simple, noninvasive way to detect early deterioration in nutrition status for which aggressive nutrition interventions are required.[41-43]

For adults, sarcopenia can be defined as either a reduction in muscle mass or muscle strength, or a combination of both.[44] However, because children are often uncooperative when subjected to strength testing, sarcopenia is most often defined as the objective reduction in muscle mass alone and total psoas muscle area <2 SDs below the mean or < the fifth percentile. Less commonly, skeletal muscle mass <2 SDs below the mean or (in steatotic liver disease) whole body muscle to fat ratio <1 SD below the mean are used as markers of sarcopenia.[44]

Although various imaging modalities allow for the measurement of muscle mass, the most reliable precise modality in children is total psoas muscle surface area on cross-sectional imaging at the L3/L4 or L4/L5 level. Sarcopenia is prevalent in 24% to 56% of various pediatric liver disease populations, and is associated with poor outcomes, including increased mortality, intensive care unit and hospital length of stay, and decreased health-related quality of life.[45] Even though obtaining cross-sectional imaging for the sole purpose of assessing sarcopenia is not recommended, most children with chronic liver disease undergo imaging for other reasons and those scans can be used to measure muscle mass.

Notably, sarcopenia may precede overt liver failure. Several pathophysiologic mechanisms lead to sarcopenia including:

- Inadequate somatic protein synthesis.
- Reduced glycogen stores.
- Increased protein catabolism.
- Increased metabolic demand.
- Reduced testosterone in post-pubertal males.
- Systemic inflammation.[6]

The subjective global nutrition assessment is a simple noninvasive tool to help classify malnutrition and predict poor outcomes in children with chronic liver disease.[46]

Specific Nutrient Requirements

Energy

Recommended caloric intakes for infants and children with end-stage liver disease are approximately 130% to 150% of the recommended dietary allowance (RDA) for age, based on ideal body weight or actual dry weight. This computes to about 130 to 150 kcal/kg/d in infants and 90 to 120 kcal/kg/d in children.[4,46]

Protein

Goals for age are generally provided unless encephalopathy with fulminant hepatic failure and an elevated ammonia level is observed. Enough protein must be provided to preserve LBM and prevent catabolism with the breakdown of endogenous protein stores, but not contribute to hyperammonemia and encephalopathy. Infants generally require 3 to 4 g/kg/d.[4,47] The use of branched-chain amino acid (BCAA) formulas or supplements in infants and children improves nitrogen balance but has fallen out of favor because the cost:benefit ratio remains low. Still, BCAA-enriched nutrition is a safe and effective therapy, and further clinical application may be beneficial.[48]

Fat

Formula or oral supplements providing 30% to 50% of dietary calories as fat, starting with 30% MCTs, are recommended to optimize fat absorption.

However, a balance is needed to provide appropriate lipid sources, an appropriate MCT:LCT ratio, and a palatable diet.[4,49] Infant formulas that contain MCT oil (preferably those highest in MCT oil) should be progressively calorie-concentrated up to a goal of 30 kcal/oz with a balance of concentrated infant formula base and modular additives of glucose polymers and/or MCT oil. Children older than 1 year of age should be trialed on oral MCT-oil-containing pediatric formulas and modular additives mixed with food items for additional calories. These formulas generally contain at least 60% MCT oil and will enhance fat absorption.

When infant formulas are concentrated to 30 kcal/oz, it may be advisable to change to a semi-elemental toddler or pediatric formula that is flavored to encourage better oral intake of an MCT-oil-containing beverage. Some manufacturers have recently developed tasteless MCT oil powder and liquid supplements that can easily be added to foods or beverages.[4,49]

Fluids

Infants and children with liver disease require adequate fluid volume to ensure appropriate caloric and protein intake to maintain LBM. Because maintaining good nutrition is more important than fluid restriction, diuretics may be required to minimize ascites and edema.[48]

Vitamins

The intestinal absorption of vitamins A, D, E, and K is strongly dependent on adequate hepatic secretion of bile acids into the intestinal lumen. Therefore, children with chronic liver disease and hepatic dysfunction are at risk of fat-soluble vitamin deficiency and should be evaluated early as deficiency can occur in infancy.[4,48] Proper monitoring of blood levels and appropriate supplementation is imperative. Table 24-2 summarizes fat-soluble vitamin supplement doses as follows:

- The recommended oral supplementation of vitamin A ranges from 1500 to 7500 mcg/d of water-miscible preparations of vitamin A per day.[50]
- Vitamin E is indicated for all infants and children who are cholestatic and should be dosed at 10 to 16/75 mg/d of a water-soluble preparation (tocopherol polyethylene glycol succinate [TPGS]).[4,51]

- Vitamin D supplementation in children with liver disease is essential, especially if there is potential for transplantation because preexisting bone loss can be further aggravated during the early posttransplant period by using corticoid steroids.[52] Vitamin D should be administered in a daily dose of ergocalciferol (D2) or cholecalciferol (D3), 3 to 10 times the RDA for age. Depending on the vitamin D level, either of these agents can be given in a dose of 800 to 8000 IU/d. Although oral cholecalciferol tends to be more bioavailable than oral ergocalciferol, cholecalciferol requires sun exposure for conversion to ergocalciferol, and in the winter, sun exposure may be reduced. Another reason for giving ergocalciferol is that most high-concentration liquid pediatric vitamin D preparations are composed of ergocalciferol rather than cholecalciferol. Mixing the water-soluble form of vitamin E (TPGS) with vitamin D improves vitamin D absorption in children with cholestasis.[53]
- Oral vitamin K supplementation of 2.5 to 5.0 mg/d should be administered to all infants and children who have chronic cholestasis.[4,51] Parenteral administration may be required during illness and bleeding because of poor enteral vitamin K absorption.

TABLE 24-2. Fat-Soluble Vitamin Recommendations

Vitamin	Amount Given
Vitamin A (aqueous)	1500−7500 mcg/d
Vitamin E	10−16/75 mg/d
25-OH vitamin D	20−200 mcg/d
Vitamin K	2.5–5.0 mg/d

Abbreviation: TPGS, tocopherol polyethylene glycol succinate.

Children should generally be started on a commercially available multivitamin supplement. A multivitamin formulation will usually maintain fat-soluble vitamins in a normal range, but if normal levels cannot be achieved, additional individual supplementation must be added.[4,51]

Minerals

Supplementation with calcium, zinc, and sometimes iron may be required. Calcium absorption is not significantly impaired in children with chronic cholestatic liver disease compared with controls, but it can be improved by vitamin D administration. Supplementation will improve calcium intake and allow for positive calcium balance. Calcium-fortified foods such as orange juice and waffles or palatable agents such as calcium carbonate or calcium soft chews can also be used for calcium supplementation in children. The repletion of magnesium levels in cholestatic children may also improve bone mineral density.

Zinc deficiency, which is required for the crucial enzymatic processes that affect liver metabolism, is common in this population. The usual dose of zinc for supplementation is 1 to 2 mg/kg/d of elemental zinc.

Because of the malnutrition associated with pediatric liver disease and recurrent gastrointestinal bleeding, these patients may be predisposed to iron deficiency; thus, iron supplementation may be required. Copper, on the other hand, is excreted into the intestinal tract via the biliary route. Therefore, in patients with cholestatic disease, copper may be retained in potentially toxic amounts.[4,47]

Enteral Nutrition

When patients are unable to consume adequate calories to maintain appropriate LBM, supplemental enteral tube feeding should be initiated. Many proprietary formulas are available for individuals with liver disease. Nasogastric tubes are the preferred route of administration because of their easy placement and use if patients can tolerate adequate formula volume in their stomachs to achieve goals. However, in many instances, nasojejunal tube placement must be used because of emesis from medications and volume intolerance secondary to abdominal distension with ascites and/or organomegaly. Importantly, esophageal varices are not a contraindication to nasoenteric tube placement, but caution should be used with placement in these patients.

Nocturnal drip feedings are commonly used so that oral feeding skills can be maintained during the day. This feeding schedule allows for

supplementation during the normal hours of fasting and may also be beneficial in patients with end-stage liver disease who are unable to maintain fasting glucose levels overnight. Nocturnal tube feedings have been theorized to disrupt circadian rhythms but there are no randomized trials to compare feeding schedules in children.[54] In many instances, these patients progress to 24-hour continuous tube-feeding infusions to achieve the increased intakes required to maintain nutrition status.

Attempting to maintain oral-motor function is essential during pretransplant care to ensure the appropriate and opportune transition to normal feedings post-transplant. In many instances, enteral tube feeding supplementation may be required for a short duration posttransplant until adequate oral intake can be achieved. As posttransplant patients normalize their daily schedules, the pain subsides, and with the added effect of appetite stimulation from higher-dose steroids, oral intake can quickly achieve and sometimes even surpass goals.[55]

Parenteral Nutrition

Parenteral nutrition (PN) may be required when complications such as severe varices, gastrointestinal bleeding, excessive emesis, or recurrent complications make it impossible to safely provide feeding enterally or when adjunctive nutrition therapy is needed in patients who are severely malnourished and cannot achieve full enteral nutrition support. PN solutions should include a balance among standard amino acids, dextrose, lipids, electrolytes, and minerals designed to meet nutrition needs while minimizing metabolic complications. In many instances, this route of nutrition support is reserved as a last resort because of its known deleterious effect on the liver, but PN has also been touted by some to successfully maintain and build LBM before orthotopic liver transplant.[56]

Whatever modality of nutrition support is used pretransplant, serial anthropometric and laboratory measurements are recommended to follow the effects and adequacy of nutrition interventions once deficiencies have been identified.[4–6]

Nutrition After Liver Transplantation

Protein-energy malnutrition and growth failure are observed in 60% of infants and children with chronic liver disease.[8,9] To prevent rapid deterioration of nutrition status and the profound complications of end-stage liver disease, liver transplantation should be performed promptly.[57] Before transplant, nutrition support goals should be focused on the prevention of any further liver injury, the minimization of nutrient depletion, the conservation of growth, the maintenance of LBM, and the control of disease-related complications. One valuable recommendation is that pediatric patients with arm-muscle circumferences below the fifth percentile be initiated on aggressive nutrition-support regimens before transplantation.[42]

In the immediate posttransplant period, clinicians should strive to manage the catabolic effect of the surgery, facilitate weaning from the ventilator, minimize infection risk, ensure wound healing, and anticipate metabolic and electrolyte issues associated with liver regeneration, medication administration, and malnutrition.[57] Refeeding syndrome is a serious complication associated with aggressive nutrition rehabilitation of malnourished patients that occurs frequently after a liver transplant. It is characterized by metabolic disturbance in potassium, magnesium, and phosphate levels; glucose and fluid intolerance; and possible cardiac and pulmonary dysfunction.[58] These metabolic issues are further complicated by the energy required for the electrolyte shifts engendered by the regeneration of hepatocyte function.[57]

PN via a central venous catheter is typically initiated within 24 to 48 hours posttransplant, after hemostasis is achieved. In most instances, substantial potassium, phosphorus, and magnesium replacements are required to cope with these refeeding and regeneration requirements. Additional magnesium can also be required to address the renal losses seen with tacrolimus administration. PN is maintained until the patient can take 50% to 75% of total caloric requirements enterally (orally or via feeding tube).[57] The intermittent shortages of some PN constituents have made parenteral replacement challenging; sometimes, early use of enteral mineral replacements with phosphorus, calcium, and magnesium is required.[59]

Oral feeding should be reinstituted as soon as gut function is restored. If patients are unable to achieve nutrition goals with oral feeding and the use of high-calorie oral supplements or fortified standard infant formulas, supplemental tube feeding support should be initiated to facilitate weaning from PN support. Patients can be given standard infant or pediatric supplements after liver transplant, as long-chain fats can again be absorbed. As oral intake improves, patients can be weaned from tube-feeding supplementation.

Most children will resume a normal diet before discharge from the hospital after transplantation, although some may require additional oral supplements to achieve catch-up goals. Some children and infants, particularly those with behavioral feeding issues from pretransplant tube feeding, may require supplemental nocturnal enteral feedings for several months to 2 years posttransplant. Some infants and younger children who have received enteral tube feeding supplementation pretransplant may have never developed normal feeding practices because they have missed their normal developmental milestones for chewing and swallowing. These feeding problems can contribute to persistent growth failure during this posttransplant period because of a lack of adequate caloric intake. Data indicate that behavioral feeding problems are common in children who were tube fed pretransplant and are a major cause of growth failure in 10% of children. However, most children who survive liver transplantation will achieve normal growth patterns within 1 year posttransplant.[60]

Posttransplant maintenance goals need to address issues surrounding quality of life. Long-term goals are focused on maximizing linear growth potential and developing optimal cognitive, physical, and emotional states. Optimal nutrition support can improve the quality of life in pediatric patients by reducing or avoiding linear growth failure, rickets from osteomalacia with related pathologic fractures, and neurodevelopmental delay. Reaching a normal height is an important aspect of quality of life for children who undergo transplantation because it impacts their social reintegration and self-esteem. The causes of poor growth in patients after liver transplantation stem from pretransplant growth failure, those associated with poor graft function, and those due to iatrogenic causes, such as the use of medications that impact metabolic and nutrition status.

Iatrogenic Factors

One of the primary goals posttransplant is to decrease complications associated with the chronic use of immunosuppressive drugs while optimizing graft survival.[61] The cornerstone of most posttransplant immunosuppressive regimens is Tacrolimus (Prograf), a calcineurin inhibitor (CNI) discovered in 1984 that suppresses T-lymphocyte activation and prevents allograft rejection after transplantation. Tacrolimus-based immunosuppression is accompanied by several inherent side effects, ranging from hypertension and abnormal renal function to nausea and abdominal pain. Metabolic and nutritional effects often include hypomagnesemia secondary to renal wasting of magnesium, hyperkalemia or hypokalemia due to altered renal handling of potassium, diabetes mellitus from the inhibitory effect on insulin production by islet cells,[61] and dyslipidemia. CNIs may also be linked to deficiency of pyridoxine levels after intestinal transplantation, possibly secondary to the accelerated catabolism of this vitamin by the drugs themselves.[62]

CNIs have also been associated with an increased incidence of posttransplant eosinophilic enteritis after solid organ transplantation. Although the exact mechanism is unknown, the differential inhibition of cytokine elaboration by tacrolimus might alter the balance between Th1 and Th2 T-cell subsets, facilitating an altered pattern of reaction to antigenic exposure.[63,64]

As the predecessor to tacrolimus, the CNI cyclosporine was introduced in 1982 as an effective immunosuppressive agent following liver transplantation. It is considered inferior to tacrolimus due to a greater incidence of steroid-resistant rejection following induction.[65,66] Even though it has a similar toxicity profile to tacrolimus, cyclosporine is less frequently associated with new-onset diabetes mellitus and more associated with gingival hyperplasia and hirsutism.[65,67]

Corticosteroids play a vital role in most immunosuppressive protocols, unfortunately, their benefit to allograft survival comes with a price. In addition to augmenting the diabetogenic, lipidemic, and hypertensive effects of other immunosuppressive medications, children on steroid-inclusive immunosuppressive regimens are often challenged by sodium and fluid retention, poor growth, osteoporosis, muscle weakness, pancreatitis,

pituitary-adrenal axis suppression, and impaired wound healing.[61,68] Of all immunosuppressives, steroids have the most profound negative effect on growth. If steroids can be weaned satisfactorily, those growth-stunting effects can be minimized.[69–71]

Azathioprine and mycophenolic acid are similar antimetabolite agents that are important adjuncts to combination immunosuppressive therapy. They both work by impeding lymphocyte proliferation. Whereas the therapeutic range of the active azathioprine metabolite 6-thioguanine has been established for the treatment of inflammatory bowel disease, the range necessary to prevent rejection remains uncertain. Even though it has a mechanism of action similar to azathioprine, mycophenolic acid has been the preferred agent in many immunosuppressive protocols because it has been associated with a lower incidence of acute cellular rejection and liver toxicity in liver transplantation.[61] Unfortunately, the commonplace gastrointestinal toxicity associated with mycophenolic acid may mandate the substitution of azathioprine.

Among patients undergoing *en bloc* liver–intestinal transplantation, histologic patterns of mycophenolic acid–induced enteropathy may be difficult to differentiate from acute allograft rejection.[72] If dose-dependent gastrointestinal side effects—including anorexia, vomiting, diarrhea, and gastrointestinal hemorrhage from mucosal ulceration—ensue during therapy with mycophenolic acid, compensation for calorie, protein, fluid, electrolyte, and mineral losses is mandatory.

Sirolimus, a mammalian target of the rapamycin (mTOR) inhibitor, is another immunosuppressive agent that has facilitated CNI-sparing immunosuppressive regimens for liver transplant patients. Sirolimus used in conjunction with tacrolimus, for example, allows for lower doses of tacrolimus and reduced severity or occurrence of CNI-induced side effects, such as tacrolimus-induced renal insufficiency. In many cases, sirolimus can substitute for tacrolimus to prevent allograft rejection. Although this strategy spares the adverse effects associated with calcineurin use, another set of adverse effects may be induced by sirolimus, including hyperlipidemia, hypercholesterolemia, gastrointestinal ulcers, impaired wound healing, peripheral edema, and myelosuppression.[68-71,73] Sirolimus-associated impaired wound healing has prompted many programs to eschew

its use for at least 6 weeks after transplantation. However, once wound healing has occurred in the late posttransplant period, sirolimus appears to be a valuable tacrolimus-sparing agent. Reducing drug doses is key to minimizing their long-term complications. Besides employing calcineurin-sparing agents, early steroid weaning has been employed by many transplantation programs.[71]

Complications

Osteopenia

Multiple factors contribute to the development of osteopenia in pediatric patients receiving liver transplants, including immobility, malnutrition, poor muscle mass, poor renal function, and chronic cholestasis pretransplant and posttransplant. High-dose corticosteroids have long been identified as the main cause of bone loss. In a retrospective study of children with end-stage liver disease who underwent orthotopic liver transplantation, 16% had bone fractures in the postoperative period. Regardless of postoperative bone density, most liver transplant recipients lose bone mass for up to 3 to 6 months posttransplant, but by 6 months, the bone loss typically ends in patients with normal allograft function and then begins to stabilize and increase. Adequate calcium and vitamin D supplementation during the pretransplant and posttransplant phases, as well as promoting physical activity and minimizing the use of osteopenia-producing medications, will help preserve bone mass during the early posttransplant phase.[52,73-76]

Nephrotoxicity

Nephrotoxicity, defined as a decreased glomerular filtration rate, has been associated with the long-term use of CNIs such as cyclosporine and tacrolimus, nephrotoxic antibiotics, rejection episodes, and hypertension.[77–80] Hypertension and chronic kidney disease occur in approximately one-third of all children at any given time posttransplant, and continue to be a serious posttransplant complication, with 10% to 30% of children requiring long-term antihypertensive treatment. Blood pressure, proteinuria, and renal function measured by glomerular filtration rate should be monitored routinely during postoperative medical follow-ups.[77–80]

Hyperlipidemia

The use of cyclosporine, sirolimus, and high-dose corticosteroids, as well as obesity and diabetes mellitus, are all associated with posttransplant hyperlipidemia. Severe hypertriglyceridemia is particularly common among patients receiving sirolimus. Among pediatric patients undergoing a liver transplant, dyslipidemia is more common in patients approaching puberty. Familial predisposition to hyperlipidemia can also be a contributing factor. In comparison with sirolimus, tacrolimus exerts a relatively minor effect on serum lipid levels. One of the major focuses of treatment for hyperlipidemia is dietary intervention. Patient and family education on proper food purchasing, low-fat substitutions, preparation techniques, menu planning, and lifestyle modifications that include an exercise regimen are essential.[81,82]

PostTransplant Diabetes Mellitus

The most significant factor that influences the development of posttransplant diabetes mellitus is the use of diabetogenic immunosuppressive medications, such as corticosteroids and CNIs. Hyperglycemia may occur in some children on tacrolimus alone or in combination with high-dose corticosteroids. When hyperglycemia is associated with corticosteroid use, it usually resolves when corticosteroid doses are reduced. When hyperglycemia is sustained, treatment with insulin is required. Detailed diabetes education on dietary modifications (carbohydrate counting), monitoring, and insulin therapy should be implemented upon diagnosis. Patients with a family history of diabetes mellitus or a diagnosis of an autoimmune liver disease have a greater risk of developing diabetes mellitus in the postoperative period.[83,84]

Obesity

Obesity after liver transplantation is more common in adult patients, but it can affect adolescent patients and children who receive a transplant during the prepubertal period. Treatment goals should focus on the patient's lifestyle change and behavior modification rather than on calorie-restricted diets, as the tendency for weight gain will be present throughout their life.[85–89]

Linear Growth Failure

Up to 20% of pediatric patients who have undergone orthotopic liver transplants experience impairment in linear growth. This impairment is more prevalent in boys than in girls, and height *z* scores are characteristically lower than predicted midparental *z* scores. Although linear growth impairment is more prevalent in the prepubertal and pubertal periods, 11% of Tanner stage V adolescents remain growth-impaired.[90] Not only does chronic undernutrition result in nutritional growth failure but the use of sirolimus may produce vascular compromise to the growth plate of long bones.[91] Whether growth hormone deficiency can be documented or not, children who are growth-impaired after transplantation consistently improve their linear growth velocity on recombinant growth hormone therapy, and are not excessively prone to acute or chronic rejection.[92,93] Therefore, growth hormone therapy appears to be warranted when posttransplant linear growth velocity is suboptimal.

Conclusion

Providing nutrition support to pediatric patients with liver disease who are listed for liver transplantation requires a concerted medical team effort. Pretransplant goals are to preserve LBM and medically manage the complications associated with the disease process. Posttransplant goals should focus primarily on ensuring quality of life; developing cognitive, physical, and emotional states; and minimizing the side effects associated with posttransplant medications. Rigorous attention to metabolic management and aggressive nutrition support during all phases of the disease is essential for optimizing transplantation outcomes.

The nutrition goals for pediatric patients with any liver disease are to optimize the potential for normal growth and development, prevent further liver injury, prevent worsening of the patient's nutrition status, minimize the risk of infection, avoid vitamin and mineral deficiency, and improve quality of life. Achievement of these goals requires detailed attention to all components of nutrition support by caregivers, the patient, and the patient's family,working as a team to provide optimal care.

Test Your Knowledge Questions

1. What is the best serial marker of nutrition status in pediatric patients with liver disease?
   A. Fat-soluble vitamin levels
   B. Upper-extremity anthropometric measurements
   C. Prealbumin levels
   D. Weight or length measurement or body mass index
   E. A and D
2. Which of the following liver disorders is most likely to be associated with exocrine pancreatic insufficiency?
   A. Hepatitis C
   B. Alagille syndrome
   C. Autoimmune hepatitis
   D. Extrahepatic biliary atresia
3. In the nutrition therapy for Wilson disease, which should be avoided?
   A. Grapefruit
   B. Red meat
   C. Endive
   D. Lobster
4. Which of the following has been used in nutrition therapy for glycogen storage disease, type I?
   A. Subcutaneous octreotide
   B. Glucagon infusions
   C. Cooked cornstarch
   D. Metformin
   E. Raw cornstarch
5. In 4-year-olds, sarcopenia can be best measured by which modality?
   A. Hand grip strength
   B. Mid-upper-arm circumference
   C. Total psoas muscle area on cross-sectional imaging
   D. Triceps skinfold thickness
6. Hypomagnesemia in liver transplant patients is most likely associated with which antirejection therapy?
   A. Tacrolimus
   B. Antithymocyte globulin

C. Sirolimus
D. Methylprednisolone

7. Which of the following is a complication associated with sirolimus use?
   A. Hypertriglyceridemia
   B. Impaired wound healing
   C. Opportunistic infection
   D. All of the above

References

1. Högler W, Baumann U, Kelly D. Endocrine and bone metabolic complications in chronic liver disease and after liver transplantation in children. *J Pediatr Gastroenterol Nutr*. 2012;54(3):313–321. https://doi.org/10.1097/mpg.0b013e31823e9412
2. Dam G, Ott P, Aagaard NK, Vilstrup H. Branched-chain amino acids and muscle ammonia detoxification in cirrhosis. *Metab Brain Dis*. 2013;28:217–220. https://doi.org/10.1007/s11011-013-9377-3
3. Tessitore M, Sorrentino E, Schiano Di Cola G, et al. Malnutrition in pediatric chronic cholestatic disease: an up-to-date overview. *Nutrients*. 2021;13(8):2785. https://doi.org/10.3390/nu13082785
4. Mouzaki M, Bronsky J, Gupte G, et al. Nutrition support of children with chronic liver diseases: a joint position paper of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr*. 2019;69(4):498–511. https://doi.org/10.1097/mpg.0000000000002443
5. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. *J Hepatol*. 2019;70(1):172–193. https://doi.org/10.1016/j.jhep.2018.06.024
6. Lai JC, Tandon P, Bernal W, et al. Malnutrition, frailty, and sarcopenia in patients with cirrhosis: 2021 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2021;74(3)1611–1644. https://doi.org/10.1002/hep.32049

7. Perteet-Jackson AD, Earthman CP, Larson-Nath CM. Body composition post pediatric liver transplant: implications and assessment. *Nutr Clin Pract*. 2021;36(6):1173–1184. https://doi.org/10.1002/ncp.10601
8. Shepherd RW, Chin SE, Cleghorn GJ, et al. Malnutrition in children with chronic liver disease accepted for liver transplantation: clinical profile and effects on outcome. *J Paediatr Child Health*. 1991;27:595. https://doi.org/10.1111/j.1440-1754.1991.tb02541.x
9. Heubi JE, Heyman MB, Shulman RJ. The impact of liver disease on growth and nutrition. *J Pediatr Gastroenterol Nutr*. 2002;35(suppl 1):S55–S59. https://doi.org/10.1097/00005176-200207001-00013
10. Ben-Ari Z, Schafer Z, Sulkes J, et al. Alterations in serum-leptin in chronic liver disease. *Dig Disease Sci*. 2002;47:183–189. https://doi.org/10.1023/a:1013248427783
11. Martínez-Uña M, López-Mancheño Y, Diéguez C, et al. Unraveling the role of leptin in liver function and its relationship with liver diseases. *Int J Mol Sci*. 2020;21(24):9368. https://doi.org/10.3390/ijms21249368
12. Plata-Salamán CR. Cytokines and anorexia: a brief overview. *Semin Oncol*. 1998;251(suppl 1):64–72.
13. Clarembeau F, Bale G, Lanthier N. Cirrhosis and insulin resistance: current knowledge, pathophysiological mechanisms, complications and potential treatments. *Clin Sci (London)*. 2020;134(16):2117–2135. https://doi.org/10.1042/cs20200022
14. Saner G, Süoglu OD, Yigitba M, et al. Zinc nutrition in children with chronic liver disease. *J Trace Elements Exp Med*. 2000;13:271–276. https://doi.org/10.1002/1520-670X(2000)13:3<271::AID-JTRA4>3.0.CO;2-B
15. Lane ER, Hsu EK, Murray KF. Management of ascites in children. *Expert Rev Gastroenterol Hepatol*. 2015;9(10):1281–92. https://doi.org/10.1586/17474124.2015.1083419
16. West RJ, Lloyd JK. The effect of cholestyramine on intestinal absorption. *Gut*. 1975;16:93–8. https://doi.org/10.1136/gut.16.2.93
17. Pettei MJ, Daftary S, Levine JJ. Essential fatty acid deficiency associated with the use of a medium-chain-triglyceride infant formula in pediatric hepatobiliary disease. *Am J Clin Nutr*. 1991;53:1217–1221. https://doi.org/10.1093/ajcn/53.5.1217

18. Hassan S, Hertel P. Overview of progressive familial intrahepatic cholestasis. *Clin Liver Dis*. 2022;26(3):371–390. https://doi.org/10.1016/j.cld.2022.03.003
19. Ayoub MD, Kamath BM. Alagille syndrome: Current understanding of pathogenesis, and challenges in diagnosis and management. *Clin Liver Dis*. 2022;26(3):355–370. https://doi.org/10.1016/j.cld.2022.03.002
20. Rovner AJ, Schall JI, Jawad AF, et al. Rethinking growth failure in Alagille syndrome: the role of dietary intake and steatorrhea. *J Pediatr Gastroenterol Nutr*. 2002;35(4):495–502. https://doi.org/10.1097/00005176-200210000-00007
21. Golson ML, Loomes KM, Oakey R, et al. Ductal malformation and pancreatitis in mice caused by conditional Jag1 deletion. *Gastroenterology*. 2009;136:1761–1771.e1. https://doi.org/10.1053/j.gastro.2009.01.040
22. Lee SP, Lai KS. Exocrine pancreatic function in hepatic cirrhosis. *Am J Gastroenterol*. 1976;65:244–248.
23. Berant M, Diamond E, Alon U, et al. Effect of infusion of bile salts into the mesenteric artery in situ on jejunal mucosal transport function in dogs. *J Pediatr Gastroenterol Nutr*. 1988;7:588–593. https://doi.org/10.1097/00005176-198807000-00019
24. Bezerra JA, Balistreri WF. Cholestatic syndromes of infancy and childhood. *Semin Gastrointest Dis*. 2001;12:54–65.
25. Feldman AG, Sokol RJ. Neonatal cholestasis: updates on diagnostics, therapeutics, and prevention. *Neoreviews*. 2021;22(12):e819–e836. https://doi.org/10.1542/neo.22-12-e819
26. Chinsky JM, Singh R, Ficicioglu C, et al. Diagnosis and treatment of tyrosinemia type I: a US and Canadian consensus group review and recommendations. *Genet Med*. 2017;19(12). https://doi.org/10.1038/gim.2017.101
27. Whitington PF. Gestational alloimmune liver disease and neonatal hemochromatosis. *Semin Liv Dis*. 2012;32:325–332. https://doi.org/10.1055/s-0032-1329901
28. Feldman AG, Whitington PF. Neonatal hemochromatosis. *J Clin Exp Hepatol*. 2013;3:313–320. https://doi.org/10.1016/j.jceh.2013.10.004
29. Wanten GJ, Naber AH. Cellular and physiological effects of medium-chain triglycerides. *Mini Rev Med Chem*. 2004;4:847–857.

https://doi.org/10.2174/1389557043403503
30. Heller S, Worona L, Consuelo A. Nutritional therapy for glycogen storage diseases. *J Pediatr Gastroenterol Nutr*. 2008;47(suppl 1):515–521. https://doi.org/10.1097/mpg.0b013e3181818ea5
31. Ross KM, Ferrecchia IA, Dahlberg KR, et al. Dietary management of the glycogen storage diseases: evolution of treatment and ongoing controversies. *Adv Nutr*. 2020;11(2):439–446. https://doi.org/10.1093/advances/nmz092
32. Massese M, Tagliaferri F, Dionisi-Vici C, et al. Glycogen storage diseases with liver involvement: a literature review of GSD type 0, IV, VI, IX and XI. *Orphanet J Rare Dis*. 2022;17(1):241. https://doi.org/10.1186/s13023-022-02387-6
33. Marion RW, Paljevic E. The glycogen storage disorders. *Pediatr Rev.* 2020;41(1):41–44. Erratum in: *Pediatr Rev*. 2020;41(2):99. https://doi.org/10.1542/pir.2018-0146
34. Derks TGJ, Rodriguez-Buritica DF, Ahmad A, et al. Glycogen storage disease type Ia: current management options, burden and unmet needs. *Nutrients*. 2021;13(11):3828. https://doi.org/10.3390/nu13113828
35. Schilsky ML, Roberts EA, Bronstein JM, et al. A multidisciplinary approach to the diagnosis and management of Wilson disease: 2022 practice guidance on Wilson disease from the American Association for the Study of Liver Diseases. *Hepatology*. 2022. https://doi.org/10.1002/hep.32801
36. Kerkar N, Rana A. Wilson disease in children. *Clin Liver Dis*. 2022;26(3):473–488. https://doi.org/10.1016/j.cld.2022.03.008
37. Weiss KH, Askari FK, Czlonkowska A, et al. Bis-choline tetrathiomolybdate in patients with Wilson's disease: an open-label, multicentre, phase 2 study. *Lancet Gastroenterol Hepatol*. 2017;2(12):869–876. https://doi.org/10.1016/s2468-1253(17)30293-5
38. Overweight and obesity statistics. U.S. Department of Health and Human Services, National Institute of Diabetes and Digestive and Kidney Diseases. Accessed July 30, 2023. https://www.niddk.nih.gov/health-information/health-statistics/overweight-obesity
39. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD practice guidance on the clinical assessment and management of

nonalcoholic fatty liver disease. *Hepatology*. 2023;77(5):1797–1835. https://doi.org/10.1097/hep.0000000000000323
40. Rinella ME, Lazarus JV, Ratziu V, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol*. 2023:S0168–8278(23)00418-X. https://doi.org/10.1016/j.jhep.2023.06.003
41. Hurtado-Lopez EF, Vasquez-Garibay EM, Trujillo X, et al. Body composition predicts growth in infants and toddlers with chronic liver disease. *J Pediatr Gastroenterol Nutr*. 2017;65:e117–e119. https://doi.org/10.1097/mpg.0000000000001746
42. Zamberlan P, Leone C, Tannuri U, et al. Nutritional risk and anthropometric evaluation in pediatric liver transplantation. *Clinics (Sao Paulo)*. 2012;67:1387–1392. https://doi.org/10.6061/clinics/2012(12)07
43. Sokol, RJ, Stall C. Anthropometric evaluation of children with chronic liver disease. *Am J Clin Nutr*. 1990;52:203–208. https://doi.org/10.1093/ajcn/52.2.203
44. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing*. 2019;48(1):16–31. https://doi.org/10.1093/ageing/afy169
45. Chen C, Ayers M, Squires JH, Squires JE. Perspectives on sarcopenia as a predictor for outcomes in pediatric patients with chronic liver disease. *Hepat Med*. 2022;14:173–183. https://doi.org/10.2147/hmer.s348888
46. Pawaria A, Khanna R, Sood V, et al. Subjective global nutritional assessment as a nutritional tool in childhood chronic liver disease. *Br J Nutr*. 2022;127(6):904–913. https://doi.org/10.1017/s0007114521001604
47. Shu X, Kang K, Zhong J, et al. Meta-analysis of branched chain amino acid-enriched nutrition to improve hepatic function in patients undergoing hepatic operation. *Zhonghua Gan Zang Bing Za Zhi*. 2014:22:43–47. https://doi.org/10.3760/cma.j.issn.1007-3418.2014.01.010
48. Nightingale S, Ng VL. Optimizing nutritional management in children with chronic liver disease. *Pediatr Clin North Am*. 2009:56:1161–1183. https://doi.org/10.1016/j.pcl.2009.06.005

49. Mouzaki M, Ng V, Kamath BM, et al. Enteral energy and macronutrients in end-stage liver disease. *J Parenter Enteral Nutr*. 2014;38:673–681. https://doi.org/10.1177/0148607114522488
50. Feranchak AP, Gralla J, King R, et al. Comparison of indices of vitamin A status in children with chronic liver disease. *Hepatology*. 2005;42:782–792. https://doi.org/10.1002/hep.20864
51. Sathe MN, Patel AS. Update in pediatrics: focus on fat-soluble vitamins. *Nutr Clin Pract*. 2010;25:340–346. https://doi.org/10.1177/0884533610374198
52. D'Antiga L, Ballan D, Luisetto G, et al. Long-term outcome of bone mineral density in children who underwent a successful liver transplantation. *Transplantation*. 2004;78:899–903. https://doi.org/10.1097/01.tp.0000136987.38729.c0
53. Argao EA, Heubi J, Hollis BW, et al. d-Alpha-tocopheryl polyethylene glycol-1000 succinate enhances the absorption of vitamin D in chronic cholestatic liver disease of infancy and childhood. *Pediatr Res*.1992;31:146–150. https://doi.org/10.1203/00006450-199202000-00011
54. Edwards S, Davis AM, Bruce A, et al. Caring for tube-fed children: a review of management, tube weaning, and emotional considerations. *J Parenter Enteral Nutr*. 2016;40(5):616–622. https://doi.org/10.1177/0148607115577449
55. Kelly DA, Bucuvalas JC, Alonso EM, et al. Long-term medical management of the pediatric patient after liver transplantation: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Liver Transpl*. 2013;19:798–825. https://doi.org/10.1002/lt.23697
56. Sullivan JS, Sundaram SS, Pan Z, et al. Parenteral nutrition supplementation in biliary atresia patients listed for liver transplantation. *Liver Transpl*. 2012;18:120–128. https://doi.org/10.1002/lt.22444
57. Hammad A, Kaito T, Uemoto S. Perioperative nutritional therapy in liver transplantation. *Surg Today*. 2015;45(3):271–83. https://doi.org/10.1007/s00595-014-0842-3
58. Dunn RL, Stettler N, Mascarenhas MR. Refeeding syndrome in hospitalized pediatric patients. *Nutr Clin Pract*. 2003:18:327–332.

https://doi.org/10.1177/0115426503018004327
59. Guenter P, Holcombe B, Mirtallo JM, et al. Parenteral nutrition utilization: response to drug shortages. *J Parenter Enteral Nutr*. 2014:38:11–12. https://doi.org/10.1177/0148607113511273
60. Alonso EM. Growth and developmental considerations in pediatric liver transplantation. *Liver Transpl*. 2008;14:585–591. https://doi.org/10.1002/lt.21488
61. Charlton M, Levitsky J, Aqel B, et al. International Liver Transplantation Society consensus statement on immunosuppression in liver transplant recipients. *Transplantation*. 2018;102(5):727–743. https://doi.org/10.1097/tp.0000000000002147
62. Matarese LE, Dvorchik I, Costa G, et al. Pyridoxal-5'-phosphate deficiency after intestinal and multivisceral transplantation. *Am J Clin Nutr*. 2009;89:204–209. https://doi.org/10.3945/ajcn.2008.26898
63. Saeed SA, Integlia MJ, Pleskow RG, et al. Tacrolimus-associated eosinophilic gastroenterocolitis in pediatric liver transplant recipients: role of potential food allergies in pathogenesis. *Pediatr Transplant*. 2006;10:730–735. https://doi.org/10.1111/j.1399-3046.2006.00538.x
64. Wasuwanich P, Batsis I, Thawillarp S, et al. Post-transplant eosinophilic gastrointestinal disorders and lymphoproliferative disorder in pediatric liver transplant recipients on tacrolimus. *Transpl Immunol*. 2021;68:101438. https://doi.org/10.1016/j.trim.2021.101438
65. Collins RH. Tacrolimus (FK506) versus cyclosporin in prevention of liver allograft rejection. *Lancet*. 1994;344:949. https://doi.org/10.1016/S0140-6736(94)92295-0
66. McAlister VC, Haddad E, Renouf E, et al. Cyclosporin versus tacrolimus as primary immunosuppressant after liver transplantation: a meta-analysis. *Am J Transplant*. 2006;6:1578–1585. https://doi.org/10.1111/j.1600-6143.2006.01360.x
67. Heisel O, Heisel R, Balshaw R, et al. New onset diabetes mellitus in patients receiving calcineurin inhibitors: a systematic review and meta-analysis. *Am J Transplant*. 2004;4:583–595. https://doi.org/10.1046/j.1600-6143.2003.00372.x
68. Smith SK, Miloh T. Pediatric liver transplantation. *Clin Liver Dis*. 2022;26(3):521–535. https://doi.org/10.1016/j.cld.2022.03.010

69. Tredger JM, Brown NW, Dhawan A. Immunosuppression in pediatric solid organ transplantation: opportunities, risks, and management. *Pediatr Transplant*. 2006;10:879–892. https://doi.org/10.1111/j.1399-3046.2006.00604.x
70. Miloh T, Barton A, Wheeler J, et al. Immunosuppression in pediatric liver transplant recipients: unique aspects. *Liver Transpl*. 2017 Feb;23(2):244–256. https://doi.org/10.1002/lt.24677
71. Vincenzi R, Fonseca EA, Roda KMO, et al. Current practice in immunosuppression in pediatric liver transplantation. *Curr Pharm Des*. 2020;26(28):3402–3405. https://doi.org/10.2174/1381612826666200614181526
72. Delacruz V, Weppler D, Island E, et al. Mycophenolate mofetil-related gastrointestinal mucosal injury in multivisceral transplantation. *Transplant Proc*. 2010;42:82–84. https://doi.org/10.1016/j.transproceed.2009.12.027
73. McPartland KJ, Pomposelli JJ. Update on immunosuppressive drugs used in solid-organ transplantation and their nutrition implications. *Nutr Clin Pract*. 2007;22:467–473. https://doi.org/10.1177/0115426507022005467
74. Ebeling PR. Approach to the patient with transplantation-related bone loss. *J Clin Endocrinol Metab*. 2009;94:1483–1490. https://doi.org/10.1210/jc.2009-0205
75. Guthery SL, Pohl JF, Bucuvalas JC, et al. Bone mineral density in long-term survivors following pediatric liver transplantation. *Liver Transpl*. 2003;9:365–370. https://doi.org/10.1053/jlts.2003.50071
76. Okajima H, Shigeno C, Inomata Y, et al. Long-term effects of liver transplantation on bone mineral density in children with end-stage liver disease: a 2-year prospective study. *Liver Transpl*. 2003;9:360–364. https://doi.org/10.1053/jlts.2001.50038
77. Matloff RG, Arnon R, Saland JM. The kidney in pediatric liver transplantation: an updated perspective. *Pediatr Transplant*. 2012;16:818–828. https://doi.org/10.1111/petr.12006
78. Lacquaniti A, Campo S, Casuscelli Di Tocco T, et al. Acute and chronic kidney disease after pediatric liver transplantation: an underestimated problem. *Clin Transplant*. 2020;34(11):e14082. https://doi.org/10.1111/ctr.14082

79. Anastaze Stell K, Belli DC, Parvex P, et al. Glomerular and tubular function following orthotopic liver transplantation in children treated with tacrolimus. *Pediatr Transplant*. 2012;16:250–256. https://doi.org/10.1111/j.1399-3046.2011.01625.x
80. Campbell K, Ng V, Martin S, et al. Glomerular filtration rate following pediatric liver transplantation—the SPLIT experience. *Am J Transplant*. 2010;10:2673–2682. https://doi.org/10.1111/j.1600-6143.2010.03316.x
81. Kniepeiss D, Iberer F, Schaffellner S, et al. Dyslipidemia during sirolimus therapy in patients after liver transplantation. *Clin Transplant*. 2004;18:642–646. https://doi.org/10.1111/j.1399-0012.2004.00253.x
82. Fellstrom B. Impact and management of hyperlipidemia posttransplantation. *Transplantation*. 2000;70(suppl 11):S51–S57.
83. Obayashi PA. Posttransplant diabetes mellitus: cause, impact, and treatment options. *Nutr Clin Pract*. 2004;19:165–171. https://doi.org/10.1177/0115426504019002165
84. Regelmann MO, Goldis M, Arnon R. New-onset diabetes mellitus after pediatric liver transplantation. *Pediatr Transplant*. 2015;19(5):452–459. https://doi.org/10.1111/petr.12523
85. Sheikh A, Cundy T, Evans HM. Growth, body composition, and bone density following pediatric liver transplantation. *Pediatr Transplant*. 2018; 22(5):e13201. https://doi.org/10.1111/petr.13201
86. Perito ER, Rhee S, Glidden D, et al. Overweight and obesity in pediatric liver transplant recipients: prevalence and predictors before and after transplant, United Network for Organ Sharing Data, 1987–2010. *Pediatr Transplant*. 2012;16:41–49. https://doi.org/10.1111/j.1399-3046.2011.01598.x
87. Rothbaum Perito E, Lau A, Rhee S, et al. Posttransplant metabolic syndrome in children and adolescents after liver transplantation: a systematic review. *Liver Transpl*. 2012;18:1009–1028. https://doi.org/10.1002/lt.23478
88. Pagadala M, Dasaratha S, Eghtesad B, et al. Posttransplant metabolic syndrome: an epidemic waiting to happen. *Liver Transpl*. 2009;15:1662–1670. https://doi.org/10.1002/lt.21952
89. Sundaram SS, Alonso EM, Zeitler P, et al. Obesity after pediatric liver transplantation: prevalence and risk factors. *J Pediatr Gastroenterol*

Nutr. 2012;55:657–662. https://doi.org/10.1097/MPG.0b013e318266243c
90. Muhammed S, Grimberg A, Rand E, et al. Long-term linear growth and puberty in pediatric liver transplant recipients. *J Pediatr*. 2013;163:1354–1360. https://doi.org/10.1016/j.jpeds.2013.06.039
91. Alvarez-García O, García-López E, Loredo V, et al. Rapamycin induces growth retardation by disrupting angiogensis in the growth plate. *Kidney Int*. 2010;78:561–568. https://doi.org/10.1038/ki.2010.173
92. Puustinen L, Jalanko H, Holmberg C. Recombinant human growth hormone treatment after liver transplantation in childhood: the 5-year outcome. *Transplantation*. 2005;79:1241–1246. https://doi.org/10.1097/01.tp.0000161668.09170.f4
93. Fuqua JS. Growth after organ transplantation. *Semin Pediatr Surg*. 2006;15:162–169. https://doi.org/10.1053/j.sempedsurg.2006.03.003

Test Your Knowledge Answers

1. The correct answer is **B**.
2. The correct answer is **B**.
3. The correct answer is **D**.
4. The correct answer is **E**.
5. The correct answer is **C.**
6. The correct answer is **A**.
7. The correct answer is **D**.

25

Intestinal Failure

Vikram Raghu, MD, MS, and Kishore R. Iyer, MBBS, FRCS (Eng), FACS

Learning Objectives

1. Define intestinal failure including the most common causes and the indications for intestine transplant.
2. Describe the process through which intestinal rehabilitation attempts to stimulate intestinal adaptation to try to achieve enteral autonomy.
3. Explain how strategies to optimize parenteral nutrition may be used to mitigate complications of intestinal rehabilitation.

Introduction

Intestinal failure (IF) in infants and children is a devastating condition that can be defined as "reduction of functional intestinal mass below that which can sustain life, resulting in dependence on supplemental parenteral support for a minimum of 60 days within an interval of 74 consecutive days."[1] Before parenteral nutrition (PN), many infants died as a consequence of insufficient bowel length or function. Infants found to have an "abdominal catastrophe" at the time of initial laparotomy for conditions such as necrotizing enterocolitis (NEC), volvulus, or gastroschisis simply had their abdomen closed and were made comfortable to await the natural course of

their tragic circumstance. However, since the development of safe PN, central line–placement and care, and improved medical and surgical management, including intestinal transplantation, infants with IF can survive and have a satisfactory or even excellent quality of life.

A long and often uncertain clinical course for the child can be challenging and frustrating for the familyas well as the medical care and support team. Intestinal adaptation associated with full enteral feeding and satisfactory weight gain and growth accompanied by discontinuation of PN can require months or years to achieve.[2] Along the way, the child is at risk for episodes of dehydration, electrolyte imbalance, macronutrient and micronutrient deficiencies, and growth failure in the long term. More importantly, life-threatening complications such as sepsis, end-stage liver disease, and vascular thrombosis may occur.

Management of children with IF is best provided by an experienced multidisciplinary team within the context of an intestinal rehabilitation program, which includes experts in pediatric gastroenterology, surgery, nutrition, nursing, social work, and feeding techniques.[3] Most management strategies have not been rigorously investigated, leaving much to experience, tradition, trial and error, or even as an "art form." Most studies of children with IF are single-center experiences, with small numbers of patients collected over many decades.[4–7] In this chapter, we review IF and outline some useful strategies for the care and management of infants and children with IF.

Definition of Intestinal Failure

The small intestine almost doubles in length during the last trimester, with a length of about 157 cm at birth for a normal, full-term infant.[8] While short bowel syndrome (SBS) is defined in the literature as the remnant intestine measuring <75 cm, Spencer and colleagues[7] proposed incorporating gestational age into the assessment, suggesting that infants with <10% of expected bowel length for gestational age are at greater risk of death than those with a longer residual bowel length.

IF is a functional description independent of bowel length and better reflects the nature of the clinical condition encountered in practice. As such,

the American Society for Parenteral and Enteral Nutrition provided the previously stated definition identifying those requiring sustained parenteral support because of their condition as having IF.[1] Such a definition acknowledges children with conditions such as immune-mediated enteropathy, enteric myopathy, mitochondrial disorders, intestinal pseudo-obstruction, tufting enteropathy, and microvillus inclusion disease who have a normal intestine length but inadequate function to sustain life without PN.

Scope of the Problem

Surprisingly, neither the incidence nor prevalence of IF and SBS in the United States is well known.[9] In 1992, Wallander et al[10] estimated the incidence of extreme SBS to be 3 to 5 per 100,000 births per year. However, improvements in neonatal intensive care, anesthesia, and surgical techniques have improved survival rates of children who would have previously died, leading some to suggest that the incidence and prevalence have increased.[11] Other estimates suggest that at least 16,000 children are on home PN (HPN) in the United States, but the precise number receiving PN support to manage IF is unknown.[12]

More importantly, we have no estimate of the number of children with SBS who have been weaned from PN but remain at risk for various nutrition and growth abnormalities as a consequence of their altered intestinal anatomy. In 2003, the annual costs for managing a PN–dependent patient with IF were estimated to range between $100,000 and $150,000 with a mortality rate of approximately 30% at 5 years for those who could not be weaned from PN.[11] More recently, patient outcomes have improved with advances in care by multidisciplinary intestinal rehabilitation programs.[3,13–19]

Etiology of Intestinal Failure

Conditions associated with IF in infants and children are generally due to congenital disease, surgical resection, motility disorders, or enterocyte abnormalities (see Table 25-1).[20] SBS is the underlying cause in the majority of these patients, and its etiology may be congenital abnormalities

such as gastroschisis, intestinal atresia, malrotation with volvulus, or acquired causes such as NEC, vascular thrombosis, or trauma. Motility disorders such as total intestinal aganglionosis and chronic intestinal pseudoobstruction represent a growing proportion of those requiring intestine transplants. Less commonly seen are enterocyte abnormalities such as microvillus inclusion disease and tufting enteropathy.

TABLE 25-1. Causes of Intestinal Failure in Children

Life Stage	Cause

Prenatal	Gastroschisis/omphalocele
	Intestinal atresia
	Total intestinal or very long-segment Hirschsprung's disease
	Constitutive enterocyte disorders
	  Tufting enteropathy
	  Microvillus inclusion disease
	Megacystis microcolon hypoperistalsis syndrome
	Malrotation/volvulus
	Bladder extrophy

Neonatal	Necrotizing enterocolitis Enteric anendocrinosis Vascular thrombosis Desquamative enteropathy (Intracellular β4 integrin mutation) Malrotation/volvulus

Postnatal	Complicated intussusception
	Trauma
	  Seatbelt injury
	  Suction evisceration (eg, swimming pool drain)
	  Riding lawn mower injury
	Extensive vascular anomaly
	Autoimmune/immune-mediated enteropathy
	  IPEX
	  Autoimmune polyglandular syndrome
	Tumor
	  Fibroma
	  Desmoid
	Sclerosing encapsulating peritonitis (abdominal cocoon)
	Munchausen syndrome by proxy
	Protracted diarrhea in infancy
	Intestinal motility disorders
	  Mitochondrial defects/mutations
	  Intestinal pseudo-obstruction

Abbreviation: IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked.

Intestinal Adaptation

Intestinal adaptation is a complex and incompletely understood process that ensues following significant bowel resection to compensate for the loss of

intestinal surface area. It is characterized by both functional and morphologic changes in the remnant bowel.[21,22] Enteral nutrition (EN) is necessary for adaptation. Clinical features associated with patients who are eventually weaned from PN include the presence of the ileocecal valve, an intact colon, small bowel length >15 cm, and placement of the small intestine in continuity with the colon, as well as the absence of jaundice or cholestasis.[6]

The underlying physiologic mechanisms by which these clinical factors might directly impact the adaptive process in humans are not completely understood. For instance, it is not clear whether the ileocecal valve must be physically present or whether its presence merely serves as a marker for a long colon segment, and inevitably the adjacent terminal ileum. Over time, the residual bowel lengthens and dilates, which are thought to be positive signs of adaptation. However, excessive intestinal dilatation may be associated with altered intestinal motility resulting in stasis of luminal contents and small intestinal bacterial overgrowth (SIBO), which can negatively impact adaptation. Surgical techniques aimed to improve intestinal function by reducing bowel diameter and incidentally increasing bowel length include the Bianchi procedure (longitudinal intestinal lengthening and tailoring [LILT]) and serial transverse enteroplasty (STEP).[23,24]

The adaptive process occurs over many months or years.[6,25] Increased enteral intake, or hyperphagia, is associated with intestinal adaptation in adults.[26] The impact of luminal nutrients on intestinal adaptation is complex, but it likely involves a direct trophic effect on the intestinal epithelium, as well as stimulation of trophic hormones and pancreaticobiliary secretions.[27] In animal models, it appears that a more complex nutrient enhances adaptation better than one that is simple or more processed. For example, disaccharides enhance adaptation more effectively than monosaccharides,[28] and whole proteins are more adaptogenic than protein hydrolysates.[29]

These findings have not been rigorously tested in humans. As such, a single formula or class of formulas cannot be prescribed for all patients as a balance must be struck between augmenting adaptation and supporting enteral tolerance, which may differ for each patient. Hormonal regulation of

the adaptation process, especially through glucagon-like peptide 2 (GLP-2) and other enterohormones, has become a prime target for pharmacologic therapy to enhance the adaptation process.[27]

The role of dietary fiber and short-chain fatty acids such as butyrate have been well-established in experimental models, but their clinical role remains uncertain.[30] The functional capabilities of the remnant intestine also impact adaptation. For instance, the complete absence of the ileum precludes absorption of bile acids and vitamin B12. The absence of the ileocecal valve appears to negatively impact intestinal adaptation for some, but not all patients.[4–6,31,32] However, as alluded to earlier, sufficient colon length may be as important (if not more) than the presence or absence of the ileocecal valve.[33,34]

A biomarker for intestinal adaptation, such as citrulline,[35] would ideally reflect the quality and quantity of intestinal function, but its clinical usefulness is uncertain. Markers of hepatic function in patients with IF have not been evaluated. Valid biomarkers are urgently needed so that successful rehabilitation regimens can be objectively identified, and adaptation failure can be recognized earlier. Translational studies to identify potential genetic susceptibilities that would favor or impede intestinal adaptation have not been performed.[36]

Management

In this section, we discuss considerations for optimizing the management of intestinal failure. As previously mentioned, this begins with the referral to an expert intestinal rehabilitation program. Such programs have the appropriate multidisciplinary staffing to care for the complex needs of those with intestinal failure. Many societies endorse the need for specific expertise to optimize management.[19] Thus, while overall guidance can be provided in reference materials like this book, individual patient care still largely depends on expertise uniquely found at these centers.

Enteral Nutrition

Luminal nutrients are essential for intestinal adaptation to occur.[37] The 2 initial considerations are formula type and how it is provided. Human milk is preferred, and its use has been associated with decreased PN duration.[4] The beneficial effects of human milk are attributable to its immunoprotective properties; inherent growth factors; effect on postnatal development of intestinal flora; and its nutrient composition including long-chain triglycerides, free amino acids, and nucleotides, as well as complex protein and fat.[38] When human milk is unavailable, formula choice is complicated by a variety of options that reflect differences in the desired complexity of protein, fat, and carbohydrate.

Complex nutrients, such as polysaccharides, long-chain triglycerides, and whole protein, increase the functional workload of the intestine, and as a result, may stimulate adaptation.[39] Despite this, some experts favor the use of amino acid–based formulas with the view that these have been associated with improved outcomes.[40] Studies to identify the ideal enteral protein[41–43] and lipid[44] have been plagued by insufficient numbers of patients or have been extrapolated from animal models. In addition, energy expenditure is variable among children with IF, making estimates of caloric needs for individual patients difficult.[45]

A variety of methods can deliver nutrients to the intestinal lumen including oral, gastric, or jejunal. Advantages of early oral feeding include stimulation of oral digestive enzymes and maintenance of oral feeding skills to prevent oral aversion.[46] If the patient is capable of oral feeding but is incapable of taking sufficient calories or if oral feedings result in excess stool output, supplemental direct enteral feeding is possible via a nasogastric tube, gastrostomy, or direct jejunal feeding although the more distally nutrients are provided, a further reduction in available small bowel mass for absorption occurs. Continuous enteral infusion was found to be more beneficial in very low birth weight infants,[47] but studies in piglets suggest that bolus feedings are more advantageous.[48] Continuous versus bolus feedings have not been thoroughly studied in older infants and children.

Clinical decisions to adjust the enteral feeding regimen are determined by several factors, primarily stool or ostomy output, evidence of malabsorption, and other less objective symptoms such as abdominal fullness, irritability, and regurgitation. Currently, decisions related to advancing enteral feeding, weaning PN, and long-term monitoring of patients at risk for growth failure are based almost completely on experience, tradition, and art rather than evidence-based algorithms. However, institutions have created feeding protocols to standardize their own practice with excellent results at expediting PN-weaning and reducing IF-associated liver disease (IFALD) incidence.[49] The understanding of the relative importance of these factors, how they are incorporated into daily management, and how they impact adaptation in patients with IF is critical if the management of infants with IF is to move beyond art and tradition and into an evidence-based practice of medicine.

Parenteral Nutrition

PN, first introduced in the late 1960s, is now an established life-saving treatment for children with IF.[50–52] Components of PN include glucose, amino acids, lipids, electrolytes, vitamins, minerals, trace elements, and water. Glucose is the primary source of energy in PN, but glucose oxidation varies depending on age and diagnosis.[53,54] Glucose infusion rates that are more than the patients' oxidative capacity will promote fat deposition.[43] While glucose infusion rates vary, an intake >10 mg/kg/min may result in the conversion of glucose to fat.[44] However, anecdotally, glucose infusion rates up to 15 mg/kg/min appear to be well tolerated in infants and young children. An amino acid solution, ranging from 3 to 4 g/kg/d for preterm infants to 1 g/kg/d for adolescents, is administered to support protein metabolism.[55] Amino acids are best utilized when balanced with a proper proportion of nonnitrogen calories. The ideal ratio of nitrogen to nonnitrogen calories is estimated to be between 1:150 and 1:400.[56]

Lipid emulsions currently available in the United States include soy-based emulsions high in ω-6 fatty acids, fish oil–based lipid emulsions high in ω-3, and combination emulsions that try to balance the two. The latter has essentially replaced soy-based emulsions as the lipid of choice in children on long-term PN as the reduced content of phytosterols and

proinflammatory ω-6 fatty acids have been shown to limit the development of cholestatic liver disease in young children .[57,58] The exclusive fish oil-based emulsions are approved as a treatment of cholestasis with essentially no phytosterol content, yet their use as a long-term primary fat source has been met with clinical concerns regarding essential fatty acid deficiency because of the minimal quantity of linoleic acid despite evidence that its use can reverse clinical deficiency.[59–61]

Doses of combination lipid emulsions >2 g/kg/d retain many of the properties of high phytosterol soy-based lipid emulsions, thus limiting the utility in preventing cholestasis. Serum electrolytes are monitored regularly and adjustments in electrolyte concentration are based on the individual needs of the patient. Guidelines for pediatric vitamin, mineral, and trace element supplementation are available, but they are supported by a paucity of data.[52] In addition, deficiencies, such as vitamin D deficiency, have been reported even in individuals receiving PN with vitamins, so monitoring and supplementation as needed are warranted.[62]

Given the host of potential complications associated with PN and IF, careful longitudinal monitoring should be implemented to reduce complications and improve outcomes. The frequency of monitoring will depend on the patient's age, PN duration, and acute changes in the clinical condition. Growth parameters (eg, height or length, weight, head circumference) should be checked at each clinical visit. Monthly visits are typical for infants and young children but for older children on stable PN, the frequency of visits can be extended to every 3 to 4 months. For more information, please see Chapter 34, "Evaluation and Monitoring of Pediatric Patients Receiving Specialized Nutrition Support."

Fluid Management

In addition to PN, children may also require supplemental fluid management to maintain satisfactory hydration. This is particularly important for children with an ileostomy or those whose intestine is in continuity but with a short length of colon. These children are at increased risk of developing sodium and water depletion and should be monitored carefully.[63,64] In particular, sodium depletion, which may only be evident based on low urine sodium, can result in poor weight gain. Unless the

child's fluid and electrolyte requirements are very consistent day to day and week to week, supplemental fluids should be calculated and administered separately from PN to allow for more rapid and less expensive adjustments in fluid and electrolyte administration.

Medications

A variety of medications are used to manage symptoms and complications associated with IF, however, none of them have been adequately studied in a randomized fashion.

Diarrhea or increased fluid volume losses through stomas are common in children with IF. Antimotility agents (eg, loperamide, diphenoxylate/atropine, and clonidine) are used in an attempt to slow intestinal transit in hopes of providing a longer duration of contact between the intestinal mucosa and luminal nutrients. Children with gastroschisis are more likely to have problems with delayed gastric emptying and nonpropulsive intestinal motility. In this setting, promotility agents (eg, metoclopramide, erythromycin, or amoxicillin-clavulanic acid) have been used to improve intestinal motility.[65] Cisapride was removed from the market in the United States because of its association with cardiac arrhythmias, and Metoclopramide now has a black box warning due to its association with tardive dyskinesia.

Antisecretory agents are used to reduce fluid secretion and stool output. Histamine-2 blockers and proton pump inhibitors might be useful during the early months following massive intestinal resection. However, continued use, in the absence of clear benefit, may place children at increased risk for SIBO or candida esophagitis as gastric acid serves a useful function in limiting fungal and bacterial growth.

Bile acid–binding resins (eg, cholestyramine) have been tried in patients with little or no ileum when increased stool output is thought to be related to bile acid malabsorption. These agents are not easily administered, have little or no palatability, and their efficacy in this clinical setting has not been tested.

Hormonal therapy

One of the major advances in the field of intestinal rehabilitation is the use of hormonal therapy to augment the adaptation process. Among the hormones studied, GLP-2 has shown the greatest clinical benefit in augmenting the adaptation response. A potential adaptive hormone effect was initially identified in patients with glucagonoma who were found to have a significant increase in intestinal mass.

In the 1990s, the specific hormone GLP-2 was identified. GLP-2 therapy leads to increased villous height and crypt depth, increased mesenteric blood flow, and decreased motility extending the contact time for small intestinal absorption. Teduglutide, the first GLP-2 analogue approved for SBS treatment, contains an alanine-to-glycine substitution that causes an increased half-life. In the Study of Teduglutide Effectiveness in PN-dependent SBS Subjects trial, teduglutide met the primary endpoint of a 20% reduction in PN volume in adults.[66]

The post-hoc analysis indicated that the greatest absolute reductions in PN volume occur in those with high ostomies but that those with modest PN dependence and intact colons were more likely to wean from PN entirely.[67] Similar results have now been shown in a pediatric trial, leading to the approval of teduglutide for treating SBS in both children and adults.[68,69] Long-term data in adults suggest that the effect of teduglutide requires continued treatment, and concerns have been raised about whether such use would predispose to gastrointestinal malignancy.[70] Coupled with the high cost, this has led to careful monitoring for response and discontinuation of therapy in those who show minimal benefit. Newer longer-acting GLP-2 formulations may decrease injection frequency with similar clinical benefits.

Other exogenous growth factors have shown limited clinical utility, such as growth hormone or somatostatin analogues. Epidermal growth factor has shown promising results in animal studies, especially in promoting intestinal lengthening, but this has not yet been demonstrated in clinical practice.[71]

Nontransplant Surgery

Half of the children with SBS will have more than one abdominal operation.[72] Following the initial surgical intervention, subsequent surgeries often address complications such as stricture, intestinal dilation, and placement of invasive feeding devices, which are all considered standard of care.[73]

LILT and STEP represent advanced techniques that both taper dilated segments of the bowel and increase intestinal length. Digestive function may improve not only because aboral flow is facilitated by a normalized luminal caliber, but also because subsequent adaptation may lead to increased intestinal surface area. LILT was first described in 1980 by Bianchi,[23] and has since been used at many centers.[20] Criteria for performing LILT vary but generally require >20 cm of symmetrically dilated intestine in the context of residual intestinal length of >40 cm.[20] Standardized indications, contraindications, and surgical guidelines have not been developed, which may explain inconsistent results reported in the literature.[74]

STEP involves applying a stapling device incompletely across a dilated loop of intestine in a serial fashion to create a zig-zag pattern that results in a lumen that is both narrower and longer. Since its description by Kim et al[74] in 2003, it has become an accepted technique at many IF centers.[75,76] A report from the International STEP Data Registry identified 13 participants who underwent a STEP procedure as a primary procedure and found it to be feasible and safe.[75,76] However, its full impact and usefulness has yet to be determined.

While a growing body of literature describes individual experiences with nontransplant surgery for children with IF, the relatively small numbers of patients, retrospective nature of data collection spanning many years, and heterogeneous definitions and patient characteristics have limited the ability to promote data-driven indications and timing for these techniques. The authors propose an approach based on the assessment of bowel dilation, cessation of any progression toward enteral autonomy, and limitations on growth. Such assessment is best performed by a coordinated team including a pediatric surgeon and gastroenterologist with expertise in SBS and in particular in those requiring such procedures. As many of these procedures

do not necessarily correct underlying dysmotility, it is common to consider repeated procedures when dilation recurs. Again, this must be done by those with experience in performing such advanced reconstructive surgeries.

General Assessment

With the understanding that management of IF is highly individualized, and that evidence-based practice supported by randomized, controlled trials is lacking, assessment of progress can be challenging. Tolerance of enteral feeds is ill-defined and difficult to assess. Stool volume can only be estimated in diapered children because urine and stool are often "mixed." Stool number is often confounded by "squirts" that are frequent but low volume. For example, 10 stools per day may be "okay" if only 3 to 4 or so are big enough to fill the diaper, the perianal area is not excoriated, the family is comfortable, and hydration is maintained. Weight gain must be adjusted for preterm infants and those who were small for gestational age, and also take into account the child's residual bowel length and function. Efforts to achieve weight gain that follows the 50th percentile may be unrealistic. The goal is to find the minimal amount of PN and the maximal amount of luminal nutrition to support reasonable weight gain and growth.

Complications

Nutrition Deficiencies

Deficiencies in vitamins, minerals, and trace elements are associated with IF.[77] Malabsorption of fat-soluble vitamins A, D, E, and K may result from an insufficient intraluminal concentration of bile acids secondary to excess fecal loss.[78] Surgical resections of the duodenum or ileum, which have unique absorptive functions, add to the risk of developing specific nutrition deficiencies. The duodenum is a primary site for iron and folate absorption and its resection can result in these micronutrient deficiencies. The absence of the ileum, with its unique ability to absorb vitamin B12 and bile acids, places the patient at risk for deficiencies of fat-soluble vitamins and vitamin B12. Calcium and magnesium deficiencies can result from binding to intraluminal long-chain fatty acids.[79,80] Deficiencies of other minerals and trace elements such as zinc, riboflavin, thiamin, biotin, and selenium can

occur.[81] In addition, nutrient deficiencies hinder intestinal adaptation, further compounding the clinical impact.[82]

Functional and Metabolic Complications

Following massive bowel resection that alters normal intestinal physiology, many acute and chronic medical complications develop that prompt an effort for medical interventions. Unfortunately, many interventions and treatments have not been adequately studied with sufficient numbers of patients.

Hypergastrinemia develops shortly after massive small bowel resection and can reduce nutrient absorption by inactivating pancreatic enzymes and precipitating bile salts, thus leading to diarrhea as well as nausea and vomiting.[83–85] Small case series have reported mixed benefits of acid reduction to improve absorption.[86–89] However, no large trials demonstrate a benefit to the use of these medications in children with IF. Indiscriminate and especially long-term use of these medications may predispose patients to SIBO, calcium and iron malabsorption, or a heightened risk of Candida esophagitis or sepsis.[90]

Bile acid malabsorption as a consequence of ileal resection can result in secretory diarrhea that complicates fat and fat-soluble vitamin absorption.[91] Rapid intestinal transit occurs following small bowel resection[92,93] and is often managed with the use of antimotility agents such as loperamide, which have mixed effects on water and salt balance.[94,95] Nephrolithiasis, when it occurs in the setting of IF, is typically due to either uric acid or calcium oxalate stones.[96] Chronic kidney disease has been associated with repeated episodes of dehydration and acute kidney injury in those with IF.

Alterations in gastrointestinal motility, along with the use of acid-blocking agents, may increase the bacterial content in the small intestine, resulting in SIBO. SIBO can result in deconjugation of luminal bile acids, making them ineffective in micellar formation, and can be associated with mucosal inflammation, nutrient deficiencies (notably vitamin B12), and D-lactic acidosis, as well as cramps, diarrhea, gastrointestinal bleeding, and arthritis. SIBO can be diagnosed with a strong index of clinical suspicion and an appropriate symptomatology. Diagnostic tests for SIBO include

breath tests, which have limited utility in SBS, and duodenal aspirates, which require invasive testing and are limited based on anatomical issues relating to symptoms. The relationship between SIBO and systemic sepsis is not well understood.[97–101] SIBO is most often treated empirically with intermittent oral or enteral doses of broad-spectrum antibiotics, and in some cases, probiotics, but many varying practices exist for the frequency and duration of administration, with no data available to evaluate relative efficacies. The risks of generating multi-drug resistant bacteria with this approach also raise concern, and addressing the underlying dysmotility or bowel dilation that leads to SIBO must be simultaneously considered.

D-lactic acidosis is a unique feature of patients with IF and was first described in children in 1983.[101] The combination of a high anion gap acidosis and altered mental status that develops after a high carbohydrate enteral feeding should prompt the clinical suspicion of D-lactic acidosis. Treatment involves discontinuation of enteral feeding, selective bowel decontamination, and if indicated, a surgical procedure aimed at decreasing intestinal diameter and reducing SIBO.[102,103] Frequent antibiotic therapy may, paradoxically, place the patient at risk for D-lactic acidosis by creating a selective advantage for D-lactate–producing bacteria.[104]

Liver Disease

Liver disease is the most frequent complication of long-term PN, with consequences that include cirrhosis, end-stage liver disease, and even death.[105] Historically, the incidence of IFALD is as high as 50% in infants who receive PN for 2 months, with end-stage liver disease developing in 90% of preterm infants on PN for >3 months.[106] However, this development is becoming less frequent with care by multidisciplinary teams and careful approaches to PN, enteral feeding, and surgical techniques. Elevated serum transaminase and bilirubin levels are commonly observed in infants on PN, but these levels can normalize, and jaundice resolves with intestinal adaptation and PN withdrawal. The long-term outcome of IFALD in patients who adapt is unknown. Preterm infants born weighing <1 kg and those with IF resulting from surgical resection are at the greatest risk for IFALD.[107–109] The etiology of IFALD is likely multifactorial, with prematurity, multiple abdominal surgeries, lack of enterally stimulated bile

flow, bacterial sepsis, and components or deficiencies of PN infusates all potential contributors.

Treatment of IFALD is empiric and imperfect. Current strategies to avert liver disease associated with long-term PN include bowel "decontamination" to treat SIBO,[108,110] vigilant catheter care,[111] and modifying PN formulations. Infusing PN calories for <24 hours, casually referred to as "cycling" PN, is thought to improve cholestasis.[112] The underlying mechanism for this action and effect is not clearly understood but may involve providing a metabolic "rest" from the continuous infusion of calories, protein, and/or carbohydrate. Administering pediatric PN formulations that include specific "targeted" amino acids including taurine[113] and limiting the infusion of dextrose to potentially decrease steatosis have also been utilized.[114] Decreasing aluminum and manganese content in PN may decrease hepatotoxicity.[115,116] Decreasing the amount or altering the type of lipids administered may improve serum transaminase levels, reverse PN–associated liver disease, or reduce lipid peroxidation.[117–119]

As already noted, fish oil–based lipid emulsions lacking phytosterols and minimizing pro-inflammatory ω-6 fatty acids have successfully been used to treat cholestasis in infants.[60,120] Phytosterols inhibit the farnesoid X receptor in the liver, leading to a decrease in enterohepatic bile acid circulation.[57,58] Treatment dosing of fish oil-based lipid emulsions typically involves providing 1 g/kg/d, however, doses as high as 1.5 g/kg/d have been used if needed to sustain adequate growth in children. Combination lipid emulsions used to prevent cholestasis development can be used at higher doses to support growth,[121,122] but anecdotal evidence suggests a higher risk of cholestasis at doses above 2 g/kg/d.

Disappointingly, hepatic fibrosis and steatosis persist in some children despite the resolution of cholestasis and achieving enteral autonomy.[123] A 2014 clinical guideline details the support of pediatric patients with IF at risk for PN–associated liver disease.[124] Once end-stage liver disease develops, portal hypertension, variceal and stomal bleeding, infection, hypoglycemia, and hyperammonemia occur, making a combined liver-

intestinal transplant the only remaining lifesaving measure for patients unable to be weaned from PN.

Central Venous Catheter Complications

Maintaining central venous catheter (CVC) access is critical in the long-term management of IF and has been the topic of a recent clinical guideline.[125] Loss of vascular access can be fatal in this population and is an indication for intestinal transplantation. As a result, salvage of the CVC is a strategy employed to preserve vascular access. In addition, newer approaches such as recanalization of a thrombosed vessel have been employed in selected patients when vascular sites are limited.[126,127] The threshold for CVC removal and referral to centers that perform recanalization is likely variable from both an institutional and physician standpoint. A greater understanding of the source of this variability will provide standardization for a best-practice model and allow participating centers to preserve access sites and better equip patients for long-term survival.

Sepsis is the leading cause of death in children with IF. Central line–associated bloodstream infections (CLABSIs) are responsible for a majority of the infectious morbidity. Children with SBS/IF have CLABSI rates as high as 50% to 70% when presenting to the emergency department with a fever, regardless of other symptoms.[128] Potential risk factors include the proximity of fecal material to line entry sites and connections, frequent line access for laboratory tests, and intestinal bacterial translocation. While translocation occurs in animal models, its proof in human populations is elusive.[129] At the same time, evidence suggests a role for bacterial translocation in IF. Enteric organisms are more frequently isolated in cultures sampled from these patients compared with other populations with CVC.[130] Furthermore, a comparison of CVC isolates with fecal flora and mesenteric lymph node cultures was highly concordant.[131] The incidence of infection increased while advancing enteral feeds.[132] Treatment strategies to manage and prevent CLABSIs include care bundles that emphasize sterile CVC care[133,134] and antimicrobial lock therapy to reduce biofilm formation.[135–137]

While CLABSIs are concerning, patients with IF are also subject to numerous other central line–related complications, of which thrombosis and line breakage are the 2 most frequent. Fortunately, the salvage rate is high, and treatment with thrombolytics or CVC repair has resulted in a high CVC salvage rate.[138] Thrombosis of great vessels has emerged as the leading indication for intestine transplant. The role of anticoagulation both therapeutically and prophylactically as well as the appropriate screening modality for assessing vascular access remain areas of debate.[125] The development of consensus guidelines based on the accrual of data across the population of individuals with IF is predicted to reduce CVC-associated complications as well as lengthen the life span of each catheter and preserve access sites critical to survival and potential transplantation.

Musculoskeletal Health

Children with SBS may have growth limitations. While some may be attributed to nutritional status, many of these children are born significantly preterm with other comorbidities that play a role, often leading to significant short stature. Many children require growth hormone replacement, which may also have a positive impact on bone health.[139] Calcium and vitamin D are typically provided in PN, but many patients require much higher doses of vitamin D that may be given adjunctively through daily enteral formulations. Adequate physical exercise is also required and can be difficult for children who have limited time off parenteral support. Even adults weaned from parenteral support have shown high rates of poor muscle mass.[140] The assessment of bone health in these children can be quite challenging, as even once they reach an age in which dual-energy x-ray absorptiometry may be performed, short stature may confound any reasonable interpretation.[141] However, the incidence of fractures in these children suggests poor bone mineralization, thus there may be a role for bisphosphonate therapy in select candidates.

Outcomes

Growth and Development

Infants and children must digest and absorb sufficient calories, vitamins, minerals, and trace elements to gain weight, grow, and develop. Children with IF are incapable of sustaining adequate growth and development without supplemental PN. Successful intestinal adaptation implies complete independence from PN while continuing to demonstrate satisfactory linear growth and weight gain.

The expected weight gain and growth of patients with IF weaned from prolonged PN is not known. Well-designed prospective studies are needed to address long-term growth and development in children with IF following PN withdrawal. A retrospective study of 87 children identified over 16 years showed that growth is greatest early after weaning from PN and begins to decline after 4 years.[25] More recent research examining the growth and pubertal development of these children indicates that children with IF have normal pubertal onset but a high incidence of short stature.[142] Children may be able to show some catch-up linear growth while on PN that declines once weaned off.[143]

Quality of Life

Studies of adult patients have identified reduced quality-of-life (QOL) scores in patients with SBS, which were further reduced for patients on HPN. Interestingly, the presence of a stoma did not appear to influence their QOL.[144] Similarly detailed studies addressing QOL and school performance of children have not been performed; however, children on HPN fared better than those hospitalized for PN.[145,146] For adults, QOL may correlate with the degree of parenteral dependence, and some adults rate being on PN for 7 days per week as "a fate worse than death."[147] This does not seem to correspond to pediatric intestinal failure, as some studies suggested that patients on PN may have an equal or even greater self-reported QOL than those being weaned or already weaned off.[148]

From a developmental standpoint, much of the challenge in assessing the effect of intestinal failure on neurodevelopment lies in the high rate of comorbidity with preterm delivery and associated conditions. Children with

intestinal failure have a range of neurodevelopmental challenges, from poor executive functioning to lower energy to decreased overall psychosocial health.[148–150]

Intestinal Transplant

Intestinal transplant is the final lifesaving option for patients with irreversible IF and life-threatening complications associated with PN administration. The term *intestine transplant* encompasses isolated small intestine transplant (with or without a colon) along with combined grafts that may include a liver (liver-small bowel transplant); stomach and duodenum (modified multivisceral transplant); or liver, stomach, duodenum, and pancreas (full multivisceral transplant). While many reports combine the various forms of intestine transplant, they are different procedures for different indications. For example, a liver–small bowel transplant is most commonly indicated for patients with severe liver disease who are PN-dependent, while a full multivisceral transplant is more common for those inquiring about the en bloc transplant for anatomical considerations (eg, for diffuse portomesenteric thrombosis).

In 1994, very few pediatric intestinal transplants were performed worldwide (approximately 25 according to the Intestinal Transplant Registry), with unsatisfactory outcomes in these early years.[20] With advances in posttransplant care and immunosuppression protocols, these outcomes have dramatically improved,[151] and more than 2500 intestinal transplants have now been performed in all age groups worldwide, with more than 1400 in the pediatric population.[4,151–153] Five-year patient survival rates exceed 50% worldwide.[6] Unfortunately, the indications for intestinal transplant are broad and subject to a significant degree of interpretation. Evidence-based parameters are needed that would improve the patient selection for intestinal transplant and determine optimal timing to maximize outcomes and minimize the need for combined organ transplantation.

Currently, intestinal transplantation is reserved for patients who have refractory PN–dependence and fail PN as defined by the Centers for Medicare and Medicaid Services. In principle, PN failure may be defined as the onset of potentially life-threatening complications of PN in the form of

progressive IFALD or catheter-related complications including recurrent life-threatening sepsis, a single episode of fungal sepsis, or loss of central venous access. Additional indications that may be more contentious include nonresectable tumors at the root of the mesentery, non-reconstructible gastrointestinal tract due to complex entero-cutaneous fistulae, or recurrent or life-threatening metabolic and fluid–electrolyte derangements that become unmanageable on PN. Newer work has proposed revisions to these original indications based on the changing landscape of IF management, although the broad categories defining PN failure remain unchanged.[154,155]

The goal of intestinal transplantation is to achieve PN autonomy, with CVC removal becoming a major milestone, which is typically achieved within a month of transplant in most cases. Nutritional management of post–intestinal transplant patients is complex, often punctuated by transplant-related complications. and is best viewed as a form of IF with the potential for rapid intestinal adaptation.

An important early nutrition complication following intestinal transplantation is the occurrence of chylous ascites in a small percentage of cases. This complication occurs because no attempt is made at lymphatic reconstitution during the intestinal transplant procedure. The risk of this complication decreases to almost zero at 4 to 6 weeks as the abdominal and diaphragmatic lymphatics appear to reconstitute in the first few weeks. This complication can be avoided by following fat-free diets for the first 2 to 4 weeks after transplant, and cautiously introducing small amounts of dietary fat thereafter.

A gastrostomy or jejunostomy feeding tube is typically placed at the time of transplant to allow for rapid weaning from PN in the first month after transplant and to provide access for supplementary enteral feedings if needed. At a time when the allograft bowel may still be recovering from ischemia-reperfusion, the feeding tube provides a means for enteral delivery of appropriate glucose-saline solutions, such as oral rehydration solution or Pedialyte, to prevent renal dysfunction secondary to dehydration. Most patients can accomplish full oral feedings and discontinue enteral access within 6 months of transplant.

A subset of patients with IF and associated liver disease may benefit from an isolated liver transplant.[156–158] IFALD may hinder bowel

adaptation and delay progression toward enteral feeding tolerance,[7] and researchers have reported remarkable bowel adaptation and feeding tolerance after isolated liver transplants for severe IFALD.[5,6,156]

Conlcusion

In summary, IF is a highly morbid condition in children and significant progress has been made to support these children to avoid complications. Intestine transplant remains the only cure for intestinal failure but modest results have limited its widespread use. Advancements in promoting intestinal adaptation through both nutritional and pharmacologic methods have allowed children with IF to survive and thrive.

Test Your Knowledge Questions

1. A 30-week-old infant with 35 cm of small bowel, an ileocecal valve, and an intact colon has an advantage over a full-term infant with the same anatomy because of which of the following?
   A. Etiologies for SBS are different between the 2 groups.
   B. Preterm infants who survive are constitutionally stronger than full-term infants.
   C. The small intestinal length doubles in the last trimester.
   D. Complications associated with PN are less frequent in preterm infants.
2. Which of the following clinical features is associated with enteral autonomy?
   A. Being female
   B. Small intestine in continuity with the colon
   C. Absent ileocecal valve
   D. Having fewer than 10 stools per day
3. IFALD is caused by which of the following?
   A. IV lipid
   B. Lack of enteral feeding
   C. Recurrent infections
   D. Multiple factors, including all of the above

4. Which is the best method to provide enteral feeding for children with IF?
   A. Gastrostomy
   B. Nasogastric tube
   C. Jejunal feeding
   D. Oral feeding

References

1. Modi BP, Galloway DP, Gura K, et al. ASPEN definitions in pediatric intestinal failure. *JPEN J Parenter Enteral Nutr.* 2022;46(1):42–59. https://doi.org/10.1002/jpen.2232
2. Squires RH, Duggan C, Teitelbaum DH, et al. Natural history of pediatric intestinal failure: initial report from the Pediatric Intestinal Failure Consortium. *J Pediatr.* 2012;161(4):723–728. https://doi.org/10.1016/j.jpeds.2012.03.062
3. Stanger JD, Oliveira C, Blackmore C, et al. The impact of multi-disciplinary intestinal rehabilitation programs on the outcome of pediatric patients with intestinal failure: a systematic review and meta-analysis. *J Pediatr Surg.* 2013;48(5):983–992. https://doi.org/10.1016/j.jpedsurg.2013.02.070
4. Andorsky DJ, Lund DP, Lillehei CW, et al. Nutritional and other postoperative management of neonates with short bowel syndrome correlates with clinical outcomes. *J Pediatr.* 2001;139(1):27–33. https://doi.org/10.1067/mpd.2001.114481
5. Goulet OJ, Revillon Y, Jan D, et al. Neonatal short bowel syndrome. *J Pediatr.* 1991;119(pt 1):18–23. https://doi.org/10.1016/s0022-3476(05)81032-7
6. Quiros-Tejeira RE, Ament ME, Reyen L, et al. Long-term parenteral nutritional support and intestinal adaptation in children with short bowel syndrome: a 25-year experience. *J Pediatr.* 2004;145(2):157–163. https://doi.org/10.1016/j.jpeds.2004.02.030
7. Spencer AU, Neaga A, West B, et al. Pediatric short bowel syndrome: redefining predictors of success. *Ann Surg.* 2005;242(3):403–409. https://doi.org/10.1097/01.sla.0000179647.24046.03

8. Struijs MC, Diamond IR, de Silva N, Wales PW. Establishing norms for intestinal length in children. *J Pediatr Surg.* 2009;44(5):933–938. https://doi.org/10.1016/j.jpedsurg.2009.01.031
9. DeLegge M, Alsolaiman MM, Barbour E, Bassas S, Siddiqi MF, Moore NM. Short bowel syndrome: parenteral nutrition versus intestinal transplantation. Where are we today? *Dig Dis Sci.* 2007;52(4):876–892. https://doi.org/10.1007/s10620-006-9416-6
10. Wallander J, Ewald U, Lackgren G, Tufveson G, Wahlberg J, Meurling S. Extreme short bowel syndrome in neonates: an indication for small bowel transplantation? *Transplant Proc.* 1992;24(3):1230–1235.
11. Schalamon J, Mayr JM, Hollwarth ME. Mortality and economics in short bowel syndrome. *Best Pract Res Clin Gastroenterol.* 2003;17(6):931–942. https://doi.org/10.1016/s1521-6918(03)00079-9
12. Colomb V. Economic aspects of paediatric home parenteral nutrition. *Curr Opin Clin Nutr Metab Care.* 2000;3(3):237–239. https://doi.org/10.1097/00075197-200005000-00013
13. Diamond IR, de Silva N, Pencharz PB, et al. Neonatal short bowel syndrome outcomes after the establishment of the first Canadian multidisciplinary intestinal rehabilitation program: preliminary experience. *J Pediatr Surg.* 2007;42(5):806–811. https://doi.org/10.1016/j.jpedsurg.2006.12.033
14. Ganousse-Mazeron S, Lacaille F, Colomb-Jung V, et al. Assessment and outcome of children with intestinal failure referred for intestinal transplantation. *Clin Nutr.* 2015;34(3):428–435. https://doi.org/10.1016/j.clnu.2014.04.015
15. Hess RA, Welch KB, Brown PI, Teitelbaum DH. Survival outcomes of pediatric intestinal failure patients: analysis of factors contributing to improved survival over the past two decades. *J Surg Res.* 2011;170(1):27–31. https://doi.org/10.1016/j.jss.2011.03.037
16. Modi BP, Langer M, Ching YA, et al. Improved survival in a multidisciplinary short bowel syndrome program. *J Pediatr Surg.* 2008;43(1):20–24. https://doi.org/10.1016/j.jpedsurg.2007.09.014
17. Sanchez SE, Javid PJ, Healey PJ, Reyes J, Horslen SP. Ultrashort bowel syndrome in children. *J Pediatr Gastroenterol Nutr.* 2013;56(1):36–39. https://doi.org/10.1097/mpg.0b013e318266245f

18. Sigalet D, Boctor D, Robertson M, et al. Improved outcomes in paediatric intestinal failure with aggressive prevention of liver disease. *Eur J Pediatr Surg.* 2009;19(6):348–353. https://doi.org/10.1055/s-0029-1241865
19. Merritt RJ, Cohran V, Raphael BP, et al. Intestinal Rehabilitation Programs in the Management of Pediatric Intestinal Failure and Short Bowel Syndrome. *J Pediatr Gastroenterol Nutr.* 2017;65(5):588–596. https://doi.org/10.1097/mpg.0000000000001722
20. Goulet O, Ruemmele F, Lacaille F, Colomb V. Irreversible intestinal failure. *J Pediatr Gastroenterol Nutr.* 2004;38(3):250–269. https://doi.org/10.1097/00005176-200403000-00006
21. Drozdowski L, Thomson AB. Intestinal mucosal adaptation. *World J Gastroenterol.* 2006;12(29):4614–4627. https://doi.org/10.3748/wjg.v12.i29.4614
22. Tavakkolizadeh A, Whang EE. Understanding and augmenting human intestinal adaptation: a call for more clinical research. *JPEN J Parenter Enteral Nutr.* 2002;26(4):251–255. https://doi.org/10.1177/0148607102026004251
23. Bianchi A. Intestinal loop lengthening—a technique for increasing small intestinal length. *J Pediatr Surg.* 1980;15(2):145–151. https://doi.org/10.1016/s0022-3468(80)80005-4
24. Javid PJ, Kim HB, Duggan CP, Jaksic T. Serial transverse enteroplasty is associated with successful short-term outcomes in infants with short bowel syndrome. *J Pediatr Surg.* 2005;40(6):1019–1023. https://doi.org/10.1016/j.jpedsurg.2005.03.020
25. Goulet O, Baglin-Gobet S, Talbotec C, et al. Outcome and long-term growth after extensive small bowel resection in the neonatal period: a survey of 87 children. *Eur J Pediatr Surg.* 2005;15(2):95–101. https://doi.org/10.1055/s-2004-821214
26. Crenn P, Morin MC, Joly F, Penven S, Thuillier F, Messing B. Net digestive absorption and adaptive hyperphagia in adult short bowel patients. *Gut.* 2004;53(9):1279–1286. https://doi.org/10.1136/gut.2003.030601
27. Jeppesen PB, Sanguinetti EL, Buchman A, et al. Teduglutide (ALX-0600), a dipeptidyl peptidase IV resistant glucagon-like peptide 2 analogue, improves intestinal function in short bowel syndrome

patients. *Gut.* 2005;54(9):1224–1231. https://doi.org/10.1136/gut.2004.061440
28. Weser E, Babbitt J, Hoban M, Vandeventer A. Intestinal adaptation. Different growth responses to disaccharides compared with monosaccharides in rat small bowel. *Gastroenterology.* 1986;91(6):1521–1527. https://doi.org/10.1016/0016-5085(86)90210-6
29. Vanderhoof JA, Grandjean CJ, Burkley KT, Antonson DL. Effect of casein versus casein hydrolysate on mucosal adaptation following massive bowel resection in infant rats. *J Pediatr Gastroenterol Nutr.* 1984;3(2):262–267. https://doi.org/10.1097/00005176-198403000-00017
30. Bartholome AL, Albin DM, Baker DH, Holst JJ, Tappenden KA. Supplementation of total parenteral nutrition with butyrate acutely increases structural aspects of intestinal adaptation after an 80% jejunoileal resection in neonatal piglets. *JPEN J Parenter Enteral Nutr.* Jul-2004;28(4):210–222. https://doi.org/10.1177/0148607104028004210
31. Gambarara M, Ferretti F, Bagolan P, et al. Ultra-short-bowel syndrome is not an absolute indication to small-bowel transplantation in childhood. *Eur J Pediatr Surg.* 1999;9(4):267–270. https://doi.org/10.1055/s-2008-1072261
32. Wasa M, Takagi Y, Sando K, Harada T, Okada A. Intestinal adaptation in pediatric patients with short-bowel syndrome. *Eur J Pediatr Surg.* 1999;9(4):207–209. https://doi.org/10.1055/s-2008-1072245
33. Jeppesen PB, Mortensen PB. The influence of a preserved colon on the absorption of medium chain fat in patients with small bowel resection. *Gut.* 1998;43(4):478–483. https://doi.org/10.1136/gut.43.4.478
34. Nightingale JM, Lennard-Jones JE, Gertner DJ, Wood SR, Bartram CI. Colonic preservation reduces need for parenteral therapy, increases incidence of renal stones, but does not change high prevalence of gall stones in patients with a short bowel. *Gut.* 1992;33(11):1493–1497. https://doi.org/10.1136/gut.33.11.1493
35. Luo M, Fernandez-Estivariz C, Manatunga AK, et al. Are plasma citrulline and glutamine biomarkers of intestinal absorptive function

in patients with short bowel syndrome? *JPEN J Parenter Enteral Nutr.* 2007;31(1):1–7. https://doi.org/10.1177/0148607107031001O1

36. Bernal NP, Stehr W, Zhang Y, Profitt S, Erwin CR, Warner BW. Evidence for active Wnt signaling during postresection intestinal adaptation. *J Pediatr Surg.* 2005;40(6):1025–1029. https://doi.org/10.1016/j.jpedsurg.2005.03.021
37. Roy CC, Groleau V, Bouthillier L, Pineault M, Thibault M, Marchand V. Short bowel syndrome in infants: the critical role of luminal nutrients in a management program. *Appl Physiol Nutr Metab.* 2014;39(7):745–753. https://doi.org/10.1139/apnm-2013-0211
38. Levy J. Immunonutrition: the pediatric experience. *Nutrition.* 1998;14(7–8):641–647. https://doi.org/10.1016/s0899-9007(98)00007-0
39. Vanderhoof JA, Langnas AN. Short-bowel syndrome in children and adults. *Gastroenterology.* 1997;113(5):1767–1778. https://doi.org/10.1053/gast.1997.v113.pm9352883
40. Gosselin KB, Duggan C. Enteral nutrition in the management of pediatric intestinal failure. *J Pediatr.* 2014;165(6):1085–1090. https://doi.org/10.1016/j.jpeds.2014.08.012
41. Bines J, Francis D, Hill D. Reducing parenteral requirement in children with short bowel syndrome: impact of an amino acid-based complete infant formula. *J Pediatr Gastroenterol Nutr.* 1998;26(2):123–128. https://doi.org/10.1097/00005176-199802000-00001
42. Ksiazyk J, Piena M, Kierkus J, Lyszkowska M. Hydrolyzed versus nonhydrolyzed protein diet in short bowel syndrome in children. *J Pediatr Gastroenterol Nutr.* 2002;35(5):615–618. https://doi.org/10.1097/00005176-200211000-00005
43. Taylor SF, Sondheimer JM, Sokol RJ, Silverman A, Wilson HL. Noninfectious colitis associated with short gut syndrome in infants. *J Pediatr.* 1991;119(1 Pt 1):24–28. https://doi.org/10.1016/s0022-3476(05)81033-9
44. Vanderhoof JA, Grandjean CJ, Kaufman SS, Burkley KT, Antonson DL. Effect of high percentage medium-chain triglyceride diet on mucosal adaptation following massive bowel resection in rats. *JPEN J*

Parenter Enteral Nutr. 1984;8(6):685–689. https://doi.org/10.1177/0148607184008006685
45. Duro D, Mitchell PD, Mehta NM, et al. Variability of resting energy expenditure in infants and young children with intestinal failure-associated liver disease. *J Pediatr Gastroenterol Nutr.* 2014;58(5):637–641. https://doi.org/10.1097/MPG.0000000000000288
46. Blackman JA, Nelson CL. Reinstituting oral feedings in children fed by gastrostomy tube. *Clin Pediatr (Phila).* 1985;24(8):434–438. https://doi.org/10.1177/000992288502400803
47. Dsilna A, Christensson K, Alfredsson L, Lagercrantz H, Blennow M. Continuous feeding promotes gastrointestinal tolerance and growth in very low birth weight infants. *J Pediatr.* 2005;147(1):43–49. https://doi.org/10.1016/j.jpeds.2005.03.003
48. Shulman RJ, Redel CA, Stathos TH. Bolus versus continuous feedings stimulate small-intestinal growth and development in the newborn pig. *J Pediatr Gastroenterol Nutr.* 1994;18(3):350–354. https://doi.org/10.1097/00005176-199404000-00017
49. Shakeel F, Newkirk M, Sellers A, Shores DR. Postoperative Feeding Guidelines Improve Outcomes in Surgical Infants. *JPEN J Parenter Enteral Nutr.* 2020;44(6):1047–1056. https://doi.org/10.1002/jpen.1726
50. Dudrick SJ, Wilmore DW, Vars HM, Rhoads JE. Long-term total parenteral nutrition with growth, development, and positive nitrogen balance. *Surgery.* 1968;64(1):134–142.
51. Rhoads JE. The development of TPN: an interview with pioneer surgical nutritionist Jonathan E. Rhoads, MD. [Interview by Carolyn T. Spencer and Charlene Compher]. *J Am Diet Assoc.* 2001;101(7):747–750. https://doi.org/10.1016/s0002-8223(01)00188-2
52. Shulman RJ, Phillips S. Parenteral nutrition in infants and children. *J Pediatr Gastroenterol Nutr.* 2003;36(5):587–607. https://doi.org/10.1097/00005176-200305000-00002
53. Lafeber HN, Sulkers EJ, Chapman TE, Sauer PJ. Glucose production and oxidation in preterm infants during total parenteral nutrition.

Pediatr Res. 1990;28(2):153–157. https://doi.org/10.1203/00006450-199008000-00015
54. Sheridan RL, Yu YM, Prelack K, Young VR, Burke JF, Tompkins RG. Maximal parenteral glucose oxidation in hypermetabolic young children: a stable isotope study. *JPEN J Parenter Enteral Nutr.* 1998;22(4):212–216. https://doi.org/10.1177/0148607198022004212
55. National Advisory Group on Standards and Practice Guidelines for Parenteral Nutrition; American Society for Parenteral and Enteral Nutrition (ASPEN). Safe practices for parenteral nutrition formulations. *JPEN J Parenter Enteral Nutr.* 1998;22(2):49–66. https://doi.org/10.1177/014860719802200249
56. Peters C, Fischer JE. Studies on calorie to nitrogen ratio for total parenteral nutrition. *Surg Gynecol Obstet.* 1980;151(1):1–8.
57. El Kasmi KC, Anderson AL, Devereaux MW, et al. Phytosterols promote liver injury and Kupffer cell activation in parenteral nutrition-associated liver disease. *Sci Transl Med.* 2013;5(206):206ra137. https://doi.org/10.1126/scitranslmed.3006898
58. Clayton PT, Whitfield P, Iyer K. The role of phytosterols in the pathogenesis of liver complications of pediatric parenteral nutrition. *Nutrition.* 1998;14(1):158–164. https://doi.org/10.1016/s0899-9007(97)00233-5
59. Anez-Bustillos L, Dao DT, Fell GL, et al. Redefining essential fatty acids in the era of novel intravenous lipid emulsions. *Clin Nutr.* 2018;37(3):784–789. https://doi.org/10.1016/j.clnu.2017.07.004
60. Gura KM, Parsons SK, Bechard LJ, et al. Use of a fish oil-based lipid emulsion to treat essential fatty acid deficiency in a soy allergic patient receiving parenteral nutrition. *Clin Nutr.* 2005;24(5):839–847. https://doi.org/10.1016/j.clnu.2005.05.020
61. de Meijer VE, Le HD, Meisel JA, Gura KM, Puder M. Parenteral fish oil as monotherapy prevents essential fatty acid deficiency in parenteral nutrition-dependent patients. *J Pediatr Gastroenterol Nutr.* 2010;50(2):212–218. https://doi.org/10.1097/MPG.0b013e3181bbf51e
62. Schwarz KB, Ternberg JL, Bell MJ, Keating JP. Sodium needs of infants and children with ileostomy. *J Pediatr.* 1983;102(4):509–513. https://doi.org/10.1016/s0022-3476(83)80175-9

63. Gomez R, Fernandez S, Aspirot A, et al. Effect of amoxicillin/clavulanate on gastrointestinal motility in children. *J Pediatr Gastroenterol Nutr.* 2012;54(6):780–784. https://doi.org/10.1097/mpg.0b013e31824204e4
64. O'Neil M, Teitelbaum DH, Harris MB. Total body sodium depletion and poor weight gain in children and young adults with an ileostomy: a case series. *Nutr Clin Pract.* 2014;29(3):397–401. https://doi.org/10.1177/0884533614528543
65. Schwartz MZ. Novel therapies for the management of short bowel syndrome in children. *Pediatr Surg Int.* 2013;29(10):967–974. https://doi.org/10.1007/s00383-013-3404-7
66. Jeppesen PB, Pertkiewicz M, Messing B, et al. Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure. *Gastroenterology.* 2012;143(6):1473–1481. https://doi.org/10.1053/j.gastro.2012.09.007
67. Jeppesen PB, Gabe SM, Seidner DL, et al. Factors associated with response to teduglutide in patients with short-bowel syndrome and intestinal failure. *Gastroenterology.* 2018;154(4):874–885. https://doi.org/10.1053/j.gastro.2017.11.023
68. Carter BA, Cohran VC, Cole CR, et al. Outcomes from a 12-week, open-label, multicenter clinical trial of teduglutide in pediatric short bowel syndrome. *J Pediatr.* 2017;181:102–111. https://doi.org/10.1016/j.jpeds.2016.10.027
69. Kocoshis SA, Merritt RJ, Hill S, et al. Safety and efficacy of teduglutide in pediatric patients with intestinal failure due to short bowel syndrome: a 24-week, phase III study. *JPEN J Parenter Enteral Nutr.* 2019:44:621–631. https://doi.org/10.1002/jpen.1690
70. Compher C, Gilroy R, Pertkiewicz M, et al. Maintenance of parenteral nutrition volume reduction, without weight loss, after stopping teduglutide in a subset of patients with short bowel syndrome. *JPEN J Parenter Enteral Nutr.* 2011;35(5):603–609. https://doi.org/10.1177/0148607111414431
71. Lim DW, Levesque CL, Vine DF, et al. Synergy of glucagon-like peptide-2 and epidermal growth factor coadministration on intestinal adaptation in neonatal piglets with short bowel syndrome. *Am J*

Physiol Gastrointest Liver Physiol. 2017;312(4):G390-G404. https://doi.org/10.1152/ajpgi.00281.2016
72. Wales PW. Surgical therapy for short bowel syndrome. *Pediatr Surg Int.* 2004;20(9):647–657. https://doi.org/10.1007/s00383-004-1268-6
73. Bianchi A. From the cradle to enteral autonomy: the role of autologous gastrointestinal reconstruction. *Gastroenterology.* 2006;130(suppl 2):S138-S146. https://doi.org/10.1053/j.gastro.2005.09.070
74. Kim HB, Fauza D, Garza J, Oh JT, Nurko S, Jaksic T. Serial transverse enteroplasty (STEP): a novel bowel lengthening procedure. *J Pediatr Surg.* 2003;38(3):425–429. https://doi.org/10.1053/jpsu.2003.50073
75. Garnett GM, Kang KH, Jaksic T, et al. First STEPs: serial transverse enteroplasty as a primary procedure in neonates with congenital short bowel. *J Pediatr Surg.* 2014;49(1):104–107. https://doi.org/10.1016/j.jpedsurg.2013.09.037
76. Modi BP, Javid PJ, Jaksic T, et al. First report of the international serial transverse enteroplasty data registry: indications, efficacy, and complications. *J Am Coll Surg.* 2007;204(3):365–371. https://doi.org/10.1016/j.jamcollsurg.2006.12.033
77. Ubesie AC, Kocoshis SA, Mezoff AG, Henderson CJ, Helmrath MA, Cole CR. Multiple micronutrient deficiencies among patients with intestinal failure during and after transition to enteral nutrition. *J Pediatr.* 2013;163(6):1692–1696. https://doi.org/10.1016/j.jpeds.2013.07.015
78. Ohkohchi N, Andoh T, Izumi U, Igarashi Y, Ohi R. Disorder of bile acid metabolism in children with short bowel syndrome. *J Gastroenterol.* 1997;32(4):472–479. https://doi.org/10.1007/bf02934085
79. Ament ME. Bone mineral content in patients with short bowel syndrome: the impact of parenteral nutrition. *J Pediatr.* 1998;132(3 Pt 1):386–388. https://doi.org/10.1016/s0022-3476(98)70006-x
80. Fleming CR, George L, Stoner GL, Tarrosa VB, Moyer TP. The importance of urinary magnesium values in patients with gut failure. *Mayo Clin Proc.* 1996;71(1):21–24. https://doi.org/10.4065/71.1.21

81. Buchman AL. Etiology and initial management of short bowel syndrome. *Gastroenterology.* 2006;130(2)(suppl 1):S5-S15. https://doi.org/10.1053/j.gastro.2005.07.063
82. Ziegler TR, Evans ME, Fernandez-Estivariz C, Jones DP. Trophic and cytoprotective nutrition for intestinal adaptation, mucosal repair, and barrier function. *Annu Rev Nutr.* 2003;23:229–261. https://doi.org/10.1146/annurev.nutr.23.011702.073036
83. Buxton B. Small bowel resection and gastric acid hypersecretion. *Gut.* 1974;15(3):229–238. https://doi.org/10.1136/gut.15.3.229
84. Go VL, Poley JR, Hofmann AF, Summerskill WH. Disturbances in fat digestion induced by acidic jejunal pH due to gastric hypersecretion in man. *Gastroenterology.* 1970;58(5):638–646. https://doi.org/10.1016/S0016-5085(70)80122-6
85. Williams NS, Evans P, King RF. Gastric acid secretion and gastrin production in the short bowel syndrome. *Gut.* 1985;26(9):914–919. https://doi.org/10.1136/gut.26.9.914
86. Cortot A, Fleming CR, Malagelada JR. Improved nutrient absorption after cimetidine in short-bowel syndrome with gastric hypersecretion. *N Engl J Med.* 1979;300(2):79–80. https://doi.org/10.1056/nejm197901113000207
87. Malagelada JR. Pathophysiological responses to meals in the Zollinger-Ellison syndrome: 2. Gastric emptying and its effect on duodenal function. *Gut.* 1980;21(2):98–104. https://doi.org/10.1136/gut.21.2.98
88. Nightingale JM, Walker ER, Farthing MJ, Lennard-Jones JE. Effect of omeprazole on intestinal output in the short bowel syndrome. *Aliment Pharmacol Ther.* 1991;5(4):405–412. https://doi.org/10.1111/j.1365-2036.1991.tb00044.x
89. Tang SJ, Nieto JM, Jensen DM, et al. The novel use of an intravenous proton pump inhibitor in a patient with short bowel syndrome. *J Clin Gastroenterol.* 2002;34(1):62–63. https://doi.org/10.1097/00004836-200201000-00012
90. Chocarro Martinez A, Galindo Tobal F, Ruiz-Irastorza G, et al. Risk factors for esophageal candidiasis. *Eur J Clin Microbiol Infect Dis.* 2000;19(2):96–100. https://doi.org/10.1007/s100960050437

91. Westergaard H. Bile acid malabsorption. *Curr Treat Options Gastroenterol.* 2007;10(1):28–33. https://doi.org/10.1007/s11938-007-0054-7
92. Nightingale JM, Kamm MA, van der Sijp JR, et al. Disturbed gastric emptying in the short bowel syndrome. Evidence for a 'colonic brake.' *Gut.* 1993;34(9):1171–1176. https://doi.org/10.1136/gut.34.9.1171
93. Reynell PC, Spray GH. Small intestinal function in the rat after massive resections. *Gastroenterology.* 1956;31(4):361–368. https://doi.org/10.1016/S0016-5085(19)35847-0
94. Nightingale JM, Lennard-Jones JE, Walker ER. A patient with jejunostomy liberated from home intravenous therapy after 14 years; contribution of balance studies. *Clin Nutr.* 1992;11(2):101–105. https://doi.org/10.1016/0261-5614(92)90019-m
95. Rodrigues CA, Lennard-Jones JE, Thompson DG, Farthing MJ. The effects of octreotide, soy polysaccharide, codeine and loperamide on nutrient, fluid and electrolyte absorption in the short-bowel syndrome. *Aliment Pharmacol Ther.* 1989;3(2):159–169. https://doi.org/10.1111/j.1365-2036.1989.tb00202.x
96. Nightingale JM. Hepatobiliary, renal and bone complications of intestinal failure. *Best Pract Res Clin Gastroenterol.* 2003;17(6):907–929. https://doi.org/10.1016/s1521-6918(03)00108-2
97. Dibaise JK, Young RJ, Vanderhoof JA. Enteric microbial flora, bacterial overgrowth, and short-bowel syndrome. *Clin Gastroenterol Hepatol.* 2006;4(1):11–20. https://doi.org/10.1016/j.cgh.2005.10.020
98. O'Keefe SJ. Bacterial overgrowth and liver complications in short bowel intestinal failure patients. *Gastroenterology.* 2006;130(2)(suppl 1):S67-S69. https://doi.org/10.1053/j.gastro.2005.09.067
99. Puwanant M, Mo-Suwan L, Patrapinyokul S. Recurrent D-lactic acidosis in a child with short bowel syndrome. *Asia Pac J Clin Nutr.* 2005;14(2):195–198. https://apjcn.nhri.org.tw/server/APJCN/14/2/195.pdf
100. Quigley KJ, Place HM. The role of debridement and antibiotics in gunshot wounds to the spine. *J Trauma.* 2006;60(4):814–819. https://doi.org/10.1097/01.ta.0000195472.99198.71
101. Perlmutter DH, Boyle JT, Campos JM, Egler JM, Watkins JB. D-lactic acidosis in children: an unusual metabolic complication of small

bowel resection. *J Pediatr.* 1983;102(2):234–238. https://doi.org/10.1016/s0022-3476(83)80527-7
102. Hosie S, Loff S, Wirth H, Rapp HJ, et al. Experience of 49 longitudinal intestinal lengthening procedures for short bowel syndrome. *Eur J Pediatr Surg.* 2006;16(3):171–175. https://doi.org/10.1055/s-2006-924251
103. Mayne AJ, Handy DJ, Preece MA, et al. Dietary management of D-lactic acidosis in short bowel syndrome. *Arch Dis Child.* 1990;65(2):229–231. https://doi.org/10.1136/adc.65.2.229
104. Coronado BE, Opal SM, Yoburn DC. Antibiotic-induced D-lactic acidosis. *Ann Intern Med.* 1995;122(11):839–842. https://doi.org/10.7326/0003-4819-122-11-199506010-00005
105. Goulet O, Ruemmele F. Causes and management of intestinal failure in children. *Gastroenterology.* 2006;130(2)(suppl 1):S16-S28. https://doi.org/10.1053/j.gastro.2005.12.002
106. Kelly DA. Liver complications of pediatric parenteral nutrition—epidemiology. *Nutrition.* 1998;14(1):153–157. https://doi.org/10.1016/s0899-9007(97)00232-3
107. Beale EF, Nelson RM, Bucciarelli RL, et al. Intrahepatic cholestasis associated with parenteral nutrition in premature infants. *Pediatrics.* 1979;64(3):342–347. https://doi.org/10.1542/peds.64.3.342
108. Kelly DA. Intestinal failure-associated liver disease: what do we know today? *Gastroenterology.* 2006;130(2)(suppl 1):S70-S77. https://doi.org/10.1053/j.gastro.2005.10.066
109. Teitelbaum DH. Parenteral nutrition-associated cholestasis. *Curr Opin Pediatr.* 1997;9(3):270–275. https://doi.org/10.1097/00008480-199706000-00016
110. Gunsar C, Melek M, Karaca I, et al. The biochemical and histopathological effects of ursodeoxycholic acid and metronidazole on total parenteral nutrition-associated hepatic dysfunction: an experimental study. *Hepatogastroenterology.* 2002;49(44):497–500.
111. Colomb V, Fabeiro M, Dabbas M, et al. Central venous catheter-related infections in children on long-term home parenteral nutrition: incidence and risk factors. *Clin Nutr.* 2000;19(5):355–359. https://doi.org/10.1054/clnu.2000.0132

112. Burstyne M, Jensen GL. Abnormal liver functions as a result of total parenteral nutrition in a patient with short-bowel syndrome. *Nutrition.* 2000;16(11–12):1090–1092. https://doi.org/10.1016/s0899-9007(00)00439-1
113. Cooke RJ, Whitington PF, Kelts D. Effect of taurine supplementation on hepatic function during short-term parenteral nutrition in the premature infant. *J Pediatr Gastroenterol Nutr.* 1984;3(2):234–238. https://doi.org/10.1097/00005176-198403000-00012
114. Bresson JL, Narcy P, Putet G, et al. Energy substrate utilization in infants receiving total parenteral nutrition with different glucose to fat ratios. *Pediatr Res.* 1989;25(6):645–648. https://doi.org/10.1203/00006450-198906000-00018
115. Advenier E, Landry C, Colomb V, et al. Aluminum contamination of parenteral nutrition and aluminum loading in children on long-term parenteral nutrition. *J Pediatr Gastroenterol Nutr.* 2003;36(4):448–453. https://doi.org/10.1097/00005176-200304000-00005
116. Kafritsa Y, Fell J, Long S, et al. Long-term outcome of brain manganese deposition in patients on home parenteral nutrition. *Arch Dis Child.* 1998;79(3):263–265. https://doi.org/10.1136/adc.79.3.263
117. Cavicchi M, Crenn P, Beau P, et al. Severe liver complications associated with long-term parenteral nutrition are dependent on lipid parenteral input. *Transplant Proc.* 1998;30(6):2547. https://doi.org/10.1016/s0041-1345(98)00720-9
118. Goulet O, de Potter S, Antebi H, et al. Long-term efficacy and safety of a new olive oil-based intravenous fat emulsion in pediatric patients: a double-blind randomized study. *Am J Clin Nutr.* 1999;70(3):338–345. https://doi.org/10.1093/ajcn/70.3.338
119. Nehra D, Fallon EM, Potemkin AK, et al. A comparison of 2 intravenous lipid emulsions: interim analysis of a randomized controlled trial. *JPEN J Parenter Enteral Nutr.* 2014;38(6):693–701. https://doi.org/10.1177/0148607113492549
120. Calhoun AW, Sullivan JE. Omegaven for the treatment of parenteral nutrition associated liver disease: a case study. *J Ky Med Assoc.* 2009;107(2):55–57.
121. Goulet O, Antebi H, Wolf C, et al. A new intravenous fat emulsion containing soybean oil, medium-chain triglycerides, olive oil, and fish

oil: a single-center, double-blind randomized study on efficacy and safety in pediatric patients receiving home parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2010;34(5):485–495. https://doi.org/10.1177/0148607110363614

122. Belza C, Wales JC, Courtney-Martin G, et al. An observational study of smoflipid vs intralipid on the evolution of intestinal failure-associated liver disease in infants with intestinal failure. *JPEN J Parenter Enteral Nutr.* 2020;44(4):688–696. https://doi.org/10.1002/jpen.1692
123. Mutanen A, Lohi J, Heikkila P, et al. Persistent abnormal liver fibrosis after weaning off parenteral nutrition in pediatric intestinal failure. *Hepatology.* 2013;58(2):729–738. https://doi.org/10.1002/hep.26360
124. Wales PW, Allen N, Worthington P, et al. ASPEN clinical guidelines: support of pediatric patients with intestinal failure at risk of parenteral nutrition-associated liver disease. *JPEN J Parenter Enteral Nutr.* 2014;38(5):538–557. https://doi.org/10.1177/0148607114527772
125. Wendel D, Mezoff EA, Raghu VK, et al. Management of central venous access in children with intestinal failure: a position paper from the NASPGHAN Intestinal Rehabilitation Special Interest Group. *J Pediatr Gastroenterol Nutr.* 2021;72(3):474–486. https://doi.org/10.1097/mpg.0000000000003036
126. Lang EV, Reyes J, Faintuch S, et al. Central venous recanalization in patients with short gut syndrome: restoration of candidacy for intestinal and multivisceral transplantation. *J Vasc Interv Radiol.* 2005;16(9):1203–1213. https://doi.org/10.1097/01.rvi.0000173013.84284.66
127. Rodrigues AF, van Mourik ID, Sharif K, et al. Management of end-stage central venous access in children referred for possible small bowel transplantation. *J Pediatr Gastroenterol Nutr.* 2006;42(4):427–433. https://doi.org/10.1097/01.mpg.0000215311.71040.89
128. Szydlowski EG, Rudolph JA, Vitale MA, Zuckerbraun NS. Bloodstream infections in patients with intestinal failure presenting to a pediatric emergency department with fever and a central line. *Pediatr Emerg Care.* 2017;33(12):e140-e145. https://doi.org/10.1097/pec.0000000000000812

129. Lichtman SN. Translocation of bacteria from gut lumen to mesenteric lymph nodes—and beyond? *J Pediatr Gastroenterol Nutr.* 1991;13(4):433–434. https://doi.org/10.1097/00005176-199111000-00020
130. Piedra PA, Dryja DM, LaScolea LJ, Jr. Incidence of catheter-associated gram-negative bacteremia in children with short bowel syndrome. *J Clin Microbiol.* 1989;27(6):1317–1319. https://doi.org/10.1128/jcm.27.6.1317-1319.1989
131. Kurkchubasche AG, Smith SD, Rowe MI. Catheter sepsis in short-bowel syndrome. *Arch Surg.* 1992;127(1):21–24. https://doi.org/10.1001/archsurg.1992.01420010027004
132. Weber TR. Enteral feeding increases sepsis in infants with short bowel syndrome. *J Pediatr Surg.* 1995;30(7):1086–1088. https://doi.org/10.1016/0022-3468(95)90347-x
133. Ardura MI, Lewis J, Tansmore JL, et al. Central catheter-associated bloodstream infection reduction with ethanol lock prophylaxis in pediatric intestinal failure: broadening quality improvement initiatives from hospital to home. *JAMA Pediatr.* 2015;169(4):324–331. https://doi.org/10.1001/jamapediatrics.2014.3291
134. Ormsby JA, Bukoye B, Lajoie D, et al. Enhanced central venous catheter bundle for pediatric parenteral-dependent intestinal failure. *Am J Infect Control.* 2018;46(11):1284–1289. https://doi.org/10.1016/j.ajic.2018.04.209
135. Chong CY, Ong RY, Seah VX, et al. Taurolidine-citrate lock solution for the prevention of central line-associated bloodstream infection in paediatric haematology-oncology and gastrointestinal failure patients with high baseline central-line associated bloodstream infection rates. *J Paediatr Child Health.* 2019;56:123–129. https://doi.org/10.1111/jpc.14506
136. Hill J, Garner R. Efficacy of 4% tetrasodium ethylenediaminetetraacetic acid (T-EDTA) catheter lock solution in home parenteral nutrition patients: a quality improvement evaluation. *J Vasc Access.* 2021;22(4):533–539. https://doi.org/10.1177/1129729820946916
137. Rahhal R, Abu-El-Haija MA, Fei L, et al. Systematic review and meta-analysis of the utilization of ethanol locks in pediatric patients

with intestinal failure. *JPEN J Parenter Enteral Nutr.* 2018;42(4):690–701. https://doi.org/10.1177/0148607117722753
138. Moukarzel AA, Haddad I, Ament ME, et al. 230 patient years of experience with home long-term parenteral nutrition in childhood: natural history and life of central venous catheters. *J Pediatr Surg.* 1994;29(10):1323–1327. https://doi.org/10.1016/0022-3468(94)90107-4
139. Tangpricha V, Luo M, Fernandez-Estivariz C, et al. Growth hormone favorably affects bone turnover and bone mineral density in patients with short bowel syndrome undergoing intestinal rehabilitation. *JPEN J Parenter Enteral Nutr.* 2006;30(6):480–486. https://doi.org/10.1177/0148607106030006480
140. Wauters L, Dermine S, de Dreuille B, et al. Malnutrition with low muscle mass is common after weaning off home parenteral nutrition for chronic intestinal failure. *Nutrients.* 2023;15(2). https://doi.org/10.3390/nu15020338
141. Ali F, Cole CR, Hornung L, et al. Age-related trajectory of bone density in children with intestinal failure: a longitudinal retrospective cohort study. *JPEN J Parenter Enteral Nutr.* 2023;47(6):736–745. https://doi.org/10.1002/jpen.2525
142. Culbreath K, Keefe G, Staffa SJ, et al. Puberty and growth in patients with pediatric intestinal failure. *J Pediatr Surg.* 2022;57(6):1045–1049. https://doi.org/10.1016/j.jpedsurg.2022.01.057
143. Neelis E, Olieman J, Rizopoulos D, et al. Growth, body composition, and micronutrient abnormalities during and after weaning off home parenteral nutrition. *J Pediatr Gastroenterol Nutr.* 2018;67(5):e95-e100. https://doi.org/10.1097/mpg.0000000000002090
144. Carlsson E, Bosaeus I, Nordgren S. Quality of life and concerns in patients with short bowel syndrome. *Clin Nutr.* 2003;22(5):445–452. https://doi.org/10.1016/s0261-5614(03)00042-6
145. Candusso M, Faraguna D, Sperli D, Dodaro N. Outcome and quality of life in paediatric home parenteral nutrition. *Curr Opin Clin Nutr Metab Care.* 2002;5(3):309–314. https://doi.org/10.1097/00075197-200205000-00011
146. Heine RG, Bines JE. New approaches to parenteral nutrition in infants and children. *J Paediatr Child Health.* 2002;38(5):433–437.

https://doi.org/10.1046/j.1440-1754.2002.00031.x
147. Ballinger R, Macey J, Lloyd A, et al. Measurement of utilities associated with parenteral support requirement in patients with short bowel syndrome and intestinal failure. *Clin Ther.* 2018;40(11):1878–1893 e1871. https://doi.org/10.1016/j.clinthera.2018.09.009
148. McCaig JK, Henry OS, Stamm DA, et al. Generic and disease-specific health-related quality of life in pediatric intestinal failure. *J Pediatr Gastroenterol Nutr.* 2021;73(3):338–344. https://doi.org/10.1097/mpg.0000000000003102
149. So S, Patterson C, Betts Z, Belza C, Avitzur Y, Wales PW. Physical activity and fatigue in children with intestinal failure on parenteral nutrition. *J Pediatr Gastroenterol Nutr.* 2021;73(1):110–114. https://doi.org/10.1097/mpg.0000000000003138
150. Bondi BC, Gold A, Belza C, et al. Predictors of social-emotional development and adaptive functioning in school-age children with intestinal failure. *J Clin Psychol Med Settings.* 2023;30(3):589–605. https://doi.org/10.1007/s10880-022-09919-z
151. Kocoshis SA, Beath SV, Booth IW, et al. Intestinal failure and small bowel transplantation, including clinical nutrition: Working Group report of the second World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr.* 2004;39(suppl 2):S655-S661. https://doi.org/10.1097/00005176-200406002-00012
152. Grant D, Abu-Elmagd K, Mazariegos G, et al. Intestinal transplant registry report: global activity and trends. *Am J Transplant.* 2015;15(1):210–219. https://doi.org/10.1111/ajt.12979
153. Raghu VK, Beaumont JL, Everly MJ, et al. Pediatric intestinal transplantation: analysis of the intestinal transplant registry. *Pediatr Transplant.* 2019;23(8):e13580. https://doi.org/10.1111/petr.13580
154. Kaufman SS, Avitzur Y, Beath SV, et al. New insights into the indications for intestinal transplantation: consensus in the year 2019. *Transplantation.* 2020;104(5):937–946. https://doi.org/10.1097/tp.0000000000003065
155. Burghardt KM, Wales PW, de Silva N, et al. Pediatric intestinal transplant listing criteria—a call for a change in the new era of

intestinal failure outcomes. *Am J Transplant.* 2015;15(6):1674–1681. https://doi.org/10.1111/ajt.13147
156. Botha JF, Grant WJ, Torres C, et al. Isolated liver transplantation in infants with end-stage liver disease due to short bowel syndrome. *Liver Transpl.* 2006;12(7):1062–1066. https://doi.org/10.1002/lt.20763
157. Diamond IR, Wales PW, Grant DR, Fecteau A. Isolated liver transplantation in pediatric short bowel syndrome: is there a role? *J Pediatr Surg.* 2006;41(5):955–959. https://doi.org/10.1016/j.jpedsurg.2006.01.016
158. Horslen SP, Sudan DL, Iyer KR, et al. Isolated liver transplantation in infants with end-stage liver disease associated with short bowel syndrome. *Ann Surg.* 2002;235(3):435–439. https://doi.org/10.1097/00000658-200203000-00016

Test Your Knowledge Answers

1. The correct answer is **C**. The small intestine doubles in length during the last trimester. Therefore, the remaining length of the small bowel has a greater inherent capacity to increase in length when the bowel resection occurs earlier in the third trimester.
2. The correct answer is **B**. Features associated with enteral autonomy include absence of cholestasis, an intact ileocecal valve, bowel in continuity, shorter duration of PN, residual intestinal length >15 cm, and an intact colon. Stool number, by itself, is not a predictor.
3. The correct answer is **D**. The cause of PN–related liver disease is likely multifactorial and not related to just one issue.
4. The correct answer is **D.** Oral feedings not only enable the infant to maintain oral feeding skills and decrease the likelihood of developing oral aversion, but oral feedings will stimulate salivary secretion of hormones such as epidermal growth factor, which is important to the intestinal adaptive process.

26

Pulmonary Disorders

Laura Padula, MS, RD, LDN; Rachel Kofsky, MA, RD, CSP, LDN, CLC; and Maria Mascarenhas, MBBS

The authors of this chapter wish to thank Suzanne Michel, MPH, RD, LDN, and Allison Mallowe, MA, RD, LDN for their contributions to previous editions of this text.

Learning Objectives

1. Understand the role of nutrition in lung disease in specific pulmonary conditions.
2. Discuss nutrition as related to complications of cystic fibrosis.
3. List components of a nutrition assessment for persons with pulmonary disease.
4. Understand micronutrient abnormalities that can occur in cystic fibrosis.

Introduction

Nutrition plays an important role in the care of patients with lung disease. In this chapter, we will discuss cystic fibrosis and bronchopulmonary dysplasia (BPD), chronic lung disease, and lung transplant. Nutrition assessment should consist of a detailed history (medical, diet, and medications), anthropometry (including data over time and growth charts if available), laboratory monitoring, and bone health assessment when indicated.

Cystic Fibrosis

Pathophysiology

Cystic fibrosis (CF) is an autosomal recessive genetic disorder that is most frequently seen in people of Irish, Western European, American, Australian, and Canadian descent. CF occurs more rarely in those of Latin American, South American, and Asian descent, although the rate in people of Hispanic descent is rising, coinciding with US population trends. CF affects approximately 32,000 people in the United States.[1] The CF gene was isolated in 1989,[2] and since then more than 1800 mutations have been identified. The gene, which is localized on the short arm of chromosome 7, is called the cystic fibrosis transmembrane regulator (CFTR) and controls the flow of sodium and chloride ions across the cell membrane. Mutations in the gene result in abnormal epithelial ion transport in multiple organs in the body. Clinical outcomes have been related to the type of mutation. With improved care and the advent of universal newborn screening programs in the United States for all 50 states, the estimated median predicted survival age in 2021 was 53.3 years.[1]

During the neonatal period, diagnosis from newborn screening results in early nutrition intervention and improved nutrition status, which may lead to a better quality of life and prolonged survival (see Exhibit 26-1 for common clinical features of CF).[3] Historically, an abnormal sweat test (chloride values >60 mEq/L) was considered diagnostic, but this standard may not always be abnormal.[4] Based on the severity of the mutation, the clinical picture is variable and gene analysis may be required for CF diagnosis.

EXHIBIT 26-1. Clinical Features and Manifestations of Cystic Fibrosis[3]

Body System
Lungs: recurrent bacterial and fungal infections, bronchiectasis, respiratory failure
Upper airways: chronic sinusitis and nasal polyps
Pancreas: exocrine pancreatic insufficiency and pancreatitis (common in patients with pancreatic sufficiency)
Liver: CF-related liver disease, fatty liver, cirrhosis
Gastrointestinal tract: meconium ileus (newborns), DIOS, malnutrition
Kidneys: kidney stones

Bones: osteoporosis, osteopenia
Reproductive: cervical mucous abnormalities, congenital bilateral absence of the vas deferens, infertility
Endocrine: cystic fibrosis–related diabetes

Abbreviations: CF, cystic fibrosis; DIOS, distal intestinal obstruction syndrome.

Adapted with permission from Elsevier from Steinberg.[3]

Because the expression of the CFTR gene is limited to epithelial cells, the primarily affected organs are mucus-producing organs such as the lungs, gastrointestinal (GI) tract, liver, pancreas, genitourinary system, and sweat glands.[3] The transport of sodium and chloride across cell membranes is regulated by cyclic adenosine monophosphate and calcium, both of which are controlled by CFTR.[5] The respiratory epithelial cells are impermeable to chloride ions, increasing airway sodium absorption. The movement of sodium into the cells results in the movement of water into the cell, leading to dehydration of the airway mucus and decreased ciliary function. The impaired transport also leads to viscous secretions in the lung, liver, pancreas, and GI tract; duct obstruction in sweat glands; and elevated sweat chloride levels.

Pulmonary involvement is initially associated with *Staphylococcus aureus* infection and later *Pseudomonas aeruginosa*. Chronic pulmonary damage, bronchiectasis, fibrosis, and decreased lung function occur over time. Impaired gas exchange occurs secondary to airflow resistance, hyperinflation, and uneven distribution of ventilation. Both bacterial adherence and colonization result in a sustained host inflammatory response. Stimulated neutrophils release large amounts of oxidants and proteases including elastase, which leads to increased mucus production, bacterial trapping, and further lung damage.[6] Clinical symptoms include cough, production of mucus, air trapping, and in some patients, severe end-stage lung disease requiring lung transplantation.

In the pancreas, thick mucus accumulates in the acinar glands, leading to an obstruction of the ducts. Damage occurs in the glands due to the release of lytic enzymes and subsequent chronic inflammation, fibrosis, fatty infiltration of the pancreas, and pancreatic insufficiency (PI).[7] These

changes can occur in utero in patients with severe mutations. According to data from 2021, PI occurs in a large proportion of patients at diagnosis.[1] Patients who have pancreatic sufficiency (PS) may develop PI over time and need to be monitored carefully. Clinical symptoms of PI include the following:

- steatorrhea
- malabsorption
- diarrhea
- weight loss
- poor growth
- vitamin deficiencies
- increased gas
- abdominal pain

Some patients, including infants, may have a voracious appetite to ingest sufficient calories to compensate for energy loss in their bowel movements due to maldigestion and malabsorption. Increasing numbers of persons with CF will develop cystic fibrosis–related diabetes (CFRD), and this number is expected to increase as life expectancy increases.[8]

Similar to what happens in the lungs, fluid and electrolyte disturbances occur in the GI tract and cause sticky mucus and stool accumulation, which can result in meconium ileus in newborns and distal intestinal obstruction syndrome (DIOS) in older children and adults. Meconium ileus, or the build-up of meconium in utero, is the earliest manifestation of CF, affecting approximately 11% of infants with CF in 2021.[1] Infants can be born with meconium plugs, intestinal obstruction, atresias, volvulus, perforations, and meconium pseudocyst. DIOS is the accumulation of sticky stool in the GI tract, primarily in the terminal ileum and cecal area. It may occur in all persons who have CF (PI and less commonly PS). Predisposing factors are decreased fluid and salt intake, fat malabsorption, mucosal inflammation, and dysmotility.[9]

In the liver, CFTR is expressed in the biliary epithelium, and abnormalities of ion transport occur. This results in decreased flow of bile, with secondary hepatocyte damage, inflammation, fibrosis, cirrhosis, and portal hypertension.[10] In a 2019 study, a venopathy was described in

patients with non-cirrhotic portal hypertension.[11] In males, obstruction of the vas deferens results in infertility, and in patients with mild mutations, infertility may be the presenting feature that leads to the diagnosis of CF later in life.

Over the past decade, much progress has been made toward improving clinical care that has resulted in improved quality of life and survival for patients with CF. CFTR modulators are a new category of drug developed to improve the function of the defective CFTR protein in CF. There are five different classes of CFTR mutations categorized by the problems they cause in the CFTR protein, with class 1 being the most severe and class 5 being the mildest. There are currently four different CFTR modulators on the market, each designed to treat a specific type of CFTR mutation:

1. Ivacaftor
2. Lumacaftor/ivacaftor
3. Tezacaftor/ivacaftor
4. Elexacaftor/tezacaftor/ivacaftor

More CFTR modulator drugs are currently in research and development to address other CFTR mutations, and the goal is for all patients with CF to be eligible for one of these drugs. These modulators have changed the landscape of care for eligible patients with CF, as they can either enhance or restore CFTR function, improving and elongating the life of the patients they affect.[12]

Nutrition Assessment

A strong correlation exists between pulmonary function (FEV1) and nutrition status, making nutrition assessment a crucial part of the overall care for patients with CF.[13] Historically, this was demonstrated by the hallmark study comparing patients with CF in Toronto and Boston, which found that the patients from Toronto who had better nutritional status also had a higher median survival age compared to the patients in Boston who had poorer nutritional status.[14] Additionally, the Cystic Fibrosis Foundation's patient registry has demonstrated that weight-for-age z-score, height-for-age z-score, and percent of height-appropriate body weight were

all significantly associated with improved lung function (FEV1).[13] As a result, children ages 2 to 20 years should have a body mass index (BMI) at or above the 50th percentile because it has been repeatedly associated with improved survival and improved lung function.[15] In children ≤ 2 years of age, the goal weight-for-length is ≥ to the 50th percentile.[15] Associations between deteriorating lung function and worsening nutrition status have been noted.[16,17]

Malnutrition results from:

- Increased caloric needs (increased metabolic rate,[18] infections, work of breathing, cough).
- Increased losses (malabsorption due to pancreatic, liver, and intestinal disease; intestinal section; vomiting; and CFRD).
- Decreased nutrient intake (anorexia, gastroesophageal reflux [GER], eating disorders, abdominal pain, constipation, malaise, medications).

Aggressive nutrition intervention is often required to improve nutrition status; however, patients who are eligible for and taking CFTR modulators may not need the high-calorie diet that has traditionally been required because of decreased energy expenditure, pancreatic function improvements, and changes to the GI microbiome.[19] A nutrition screen should be performed at every visit to identify inadequate weight gain, weight loss, and faltering of linear growth.[20] When these occur, a nutrition assessment must be performed, causes should be identified, and appropriate interventions should be implemented.

Nutrition assessment is an important component in the care of persons with CF and should be completed at diagnosis, monthly for the first 6 months of life, up to every other month until 1 year of age, and up to quarterly until 2 years of age. All patients with CF should be assessed annually at a minimum if older than 2 years of age or when their disease or treatment course changes.[15] The following factors affect nutrition status:

- Maldigestion and malabsorption of fat, protein, carbohydrates, and fat-soluble vitamins
- Decreased pulmonary function
- Chronic pulmonary infections and increased oxidative stress

- Decreased energy intake
- Increased energy requirements
- CFRD

Nutrition assessment consists of the following:

1. growth, including weight and height patterns based on the growth curve, head circumference (as appropriate), and BMI percentile[20]
2. biochemical indicators such as vitamin and mineral levels
3. nutrient intake
4. eating behavior and family eating patterns
5. pancreatic enzyme replacement therapy (PERT) management
6. physical activity
7. severity of lung disease
8. presence of any comorbidity such as CFRD, chronic infections, cirrhosis, or bacterial overgrowth
9. factors that may impact the patient's ability to meet nutrition goals including psychosocial factors
10. CFTR modulator eligibility and adherence

Dual-energy absorptiometry (DXA) should be performed at a minimum by age 18 years or starting at age 8 years for those with high-risk factors (ie, malnutrition, delayed puberty, history of fractures, severe lung disease, prolonged glucocorticosteroid use). Growth parameters (height, weight, head circumference, weight for length, or BMI) should be assessed and monitored at every visit as indicated. Body composition data from DXA can be used to monitor lean body mass (increasingly recognized as important for lung function).[15,20,21] Mid-upper arm circumference with skinfold measures may be used to assess body composition when DXA is not feasible.[15] Based on the information obtained during the nutrition assessment, caloric requirements and anthropometric goals are calculated and vitamin and mineral prescriptions are adjusted.

Nutrition Recommendations

Historically, CF patients and their families have been advised that a high energy intake can be achieved by consuming preferred foods, without

consideration of their micronutrients or fiber content. With the advent of CFTR modulators and the changing landscape of the nutrition needs of patients with CF, this recommendation must be reconsidered. Patients are now advised on an age-appropriate, healthy diet with foods that promote positive health outcomes. Energy-dense foods may be recommended in certain clinical situations where weight gain or catch-up growth is needed, but this should be done with a healthy, well-balanced diet.[15,22]

Macronutrients

Energy

As previously described, individuals who have CF may have increased energy needs. Exact caloric prescriptions and formulas to calculate caloric needs are difficult to provide because of individual patient variation, but improved weight status has been indicated at intakes ranging from 110% to 200% of energy needs for the healthy population.[22] Patients' energy needs should be assessed on an individual basis and reflect the pattern of weight gain and fat stores.[23] Indirect calorimetry is considered the gold standard in estimating energy needs; however, this is not typically feasible in a clinical setting. An estimation of individual caloric needs should be based on the following:

- nutrition status
- growth pattern
- fat stores
- current dietary intake
- degree of fat malabsorption
- clinical status (including pulmonary function)
- level of physical activity
- medications (including CFTR modulators)[19,20]

Fat

Historically, it has been recommended that patients with CF consume a high-fat diet to meet their higher energy needs. Recent evidence suggests that patients with CF who are not at risk for malnutrition should consume fat in the same distribution as is recommended for their age-matched

population.[20] Some patients may require higher energy needs and, in these cases, higher-energy foods can be promoted and recommended, but they do not always need to be high in fat.

Protein

Specific protein intake recommendations for patients with CF are not available, although some evidence shows that protein needs are met with a higher-calorie diet.[24] Patients generally consume adequate amounts of protein with their typical diet if they are meeting their nutrition goals.[24]

Carbohydrate

The diet should contain sufficient carbohydrate to meet energy needs, and it is best if the source is from foods that contribute to the overall nutrient intake, including fiber. Patients with CF who are at risk for developing CF–related diabetes (CFRD) should limit intake of high-sugar foods and beverages with low nutrient density. Fiber needs are not elevated in patients with CF and dietary intake in line with the recommended needs for the general population should be tolerated and does not increase the risk of constipation or gastrointestinal complications.[20]

Micronutrients

All persons with CF, both with PI using PERT and with PS, typically require supplementation with micronutrients[20,22] although this is changing with the use of CFTR modulators. Some patients have had improvements in pancreatic function and improved micronutrient levels. Deficiencies of fat-soluble vitamins and zinc have been demonstrated in infants diagnosed through newborn screening and do not correct without appropriate supplementation, and if indicated, PERT.[23,25] Children and adolescents are at risk for micronutrient deficiencies due to the following:[20,21]

- Inadequate intake
- Malabsorption due to pancreatic insufficiency and suboptimal PERT
- Malabsorption due to incomplete bile salt absorption
- Poor clinical status and poor lung function
- Increased utilization and reduced bioavailability

- Liver disease
- Bowel resection
- Late diagnosis of CF
- Poor adherence to or inappropriate supplementation

Fat-Soluble Vitamins

Multivitamins designed to meet the fat-soluble vitamin needs of persons with CF (CF-specific multivitamins) are available in North America (see https://mvwnutritionals-assets.s3.amazonaws.com/wp-content/uploads/2024/04/11111124/Vitamin-Comparison-Chart-4_11_2024-FINAL.pdf). These vitamins contain fat-soluble and water-soluble vitamins and zinc. The content reflects the recommendations provided in the U.S. Pediatric Nutrition Consensus Report,[21] the European Nutrition Consensus Report,[27] the U.S. Bone Consensus Report,[28] and/or current research. The dosage and form of the CF-specific multivitamin supplementation depends on the patient's age and laboratory evaluation results of vitamin levels. Patients may require additional single-nutrient supplements (ie, vitamins A, E, D, K) if blood levels cannot be maintained on the CF-specific multivitamins. If the CF-specific multivitamin is unavailable, single-vitamin supplements are necessary to make up the difference in content of traditional multivitamins compared to recommendations. For additional information on CF-specific multivitamin content, refer to the charts on the MVW Nutritionals website (https://mvwnutritionals-assets.s3.amazonaws.com/wp-content/uploads/2024/04/11111124/Vitamin-Comparison-Chart-4_11_2024-FINAL.pdf).

Vitamin A

Vitamin A plays an important role in vision, immunity, lung health, and overall health, yet excessive intake of retinol can cause liver and/or bone complications. Retinol is an acute phase reactant and is best measured when the patient is not ill. Liver disease or zinc deficiency can cause low serum retinol levels. A low retinol-binding protein should be corrected before increasing the vitamin A dose. The total vitamin A content of CF-specific multivitamins is based on both retinol and β-carotene. The risk of toxicity is avoided with a higher concentration of β-carotene.

Vitamin E

Optimizing serum vitamin E will prevent neurological complications previously observed in people with CF. Vitamin E is transported in the body with lipids, including cholesterol. People who have CF often have low cholesterol levels, therefore serum levels should be assessed as a ratio of vitamin E to total lipid or total cholesterol.[29] The equation used to assess vitamin E status is the ratio of α-tocopherol to total lipids (cholesterol, triacylglycerol, and phospholipid). A ratio of α-tocopherol to total lipids < 0.8 mg/dL or a ratio of α-tocopherol to cholesterol <2.47 mg/g indicates vitamin E deficiency.[29] Liver disease can cause low vitamin E levels.

Vitamin D

Persons who have CF are at risk for low serum vitamin D. Serum 25-hydroxyvitamin D [25(OH)D] should be assessed annually, preferably in the late fall, and if necessary, treated daily with vitamin D3-cholecalciferol. Consensus recommendations state that the goal serum level for patients with CF is a minimum of 30 ng/mL. All current CF vitamin brands contain sufficient vitamin D for maintenance therapy for various age groups with some brands containing step-up vitamin D content to treat deficiencies. If serum vitamin D levels remain low after confirming adherence to regular CF multivitamin therapy, a stepwise approach is recommended to replete low levels.[30] Vitamin D doses should be increased using a vitamin D-only formulation rather than doubling the CF-specific multivitamin and risking excess amounts of other vitamins and minerals. Increases in vitamin D doses are age-dependent, and the initial recommendation is to double the total vitamin D dose. If vitamin D levels cannot be corrected to normal after following the stepwise increases, patients should be referred to an endocrinologist for further management of vitamin D deficiency.

Vitamin K

Vitamin K is essential for normal blood clotting and bone health. Persons who have CF are at risk for vitamin K deficiency due to fat malabsorption and routine use of antibiotics. Additionally, any patient who has CF and liver disease is at greater risk for vitamin K deficiency. Clotting time, or prothrombin time, has been the standard test for assessing overall vitamin K

nutrition, but several studies using PIVKA II (proteins induced by vitamin K absence) provided evidence that in CF, vitamin K deficiency exists in patients with normal prothrombin time.[31,32] Currently, the PIVKA II test is not available clinically and patients are supplemented based on abnormalities in prothrombin time. Over-the-counter multivitamins contain insufficient vitamin K to meet the needs of persons who have CF. The vitamin K content of CF-specific multivitamins is sufficient for most patients, although some people may require additional supplementation based on laboratory results. Patients with CF-related liver disease may also require additional vitamin K.

Water-Soluble Vitamins

Deficiency of water-soluble vitamins in CF is rare but has been reported in patients who are not receiving multivitamins and/or receiving medications interfering with B vitamins.[33] Typically vitamin B12 deficiency has not been seen and high levels have been noted.[34] Patients who have had a resection of the terminal ileum may develop vitamin B12 deficiency requiring supplementation and should be monitored.[21]

Minerals

Sodium Chloride

Persons who have CF lose excessive sodium in their sweat and require supplementation throughout the year, especially in the summer months and during times of physical activity where excessive sweating may be more common. Inadequate salt intake can be life-threatening and/or result in poor appetite with subsequent poor growth. All infants who have CF and an elevated sweat test should be supplemented with 12.6 mEq (⅛ teaspoon) of salt daily from birth to 6 months of age, at which time the dose is increased to 25.2 mEq (¼ teaspoon) daily.[35] The salt is added in small, frequent amounts to baby formula or applesauce until the daily dose is met. Salt supplementation is continued until the child is eating a diet rich in salt and added salt. Children and adolescents should be counseled to consume salt over and above their usual intake when participating in physical activity. It may be necessary to add salt to sports drinks to meet sodium chloride needs (⅛ teaspoon to 12 oz).[35] With the advent of CFTR modulator drugs and the

normalization of sweat chloride levels in some patients, not all patients require additional salt supplementation.

Zinc

Before treatment with PERT, infants with pancreatic insufficiency lose excessive zinc in their stool. Acrodermatitis enteropathica–like rash, which resembles a severe rash in the diaper area and the perioral area, is a clinical symptom of zinc deficiency and is treated with PERT and zinc supplementation. More subtle symptoms of zinc deficiency that can be seen at any age include lack of appetite, dysgeusia, poor growth, and compromised immunity. Laboratory studies to determine zinc status are generally uninformative as they are not always sensitive to zinc stores in the body and can be easily influenced by contamination of the blood sample.

When zinc deficiency is suspected it is often treated prophylactically with a typical dose of 1 mg elemental zinc per kilogram daily for 6 months in addition to that contained in the patient's daily multivitamin. It should be noted that oral zinc supplementation can interfere with the absorption of copper and iron. Over-the-counter infant vitamin drops do not contain zinc. Over-the-counter children's chewable vitamins and adult formulations contain zinc as do CF-specific multivitamins. When choosing a zinc preparation, it is important to note which zinc salt is in the chosen product so that the correct dose can be determined. For example, zinc sulfate is 23% elemental zinc, but zinc gluconate is only 14% elemental zinc.

Iron

Iron status in the general population is affected by dietary intake, blood loss, and medications. For persons with CF, all these factors plus malabsorption, hemoptysis, short bowel syndrome, bacterial overgrowth, liver and renal diseases, and chronic inflammation contribute to altered iron status. Patients can have iron-deficiency anemia, anemia of chronic disease, or a combination of both.[36] Before prescribing iron supplementation, the anemia type must be defined. Assessing iron status in CF is complicated by chronic inflammation. Serum ferritin, an acute-phase reactant, may be falsely elevated in CF, thus masking iron-deficiency anemia. Measurement of soluble transferrin receptor levels may be helpful in diagnosis.

Calcium

It is important to optimize the calcium intake of persons who have CF. Instead of specific calcium recommendations for persons who have CF, registered dietitians should refer to those in the adequate intake (AI) for infants <1 year of age and the RDA for patients >1 year of age.[37] Refer to the Cystic Fibrosis Foundation Bone Consensus Report for more detail regarding bone health and CF.[28,38]

Magnesium

Patients receiving aminoglycosides may require supplemental magnesium. Blood levels should be monitored.[39]

Fluoride

CF-specific vitamins do not contain fluoride; therefore, the patient's primary care physician may need to prescribe a supplement if local water is not fluoridated.

Essential Fatty Acids

Essential fatty acid (EFA) deficiency has been reported in animal models of CF[40] and malnutrition, ongoing malabsorption, short bowel syndrome, liver disease, restricted diets, and frequent infections.[41] Screening patients who have these risk factors, signs, and symptoms should be done by monitoring a fatty acid panel.[42] Treatment consists of providing oils with high EFA content added to food or intravenous fat infusions if receiving parenteral nutrition.

Laboratory Evaluation

Blood levels of fat-soluble vitamins should be measured at diagnosis for patients diagnosed >1 year of age and annually thereafter.[21] For newly diagnosed infants, it is recommended that levels of vitamins E, A, and D be assessed 1 to 3 months after starting supplementation and annually thereafter.[21] Prothrombin time is insensitive to vitamin K deficiency in CF. PIVKA II provides a better indicator of vitamin K nutrition and should be measured, if available. Serum electrolytes and a complete blood count are

measured at 2 to 3 months of age and annually or as indicated.[21] For children and adolescents, assessment of fat-soluble vitamins, including PIVKA II and complete blood count with differential, is done at diagnosis and annually, unless otherwise indicated. Laboratory studies for individual micronutrients may be necessary when modifying the treatment care plan, such as initiating enteral nutrition support.

Special Considerations

Infants

Infants require a diet that will promote optimal weight gain and, when indicated, catch-up growth. Human milk or standard infant formula is recommended. When necessary to regain birth weight z-score and achieve normal growth for age, fortified human milk or calorically dense infant formula may be used to promote and maintain weight gain.[43] To achieve catch-up growth, infants may require 120 to 150 kcal/kg/d. Infants with CF have specific and higher sodium requirements than those without CF.[43] Hydrolyzed protein formulas containing medium-chain triglycerides are not typically indicated in the absence of a medical reason, such as bowel surgery with significant bowel resection due to meconium ileus or liver abnormalities. In infants who have CF, solids are added to their diet on the same schedule used for nonaffected infants.[43] Care must be taken when adding solids to avoid replacing nutrient-rich and energy-rich infant milk with low-calorie, low-nutrient foods. Adding oil to commercially jarred infant food will increase calories; up to 1 teaspoon of oil to every 4 oz of baby food is suggested.

Early introduction of allergenic foods is now recommended for infants by approximately 6 months to reduce the risk of food allergy. [44] The addition of non-choking forms of peanut and tree nuts can be useful additions to the solid foods provided to infants with CF to increase calories using healthy fats. Parents who wish to prepare homemade solids require instruction to ensure adequate nutritional intake. Positive feeding behaviors should be encouraged throughout the feeding experience.[44]

Pancreatic Enzymes

Persons with PI require PERT. Pancreatic damage and destruction occur in utero or after birth, resulting in the absence of bicarbonate-rich and enzyme-containing pancreatic juice in the duodenum to help digest food. PERT has played a pivotal role in improving the care and outcomes of persons with CF.[21] A variety of enzymes are available, with subtle differences among brands and forms. As of this writing, the approved enteric-coated products in the United States are Creon by AbbVie, Zenpep by Nestlé, Pertyze by Digestive Care, and Pancreaze by Vivus Pharmaceuticals. Refer to Table 26-1 for detailed information about the various dosage forms and contents of each enzyme brand. A nonenteric coated form of pancrealipase, such as Viokace by Nestlé is subject to destruction by the acidic gastric environment but has utility in some clinical situations such as enteral feedings.

TABLE 26-1. Pancreatic Enzyme Formulations

Product/Manufacturer/Dosage Form/Strength	Lipase USP Units	Amylase USP Units	Protease USP Units
Creon (AbbVie Inc.) Pancrelipase			
3,000	3,000	15,000	9,500
6,000	6,000	30,000	19,000
12,000	12,000	60,000	38,000
24,000	24,000	120,000	76,000
36,000	36,000	180,000	114,000
Pancreaze (Vivus, Inc.), Pancrelipase			
2,600 (MT2)	2,600	15,200	8,800
4,200 (MT4)	4,200	24,600	14,200
10,500 (MT10)	10,500	61,500	35,500
16,800 (MT16)	16,800	98,400	56,800
21,000 (MT20)	21,000	83,900	54,700
37,000 (MT37)	37,000	149,900	97,300
Zenpep (Nestlé) Pancrelipase			
3,000	3,000	14,000	10,000
5,000	5,000	24,000	17,000
10,000	10,000	42,000	32,000
15,000	15,000	63,000	47,000
20,000	20,000	84,000	63,000
25,000	25,000	105,000	79,000
40,000	40,000	168,000	126,000
60,000	60,000	189,600	252,600
Viokace (Nestlé) Tablet*, * not enteric-coated			
10,440	10,440	39,150	39,150
20,880	20,880	78,300	78,300
Pertzye (Digestive Care) Pancrelipase, Bicarb Buffered			
4,000	4,000	14,375	15,125
8,000	8,000	30,250	28,750
16,000	16,000	60,500	57,500

Product/Manufacturer/Dosage Form/Strength	Lipase USP Units	Amylase USP Units	Protease USP Units
24,000	24,000	90,750	86,250

The enteric-coated products consist of microspheres and micro tablets. The enteric coating is designed to protect the enzyme from the acidic gastric milieu and allow activation of the enzyme to occur in the alkaline pH of the duodenum, distal to the acidic gastric contents. If the pancreas is unable to deliver bicarbonate pancreatic juice to the duodenum, gastric acid from the stomach is not neutralized, resulting in an acidic duodenal pH. Acidity in the GI tract may prevent or retard the dissolution of enteric-coated pancreatic enzymes.[45] If activation does not take place in the small intestine, absorption of macronutrients and micronutrients cannot occur. Relizorb by Alcresta is a digestive enzyme cartridge that contains lipase and has been available since 2015 for use only with continuous enteral feedings. It connects directly to a feeding tube system and as formula passes through the cartridge, it makes contact with the lipase, breaking it down into an absorbable form for the patient. Additional medications that reduce or block gastric acid production and raise the duodenal pH may be needed to enhance PERT effectiveness.[46] Even so, all nutrients may not be fully absorbed. If fat malabsorption persists, consider lack of bile acids, liver disease, small bowel bacterial overgrowth, and other GI etiologies.[21] Consultation with a pediatric gastroenterologist may be needed.

The PERT products contain lipase, protease, and amylase for the digestion of fat, protein, and carbohydrates, respectively. Enzyme activity or potency is based on the amount of lipase per capsule or gel cap. For example, for Creon, 6 the 6 refers to 6000 lipase units per capsule. Creon 6 also contains 30,000 amylase units and 19,000 protease units. Refer to the manufacturer's websites for each brand of enzyme and more detail on enzyme contents. The recommended PERT starting dose for infants is 2000–4000 units of lipase per 120 mL of formula or human milk.[21] Although dosing is best calculated using units of lipase per gram of fat ingested, it is perhaps more practical to use a dosing schedule with weight-adjusted guidelines.[21]

For children <4 years of age, the recommendation is to begin at 1000 lipase units per kilogram per meal, and for children >4 years of age, 500 lipase units per kilogram per meal. Dosing for snacks is routinely half of the usual meal dose.[45,47] It is recommended not to exceed a dose of 2500 units of lipase per kilogram body weight per meal or 10,000 lipase units per kilogram per day, based on a usual intake of 3 meals plus 2 snacks per day.[45,47] Enzymes can also be dosed based on grams of fat using the guidelines of 500–4000 units of lipase per gram of fat, with an average therapeutic dose being 2000 units per 1 gram of fat.[45,47] Fibrosing colonopathy is a complication associated with very high PERT doses but is rare.[48]

Persons with CF should be assessed individually regarding dosing and response to PERT.[52] Careful monitoring of growth, stool pattern, and specific GI symptoms is necessary to determine the adequacy of therapy. For infants and children who are unable to swallow enzyme capsules, the enzyme beads can be removed from the capsules and mixed with a small amount of applesauce and given at each feeding.[47] To avoid the breakdown of the enteric coating, beads should not be added to liquids or alkaline foods. PERT is given at the beginning of the feeding or meal. If the meal lasts more than 30 minutes, the dose can be split and given at the beginning and halfway through the meal. For infants, to avoid mucosal erosion, the mouth should be checked for beads following each feeding. The infant's perianal area may require protection against enzyme excreted in the stool, so caregivers can apply a thick layer of barrier cream to protect the skin around the anus.

Persons with CF who utilize a nasogastric tube, gastrostomy tube (G-tube), or jejunostomy for enteral nutrition will most likely need PERT supplementation. The amount and type of enzyme can vary depending on the formula type, the patient's ability to take enzymes orally, and the mode and schedule of tube feedings. However, with recent developments, Relizorb cartridges are currently the most-used enzyme mode for overnight enteral nutrition. During the day, oral PERT is best given before each bolus, and this dose is dependent on the amount and type of fat in the bolus.

In some clinical scenarios, Viokace tablets can be crushed and added directly to the formula approximately 20 minutes before tube feed

administration.[47,49] This method allows the nutrients in the formula to predigest before reaching the patient. Less common options include using enzyme microspheres mixed in a thickened fruit juice and administering via syringe into a 10 French or larger G-tube prior to feedings.[47,49] Enzyme beads can also be dissolved in a bicarbonate solution and the mixture can be administered directly into the feeding tube before administering formula, or the mixture can be put directly into the formula. Again, with recent changes in practice, these are less commonly used. A concern exists about excessive bicarbonate administration resulting in alkalosis.

Alternatively, enzyme beads can also be manually crushed into powder and added directly to the formula for predigestion of nutrients.[47,49] However, the manufacturers do not recommend crushing the beads because crushing the enteric coating would expose the mucosal surfaces of the mouth and esophagus to active enzyme and may cause irritation if taken by mouth. This method is also not recommended by most CF centers. Breaking the enteric coating exposes the enzymes to the acidic environment of the stomach, thus rendering the enzymes inactive. Yet, when beads are crushed and added to enteral formula, these concerns are negated because digestion of the formula occurs in the container. Providers should use discretion to determine which of these methods is best for the patient, and the clinical response should be monitored. With any of the aforementioned approaches, the amount of fat in the enteral feeding should be considered. Feeding intolerance and obstruction of feeding tubes have been noted with the above practices.[50]

Eating Behaviors and CF

The significance of nutrition in patients with CF is well recognized because of its important relationship with lung function and survival. There is often increased pressure regarding the importance of nutrition that includes improving and maintaining weight and adherence to PERT, as well as supplemental vitamins and/or minerals. As a result, mealtimes can become challenging. Parents of children with CF commonly report mealtime behavior problems including poor appetite, talking to avoid eating, and spitting out food.[51]

Young children whose parents feel unusually concerned about their health and caloric/food intake appear to be particularly at risk for behavioral difficulties at mealtime.[51,52] For parents of infants with CF, the transition from formula to solids may present a challenge, and parents may need guidance regarding positive eating behaviors and high-caloric solids. The toddler stage is typically characterized by changing food interests and neophobia (fear of new foods), which for children with CF may complicate high-fat food selection and additives.[51,52] Guidance on preventing and managing food refusal behaviors may be beneficial for parents. Anticipatory guidance might include education regarding avoiding parental behaviors that may inadvertently reinforce noneating behaviors and advice directed toward reinforcement of desired behaviors through praise and limit-setting.[51,52]

As children become adolescents, a struggle for control and independence may ensue, and it may be challenging to provide education and direction so that the child/adolescent makes appropriate choices that improve or maintain optimal nutrition. According to Birch et al,[53] the foundation for teen and adult eating styles is laid in childhood as the parent and child work through issues of control regarding feeding and eating. CF care teams typically include a social worker and a psychologist to help families understand feeding difficulties and provide support for their children.

With newly added CFTR modulator treatments, excessive weight gain has been noted. The typical unrestricted high-calorie, high-fat CF diet that was encouraged for many years likely contributes to positive energy balance promoting weight gain.[20] For years, families and patients with CF have received different messaging regarding nutrition than the general population, and some are having difficulty making adjustments to these long-standing eating patterns. In persons with CF, weight stigma and body changes are associated with eating disturbances, depression, anxiety, and body image issues and negative self-esteem.[53,54] Individual plans and counseling techniques should be applied as the community navigates a new normal in the age of CFTR modulators. With these changes, it is more important than ever to screen for disordered eating, including anorexia nervosa and avoidant restrictive food intake disorder.

Nutrition Support

A positive correlation exists between pulmonary function and weight, and a better nutrition status earlier in life is associated with improved lung function and better survival later in life. Given the increase in obesity and overweight status seen with CFTR modulators, nutrition recommendations will likely continue to change as more research is done. Currently, the Cystic Fibrosis Foundation recommends the following nutrition goals:

- Infants: Weight for length at the 50th percentile by 2 years of age on the World Health Organization growth curve
- Children 2–20 years of age: BMI percentile at or above the 50th percentile on Centers for Disease Control growth curves
- Adults: BMI of 22 for women and 23 for men[15]

Additionally, children are expected to meet their genetic growth potential. Therefore, nutrition interventions to reach and maintain weight and growth goals are necessary. Behavioral interventions for parents, caregivers, and patients may also help improve caloric intake, thus allowing weight gain. Weight percentiles are believed to be at their lowest during the first 2 years of life and early adolescence, therefore making aggressive nutrition intervention important during these periods.[51,52] Currently, z-scores are being used rather than percentiles as they more accurately describe nutrition status. For toddlers and older children, initially using high-caloric oral supplements or additives may be indicated. Infant formula can be concentrated or high-caloric modulars can be added to provide adequate calories. However, in some children, this may not be sufficient to sustain a desired weight and growth status, thus enteral feeding may be indicated.

No specific guidelines exist regarding when to initiate enteral feeding in the pediatric CF population. The Cystic Fibrosis Foundation clinical practice guidelines subcommittee on growth and nutrition has determined that oral or enteral supplementation should be used for children with growth deficits to improve the rate of weight gain.[55] Enteral nutrition may include a G-tube, GJ tube, NG tube, NJ tube, or a surgically placed jejunal tube. A nasogastric tube can be inserted and removed daily for short-term use. Adherence to this intervention may prove difficult. A G-tube may be more

appropriate and allow for flexibility of feeding. G-tube feeding can be intermittent, bolus, or continuous. Continuous feeds generally occur nocturnally, allowing for regular meal and snack patterns during the day, which is appropriate for most children with CF. An intact protein or semi-elemental protein formula may be used.

Enteral nutrition may be complicated by early morning fullness and vomiting, bed wetting, loss of appetite, poor body image, and self-esteem concerns.[53,56] It is important to find a balance between the initiation of enteral feeding and the severity of lung disease to optimize the intervention benefits. Feeding via a jejunostomy tube is infrequent in patients with CF and usually occurs in patients with significant upper GI dysmotility, failure of anti-reflux procedures, intubation, and certain postoperative states. Parenteral nutrition (PN) is a more aggressive intervention and is not routinely used in the daily management of CF.

Nutrition-Related CF Complications

CF-Related Bone Disease

CF–related bone disease (CFBD) is increasingly recognized in persons who have CF, and the CF Patient Registry reports an incidence of 18.3% as of 2021 for all age groups and diagnoses.[1] This incidence is expected to increase with increased life expectancy. The incidence of osteoporosis and fractures increases with age and is present in adult patients and in those with end-stage lung disease. CFBD is a multifactorial disease, and predisposing factors include malnutrition, increased inflammatory cytokines, vitamin D deficiency, inadequate calcium intake, use of corticosteroids, hypogonadism, short bowel syndrome, male sex, advanced lung disease, liver disease, CFRD, and possible genetic factors (F508del-CFTR is associated with reduced bone density in adults with CF).

The Cystic Fibrosis Foundation guidelines recommend a baseline DXA at age 18 years or age 8 years if there are significant risk factors present (low body weight, compromised pulmonary function, glucocorticoid use, delayed puberty, or fractures). If results are normal, then a repeat DXA should be done every 5 years. If the DXA z-score is between −1 and −2, then the scan should be repeated every 2 to 4 years. If the z-score is worse

than −2, then the scan should be repeated yearly. Normative data are available for DXA scans for children >3 years of age. Treatment includes optimizing nutrition (calcium, vitamins D and K, and nutrition status), increasing physical activity, controlling underlying inflammation, decreasing corticosteroid use (if possible), treating CFRD, and addressing any hormone deficiencies. In adults, bisphosphonates have been used in patients with osteoporosis and stress fractures, but there is limited data regarding their safety in children.[57,58]

CF-Related Diabetes

CFRD is being increasingly recognized in individuals with CF. This may be due in part to increased screening and improved survival. Incidence rates previously studied are now increasing with median life expectancy. In a large study of the European CF Foundation registry published in 2020, the prevalence of CFRD in patients was 0.8% in patients <10 years of age, 9.7% in ages 10 to 29 years, and 32.7% in ages >30 years. [60] CFRD differs from type 1 and 2 diabetes mellitus; it is seen in patients with more severe phenotypes with PI and is considered an insulin-insufficient state.[61]

Obstruction of the pancreatic ducts leads to islet cell damage, fibrosis, and fatty infiltration. Delayed and blunted insulin and C-peptide secretion are typically observed on an oral glucose tolerance test (OGTT) in patients with CF, even in the absence of CFRD. Abnormalities in glucagon-like peptide-1 and gastric inhibitory polypeptide levels have also been reported.[60,61] With age, β-cell function declines abnormally, and this decline may be more prominent in patients with CF, leading to the increased incidence of CFRD as patients with CF age. While insulin deficiency is the primary defect, insulin resistance may also play a role during an acute pulmonary exacerbation, chronic severe lung disease, and glucocorticoid therapy and in individuals with CF who have obesity.

A nearly six-fold mortality rate increase has been observed in patients with CFRD,[61,62] although the University of Minnesota has reported improved survival rates with early identification and treatment of CFRD. BMI and pulmonary function decreased in the years prior to CFRD diagnosis. Patients treated with insulin have improved weight. Complications of CFRD such as retinopathy, microalbuminemia, autonomic

neuropathy, gastroparesis, and nephropathy can also occur.[62] Because the onset of CFRD is insidious and associated with negative outcomes, annual screening is essential. In CFRD, the classic type 1 diabetes symptoms of polyuria and polydipsia are seldom reported. Instead, weight loss, poor growth, and a decline in pulmonary function may be the first indications of glucose intolerance.[62]

The Cystic Fibrosis Foundation offers the following recommendations[61]:

1. OGTT should be done annually at age 10 years and before transplant.
2. Fasting and 2-hour postprandial glucose monitoring should be done during hospitalization and in the outpatient setting during intercurrent illness, intravenous antibiotics, or systemic glucocorticoid use and with enteral feeds.
3. Hemoglobin A1C (HbA1C) levels <6.6 do not exclude CFRD. Levels can be falsely low in CF due to accelerated red blood cell turnover.
4. Diagnosis recommendations: Patients need one abnormal OGTT plus a confirmatory test or classic symptoms. The confirmatory tests can include
   A. 2-hour OGTT plasma glucose ≥ 200 mg/dL
   B. fasting plasma glucose ≥ 126 mg/dL
   C. HbA1C ≥ 6.5
   D. classic symptoms of polyuria and polydipsia in the presence of a casual glucose level of ≥ 200 mg/dL

For further details, refer to the Cystic Fibrosis Foundation guidelines.[61]

Insulin is the treatment of choice for CFRD. The regimen is individualized and should be managed by an endocrinologist experienced in caring for patients with CF. Oral hypoglycemic agents are typically not recommended. Carbohydrate ingestion is not discouraged. Avoiding foods that are high in simple sugars (soda, sugary sweets) helps maintain more stable glucose levels, and the ingestion of high-carbohydrate foods with foods containing fat and protein helps avoid large blood sugar spikes. PERT helps with fat absorption and stabilization of glucose levels. Education is very important given the treatment burden from insulin injections, blood glucose, and diet monitoring. In addition, patients need to understand the effects of food intake, stress, illness, and physical activity on insulin needs

including the treatment of hypoglycemia and hyperglycemia. *Managing Cystic Fibrosis–Related Diabetes: An Instruction Guide for Patients and Families* is a useful resource that is available online from the Cystic Fibrosis Foundation (https://www.cff.org/medical-professionals/cystic-fibrosis-related-diabetes-clinical-care-guidelines).

Gastrointestinal Complications of CF

GI manifestations are frequently observed in persons with CF and involve all parts of the GI tract.[9] If a gastroenterologist is not on the treatment care team, a referral should be made for collaborative management in most cases. GER occurs at all ages and the incidence varies between 25% and 100% depending on the study. Complications of GER include the following:

- feeding disorders
- decreased caloric intake
- malnutrition apnea in infants
- vomiting
- esophagitis
- worsening of lung disease
- esophageal strictures
- Barrett's esophagus

GER can be a significant problem in lung transplant recipients and is associated with rejection in the posttransplant period. Often a fundoplication is recommended in the pretransplant period to prevent bronchiolitis obliterans. Gastroparesis and constipation can occur in patients with CF, and the latter may be 3 times more frequent than DIOS. Bacterial overgrowth occurs in up to 60% of patients.[63] Predisposing factors include frequent antibiotic use, intestinal dysmotility, history of previous GI surgery, and sticky intestinal secretions that trap bacteria. DIOS is seen in all persons with CF, not just in those with PI. Dehydration of the intestinal secretions, coupled with electrolyte imbalances and sticky mucus, and poor motility lead to the accumulation of stool in the ileocecal junction, resulting in abdominal pain and vomiting.

Treatment/prophylaxis consists of fluid and electrolyte intake optimization, malabsorption correction, and laxative/stool softener use, such as polyethylene glycol. Prevention of constipation is vital, and an attempt to find the precipitating factor for every episode should be made. Celiac disease, inflammatory bowel disease, eosinophilic esophagitis, and GI malignancies may also occur in patients with CF.

Patients with PS are at risk for recurrent bouts of pancreatitis. Over time, some of these patients may develop PI. The most common liver lesions in patients with CF are fatty liver; hepatitis, hepatic fibrosis, and cirrhosis with portal hypertension are also seen. Gallbladder dysfunction is frequent, and a nonfunctioning gallbladder or gallstones can be seen on ultrasound examination. Biliary dyskinesia can result in right upper quadrant abdominal pain. Some patients with liver disease will progress to end-stage liver disease and develop complications from cirrhosis, portal encephalopathy, and variceal bleeds that may require liver transplantation.[10,11]

Other Chronic Lung Diseases

There are other pediatric pulmonary conditions that benefit from specific nutrition considerations, including bronchopulmonary dysplasia, asthma, respiratory failure, and lung transplantation.

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) is a form of chronic lung disease that affects newborns.[64] Most often, it develops in preterm infants who are given positive pressure ventilation and oxygen. The pathophysiology is complex and arises from small airway damage, abnormal alveolar development, and decreased surface area for gas exchange.[65] Additionally, there is damage to small blood vessels in the lungs and secondary damage to the heart and brain.

BPD is most prevalent in preterm infants with a birth weight between 1000 g and 1500 g and <30 weeks of gestational age.[66] Males tend to be more affected. Surfactant therapy is used soon after birth to prevent lung damage. Energy requirements are usually increased and range from 140

kcal/kg/d to 150 kcal/kg/d.[67,68] Patients with BPD have large insensible water losses and need extra fluid, which may result in opening of the patent ductus arteriosus and further stress on the lungs. Fluid intake of patients with BPD should be monitored closely to ensure adequate hydration and energy intake without causing fluid overload to the lungs.

Infants with BPD are also at risk for decreased bone mineralization resulting from decreased calcium intake (inadequate amounts of calcium in enteral feeds and PN solutions because of limited calcium solubility in PN) and increased losses in urine from diuretic use. Calcium status should be monitored and an adequate intake of calcium (120–140 mg/kg/d), phosphorus (60–90 mg/kg/d), and vitamin D should be ensured.[68] Adequate intakes of protein (3–3.5 g/kg/d) and antioxidants (copper, zinc, manganese) are also required. These patients often receive corticosteroids and diuretics for treatment of the lung disease, often with significant consequences: increased sodium, potassium, and magnesium losses; kidney stones; gallstones; and bone disease.

Infants with severe BPD are at high risk for pulmonary infections, frequent hospitalizations, reactive airway disease (RAD), and more frequent visits to the doctor during the first 2 years of life. They may also have developmental delays, poor muscular development, poor feeding skills, poor growth, and chronic lung disease. Infants with BPD often have impaired weight for length and problems with oxygen diffusion, resulting in a chronic oxygen requirement. Caloric needs can be high because catch-up growth is often a goal. However, as respiratory support is weaned, nutritional needs may decrease and should be adjusted accordingly to avoid excessive growth rates.

The coexistence of GER and BPD can exacerbate poor oral motor function and worsen feeding problems in patients with developmental delays. GER can also worsen lung disease. Supplemental feeds or calorically dense feedings are often required. For children with BPD, it is best to monitor growth regularly. Anthropometrics provide critical information regarding infant/child growth. In infants with BPD, increased basal metabolic rate, increased work of breathing, chronic illness or infections, and respiratory distress or metabolic complications may increase caloric requirements.[67] Infants may have interrupted feeding skill

development and therefore may be poor oral feeders.[68] Interprofessional collaboration between team members is indicated, and occupational or speech therapists should provide oral therapy to maximize future feeding potential.

Asthma

Asthma or RAD is the most common cause of hospital admissions in children, and the prevalence is steadily rising. Approximately 9.5% of children ages 0 to 17 years of age have asthma[69,70] This chronic pediatric lung disease involves chronic inflammation of the airways involving eosinophils, mast cells, T lymphocytes, macrophages, neutrophils, and epithelial cells. Additionally, variable airflow obstruction is present along with increased bronchial responsiveness to a variety of environmental stimuli. Airway edema and mucus contribute to the obstruction and bronchial reactivity.[71]

Environmental triggers affect the normal development of the respiratory and immune systems in genetically predisposed individuals. Patients often require chronic inhaled corticosteroids or pulses of systemic corticosteroids. Excessive oral corticosteroid use over time can result in growth failure, fluid and sodium retention, a large appetite, excessive weight gain, hypertension, glucose intolerance, and obesity. Chronic corticosteroids can result in decreased bone density,[69] thus adequate calcium and vitamin D supplementation are vital to maintain bone health. Diet assessment (for calcium and vitamin D intake), a 25-OH vitamin D level, and a DXA scan should be considered for patients at risk of bone disease. Normative data are available for DXA scans for children >3 years of age. There is also considerable variation in the side effects of inhaled corticosteroids. Growth, puberty, and bone health can be affected depending on the duration of therapy and dose.[72] Early data suggest that the use of antioxidants, *Lactobacillus*, and ω-3 fatty acids reduces symptoms and the development of asthma in those with atopy.[73]

A linear association between obesity (increased BMI) and asthma has been observed in children, with a 6% increase in prevalence per unit increase of BMI.[74] In studies of vitamin D levels in patients with asthma, deficiency is associated with increased symptoms of asthma, lower lung

function, and worsened asthma control. It is important to monitor vitamin D levels in patients with asthma and supplement with vitamin D if serum levels are low.[75] Recent research supports increasing fruit and vegetable intake and decreasing overall dairy and saturated fat.[76]

Children With Respiratory Failure Requiring Medical Technology

Children with chronic respiratory failure may require chronic ventilatory support. At-risk children include those with spinal muscular atrophy, Duchenne Muscular Dystrophy, spinal cord injuries, BPD, congenital diaphragmatic hernia, severe lung malformations, congenital hypoventilation syndrome, and myelomeningiocoele. Among patients who require ventilator support, those with BPD and neuromuscular dystrophy are the most frequent diagnoses. Respiratory support can be provided in two ways: (1) non-invasive ventilation with a mask via continuous positive airway pressure (CPAP) or (2) bilevel positive airway pressure (BIPAP). Invasive support is provided via tracheostomy and a ventilator machine. The indication for these support systems includes the following:

- Respiratory insufficiency (seen in BPD and pulmonary hypoplasia)
- Secondary damage to the lungs from severe cardiac disease resulting in decreased surface area
- Decreased oxygen absorption
- Increased carbon dioxide retention
- Poor lung development
- Small-volume lungs
- Insufficient vascular bed

There may also be decreased central drive for respiration as observed in persons with congenital central hypoventilation syndrome. Because these patients have decreased breathing effort from the machine assistance, their energy requirements are lower. Thus, special attention must be given to their nutrition regimens or they can have excessive weight gain, which can further negatively impact their respiratory status. A commercially available enteral formula offers reduced calories (0.6 kcal/mL) in a nutritionally complete formulation for use in circumstances in which calories need to be

decreased without changing the volume of the formula. Often, when attempting to decrease calories, overall nutrient intake, especially protein and mineral intake, can suffer. These patients may also be at risk for bone disease because of decreased weight-bearing status and micronutrient deficiencies (vitamin D and calcium).

Lung Transplantation

Lung transplantation remains the most aggressive therapy for end-stage lung disease. Persons with CF and other lung diseases are candidates for lung transplantation when they exhibit severely reduced lung function and progressive deterioration in their health and quality of life. For children and adults, the largest obstacle to long-term survival is chronic allograft rejection secondary to the development of bronchiolitis obliterans. No level of malnutrition is an absolute contraindication to lung transplantation; however, a BMI >17 kg/m^2 or an ideal body weight (according to standard adult calculations) >80% is recommended to improve outcomes posttransplant.

Several modes of support may be used prior to transplant, including enteral feeding tubes and oral supplements. Weight gain is common after transplant, likely resulting from decreased energy needs, long-term steroid use, and overall improved health. There is no pediatric weight criterion for lung transplant; however, one recent study showed no significant negative impact on children specifically with CF who were underweight before transplant. In the largest cohort examined, decreased survival rates were observed among patients with underweight, overweight, and obesity compared to patients with normal weight ranges.[77,78] Both CF and non-CF groups with overweight before surgery had decreased survival rates and worse outcomes after transplant. Further research on weight and nutrition status is needed in the pediatric lung transplant population.[79]

Very little research has been done regarding specific nutritional intake and macronutrients in lung transplant patients.[80] Hyperglycemia (not in the diabetes setting) is a common disorder that occurs in the early post-transplant period because of the stress of the surgery, enhancing epinephrine and cortisol secretion. Corticosteroids also affect glucose metabolism in this population.[81] New-onset diabetes after transplant affects 40% of patients 2

years post-transplant and is associated with mortality. There are no evidence-based recommendations for specific nutritional interventions because of limited research. A team approach including an endocrinologist should be considered.

Protein needs are extremely variable in the post-operative period and should be adjusted on an individual basis. Serum lipid changes often occur after lung transplant and depend on several factors, including medications. Dietary modifications should be individualized. Limited data exist regarding specific vitamin and mineral recommendations for lung transplants, however, vitamin D is involved in the regulation of lung function and immune responses.[82] One study showed vitamin D insufficiency (<30 ng/ml) in post-transplant recipients up to 1 year post-transplant had more bacterial, fungal, cytomegalovirus, and non-tuberculosis mycobacterial infections and lower survival compared to those with vitamin D sufficiency.[83] Levels should be carefully monitored and supplemented as needed. Serum levels of vitamins A and E increase after lung transplant, particularly in the CF population. High levels were found 6 months post-transplant and remained elevated after more than 4.5 years of follow-up despite no adjustment to vitamin therapy.[84] It is suggested that these levels are related to immunosuppressive therapy rather than excessive intake. After lung transplantation, vitamin E and A levels should be monitored closely and supplementation should be discontinued if levels increase.

Conclusion

Nutrition support is an important part of managing children who have CF and other lung diseases. In general, the goal is normal growth and development and correction of nutritional abnormalities that result from the underlying medical condition and the therapies used to treat the disease. Good nutrition status has been associated with improved lung function and outcomes in patients with CF.

Test Your Knowledge Questions

1. Pancreatic enzymes are available in non-enteric-coated and enteric-coated forms. How does enteric coating help with nutrient absorption?
   A. Enteric coating is subject to destruction by the harsh acid–peptic gastric environment.
   B. The coating allows the enzymes to get through the buildup of thick mucus in the pancreatic ducts.
   C. Enteric coating allows for the activation of enzymes to occur in the alkaline pH of the duodenum, past the gastric contents of the stomach.
2. Which fat-soluble vitamin blood levels should be checked in persons with CF and why?
   A. Vitamins A, D, and zinc
   B. Vitamins A, D, and E and prothrombin time to assure adequacy
   C. Vitamins A, D, and E
3. A baseline DXA scan is recommended at 8 years of age, especially if risk factors are present. Which of the following set of risk factors is necessary to be aware of?
   A. Small body size, low weight-for-height measures, decreased physical activity, low vitamin D levels, corticosteroid usage, delayed puberty, low calcium intake, history of fractures, family history of osteoporosis, significant lung disease, short bowel syndrome, and liver disease
   B. Increased physical activity, large body frame, and asthma
   C. Increased physical activity and constitutional delay in linear growth
4. Patients with asthma often require multiple courses of oral corticosteroids to control symptoms. What is not a nutrition concern in these patients?
   A. Growth failure
   B. Poor weight gain
   C. Glucose intolerance

References

1. Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry 2021. Cystic Fibrosis Foundation. Accessed February 6, 2024. https://www.cff.org/medical-professionals/patient-registry
2. Riordan J, Rommens J, Kerem B, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science*. 1989;245(4922):1066–1073. https://doi.org/10.1126/science.2475911
3. Shteinberg M, Haq IJ, Polineni D, Davies JC. Cystic fibrosis. *Lancet.* 2021;397:2195–211. https://doi.org/10.1016/s0140-6736(20)32542–3
4. Farrell PM, White TB, Ren CL, et al. Diagnosis of cystic fibrosis; consensus guidelines from the Cystic Fibrosis Foundation. *J Pediatr.* 2017;181S:S4–S15. https://doi.org/10.1016/j.jpeds.2016.09.064
5. Carrageta DF, Bernadino RL, Alves MG, et al. CFTR regulation of aquaporin-mediated water transport. *Vitam Horm*. 2020;112:163–177. https://doi.org/10.1016/bs.vh.2019.08.004
6. Turcios NL. Cystic fibrosis lung disease: an overview. *Respir Care.* 2020;65(2):233–251. https://doi.org/10.4187/respcare.06697
7. Katkin JP, Baker RD, Baker SS. Cystic fibrosis: assessment and management of pancreatic insufficiency. UpToDate. Updated December 4, 2023. Accessed February 6, 2024. https://www.uptodate.com/contents/cystic-fibrosis-assessment-and-management-of-pancreatic-insufficiency?search=cystic%20fibrosis&topicRef=6367&source=see_link#H16
8. American Academy of Pediatrics, Committee on Nutrition. Kleinman RE, Greer F, eds. *Pediatric Nutrition Handbook*. 8th ed. The American Academy of Pediatrics; 2019.
9. Sabharwal S. GI manifestations of CF. *Gastroenterol & Hepatol*. 2016;12(1):43–47.
10. Leung DH, Narkewicz M. Cystic fibrosis-related cirrhosis. *J Cyst Fibros.* 2017;16(2):S50–61. https://doi.org/10.1016/j.jcf.2017.07.002
11. Wu H, Vu M, Dhingra S, et al. Obliterative portal venopathy without cirrhosis is prevalent in pediatric cystic fibrosis liver disease with portal hypertension. *Clin Gastroenterol Hepatol.* 2019;17(10):2134–2136. https://doi.org/10.1016/j.cgh.2018.10.046

12. Dana J, Debray D, Beaufrere A, et al. Cystic fibrosis-related liver disease: clinical presentation, diagnostic and monitoring approaches in the era of CFTR modulator therapies. *J Hepatol*. 2022;76(2):420–434. https://doi.org/10.1016/j.jhep.2021.09.042
13. Zemel BS, Jawad AF, FitzSimmons S, et al. Longitudinal relationship between growth, nutritional status and pulmonary function in children with cystic fibrosis: analysis of the Cystic Fibrosis Foundation National CF Patient Registry. *J Pediatr.* 2000;137(3):374–80. https://doi.org/10.1067/mpd.2000.107891
14. Corey M, McLaughlin FJ, Williams M, et al. A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. *Epidemiol.* 1988;41(6):583–91. https://doi.org/10.1016/0895-4356(88)90063-7
15. Stallings VA, Stark LJ, Robinson KA, et al. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. *J Am Diet Assoc.* 2008;108(5):832–839. https://doi.org/10.1016/j.jada.2008.02.020
16. Yen E, Quinton H, Borowitz, et al. Better nutritional status in early childhood is associated with improved clinical outcomes and survival in patients with cystic fibrosis. *J Pediatr.* 2012;162(3):530–535. https://doi.org/10.1016/j.jpeds.2012.08.040
17. Patel D, Shan A, Matthews S, et al. Understanding cystic fibrosis comorbidities and their impact on nutritional management. *Nutrients.* 2022;14(5):1028. https://doi.org/10.3390/nu14051028
18. Stallings VA, Tomezsko JL, Schall JI, et al. Adolescent development and energy expenditure in females with CF. *Clin Nutr.* 2005;24:737–745. https://doi.org/10.1016/j.clnu.2005.02.005
19. Bass, R.; Brownell, J.N.; Stallings, V.A. The impact of highly effective CFTR modulators on growth and nutrition status. *Nutrients*. 2021;13(9): 2907. https://doi.org/10.3390/nu13092907
20. McDonald CM, Alvarez JA, Bailey J, et al. Academy of Nutrition and Dietetics: 2020 cystic fibrosis evidence analysis center evidence-based nutrition practice guideline. *J Acad Nutr Diet*. 2021;121(8):1591–1636. https://doi.org/10.1016/j.jand.2020.03.015

21. Sheikh S, Zemel B, Stallings VA et al. Body composition and pulmonary function in cystic fibrosis. *Frontiers Pediatr*. 2014;2(33):1–7. https://doi.org/10.3389/fped.2014.00033
22. Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr.* 2002;35:246–259. https://doi.org/10.1097/00005176-200209000-00004
23. Calella P, Valerio G, Thomas M, et al. Association between body composition and pulmonary function in children and young people with cystic fibrosis. *Nutrition*. 2018;48:73–76. https://doi.org/10.1016/j.nut.2017.10.026
24. Thoracic Society of Australia & New Zealand. Nutrition guidelines for cystic fibrosis, 2017. Cystic Fibrosis Australia. Published May 8, 2017. Accessed February 6, 2024. https://thoracic.org.au/wp-content/uploads/2021/06/NHMRC-NutritionGuidelines-CF-ANZ-final-web.pdf
25. Feranchak AP, Sontag MK, Wagerner JS, et al. Prospective, long-term study of fat-soluble vitamin status in children with cystic fibrosis identified by newborn screen. *J Pediatr.* 1999;135(5):601–610. https://doi.org/10.1016/s0022-3476(99)70059-4
26. Bauer SE, Lai HJ, McDonald CM, et al. Zinc status and growth in infants and young children with cystic fibrosis. *Pediatr Pulmonol.* 2021;56(12):3768–3776. https://doi.org/10.1002/ppul.25666
27. Smyth AR, Bell SC, Bojcin S, et al. European Cystic Fibrosis Society standards of care: best practice guidelines. *J Cyst Fibros*. 2014;13(1):S23–S42. https://doi.org/10.1016/j.jcf.2014.03.010
28. Aris RM, Merkel PA, Bachrach LK, et al. Consensus statement: guide to bone health and disease in cystic fibrosis. *J Clin Endocrinol Metab.* 2005; 90:1888–1896. https://doi.org/10.1210/jc.2004-1629
29. Huang SH, Schall JI, Zemel BS, Stallings VA. Vitamin E status in children with cystic fibrosis and pancreatic insufficiency. *J Pediatr.* 2006;148:556–559. https://doi.org/10.1016/j.jpeds.2005.11.016
30. Tangpricha V, Kelly A, Stephenson A, et al. An update on the screening, diagnosis, management, and treatment of vitamin D deficiency in individuals with cystic fibrosis: evidenced-based recommendations from the Cystic Fibrosis Foundation. *J Clin*

Endocrinol Metab. 2012;97(4):1082–1093. https://doi.org/10.1210/jc.2011-3050
31. Conway SP, Wolfe SP, Brownlee KG, et al. Vitamin K status among children with cystic fibrosis and its relationship to bone mineral density and bone turnover. *Pediatrics.* 2005;115:1325–1331. https://doi.org/10.1542/peds.2004-1242
32. Hatziparasides G, Loukou I, Moustaki M, et al. Vitamin K and cystic fibrosis: a gordian knot that deserves our attention. *Respir Med*. 2019:155:36–42. https://doi.org/10.1016/j.rmed.2019.07.005
33. Michel SH, Maqbool A, Hanna MD, et al. Nutrition management of pediatric patients who have cystic fibrosis. *Pediatr Clin N Am*. 2009;56(5):1123–1141. https://doi.org/10.1016/j.pcl.2009.06.008
34. Maqbool A, Schall J, Mascarenhas M, et al. Vitamin B12 status in children with cystic fibrosis and pancreatic insufficiency. *Pediatr Gastroenterol Nutr*. 2014;58(6): 733–738. https://doi.org/10.1097/MPG.0000000000000313
35. Kriemler S, Wilk B, Schurer W, et al. Preventing dehydration in children with cystic fibrosis who exercise in the heat. *Med Sci Sports Exerc.* 1993;31:774–779. https://doi.org/10.1097/00005768-199906000-00003
36. Gettle L, Harden A, Bridges M, Albon D. Prevalence and risk factors for iron deficiency in adults with cystic fibrosis. *Nutr Clin Prac.* 2020;30:1101–1109. https://doi.org/10.1002/ncp.10454
37. Ross AC, Manson JE, Abrams SA, et al. The 2011 Dietary Reference Intakes for calcium and vitamin D: what dietetics practitioners need to know. *J Am Diet Assoc*. 2011;111:524–527. https://doi.org/10.1016/j.jada.2011.01.004
38. Marquette M, Haworth C. Bone health and disease in cystic fibrosis. *Paediatr Respir Rev* 2016;20(suppl 1):2–5. https://doi.org/10.1016/j.prrv.2016.06.003
39. von Vigier RO, Truttmann AC, Zindler-Schmocker K, et al. Aminoglycosides and renal magnesium homeostasis in humans. *Nephrol Dial Transplan.* 2000;15:822–826. https://doi.org/10.1093/ndt/15.6.822
40. Hryciw D, Jackson C, Shrestha N, et al. Role for animal models in understanding essential fatty acid deficiency in cystic fibrosis. *Cellular*

and Molecular Life Sciences. 2021;78:7991–7999. https://doi.org/10.1007/s00018-021-04014-2

41. Maqbool A, Schall JI, Garcia-Espana JF, et al. Serum linoleic acid status as a clinical indicator of essential fatty acid status in children with cystic fibrosis. *J Pediatr Gastroenterol Nutr.* 2008;47(5):635–644. https://doi.org/10.1097/mpg.0b013e31817fb76b
42. O'Brien CE, Harden H, Com G. A survey of nutrition practices for patients with cystic fibrosis. *Nutr Clin Pract.* 2013;28:237–241. https://doi.org/10.1177/0884533612466113
43. Borowitz D, Robinson KA, Rosenfeld M, et al. Cystic fibrosis evidenced-based guidelines for management of infants with cystic fibrosis. *J Pediatr*. 2009;155:S73–S93. https://doi.org/10.1016/j.jpeds.2009.09.001
44. Fleischer DM, Chan ES, Venter C, et al. A consensus approach to the primary prevention of food allergy though nutrition: guidance from the American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology and the Canadian Society for Allergy and Clinical Immunology. *J Allergy Clin Immunol Pract*. 2021;9(1):22–23. https://doi.org/10.1016/j.jaip.2020.11.002
45. Freswick PN, Reid EK, Mascarenhas MR. Pancreatic enzyme replacement therapy in cystic fibrosis. *Nutrients.* 2022;14(7):1341. https://doi.org/10.3390/nu14071341
46. DiMagno EP. Gastric acid suppression and treatment of severe exocrine pancreatic insufficiency. *Best Pract & Res Clin Gastroenterol*. 2001;15(3):477–486. https://doi.org/10.1053/bega.2001.0195
47. Children's Hospital of Philadelphia. Clinical pathway for pancreatic replacement therapy (PERT) in children with or at risk for exocrine pancreatic insufficiency (EPI). Children's Hospital of Philadelphia. Updated April 2024. Accessed April 16, 2024. https://www.chop.edu/clinical-pathway/initiating-pancreatic-enzyme-replacement-therapy-pert-clinical-pathway
48. Borowitz DS, Grand RJ, Drurie PR, et al. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. *J Pediatr.* 1995;127(68):1. https://doi.org/10.1016/s0022-3476(95)70153-2

49. Ferrie S, Graham C, Hoyle M. Pancreatic enzyme supplementation for patients receiving enteral feeds. *Nutr Clin Pract.* 2011;26:349–351. https://doi.org/10.1177/0884533611405537
50. Nicolo M, Stratton K, Rooney W, Boullata J. Pancreatic enzyme replacement therapy for enterally fed patients with cystic fibrosis. 2013;28(4):485–489. https://doi.org/10.1177/0884533613491786
51. Papantoni A, Reinblatt SP, Findling RL, et al. Appetite characteristics in children with cystic fibrosis: questionnaire validation and associations with nutritional status. *Appetite.* 2019:139:90–94. https://doi.org/10.1016/j.appet.2019.03.034
52. Powers SW, Byars KC, Mitchell MJ, et al. A randomized pilot study of behavioral treatment to increase caloric intake in toddlers with cystic fibrosis. *Child Health Care.* 2003;32(4):297–311. https://doi.org/10.1207/S15326888CHC3204_5
53. Powers SW, Mitchell MJ, Patton SR, et al. Mealtime behaviors in families of infants and toddlers with cystic fibrosis. *J Cyst Fibros*. 2005:4(3):175–182. https://doi.org/10.1016/j.jcf.2005.05.015
54. Leonard A, Bailey J, Bruce A, et al. Nutritional considerations for a new era: a CF foundation position paper. *J Cyst Fibros*. 2023;S1569-1993(23)00140-6. https://doi.org/10.1016/j.jcf.2023.05.010
55. Darukhanavala A, Merjaneh L, Mason K, Le T. Eating disorders and body image in cystic fibrosis. *J Clin Transl Endocrinol.* 2021;26:100280. https://doi.org/10.1016/j.jcte.2021.100280
56. Schwarzenberg S, Hempstead S, McDonald C, et al. Enteral tube feeding for individuals with cystic fibrosis: Cystic Fibrosis Foundation evidence-informed guidelines. *J Cystic Fibrosis.* 2016;15:724–735. https://doi.org/10.1016/j.jcf.2016.08.004
57. Gilchrist FJ, Lenney W. Distorted body image and anorexia complicating cystic fibrosis in an adolescent. *J Cystic Fibros.* 2008;7(5):437–439. https://doi.org/10.1016/j.jcf.2008.04.003
58. Stalvey MS, Clines GA. Cystic fibrosis-related bone disease: insights into a growing problem. *Curr Opin Endocrinol Diabetes Obes.* 2013;20:547–552. https://doi.org/10.1097/01.med.0000436191.87727.ec
59. Ullal J, Kutney K, Wiliams K, Weber D. Treatment of cystic fibrosis related bone disease. *J Clin Transl Endocrinol.* 2022;27:100291.

https://doi.org/10.1016/j.jcte.2021.100291
60. Olesen, HV, et al. Cystic fibrosis related diabetes in Europe: prevalence, risk factors and outcome. *J Cyst Fibros*. 2020;19(2):321–327. https://doi.org/10.1016/j.jcf.2019.10.009
61. Moran A, Brunzell C, Cohen RC, et al. Clinical care guidelines for cystic fibrosis-related diabetes. *Diabetes Care*. 2010;33(12):2697–2708. https://doi.org/10.2337/dc10-1768
62. Frost F, Walshaw MJ, Nazareth D. Cystic fibrosis related diabetes - an update. *QJM: An Int J Med*. 2022;582–585. https://doi.org/10.1093/qjmed/hcaa256
63. Fridge JL, Conrad C, Gerson L, Cox K. Risk factors for small bowel bacterial overgrowth in cystic fibrosis. *J Pediatr Gastroenterol Nutr.* 2007;44(2):212–218. https://doi.org/10.1097/mpg.0b013e31802c0ceb
64. Ambalavanan N. Bronchopulmonary dysplasia. Medscape. Updated January 13, 2020. Accessed February 6, 2024. http://reference.medscape.com/article/973717-overview
65. Children's Hospital of Philadelphia. Infant chronic lung disease. Children's Hospital of Philadelphia. Accessed February 6, 2024. https://www.chop.edu/conditions-diseases/infant-chronic-lung-disease
66. Cox JH. Bronchopulmonary dysplasia. In: Groh-Wargo S, Thompson M, Cox JH, eds. *Nutritional Care for High-Risk Newborns.* Precept Press Inc.; 2000:369–390.
67. Dani C, Poggi C. Nutrition and bronchopulmonary dysplasia. *J Matern Fetal Neonatal Med*. 2012;25(S3):37–40. https://doi.org/10.3109/14767058.2012.712314
68. Redding E, Despino S. Pulmonary diseases. In: Queen Samour P, King K, eds. *Handbook of Pediatric Nutrition.* 5th ed. Jones & Bartlett; 2012:239–271.
69. Morris MJ. Asthma. Updated July 31, 2023. Accessed February 6, 2024. http://emedicine.medscape.com/article/296301-overview#aw2aab6b2b2
70. Moorman JE, Akinbami LJ, Bailey CM, et al. National surveillance of asthma: United States, 2001–2010. *Vital Health Stat 3*. 2012;35:1–58.
71. Sly PD. Asthma: Disease mechanisms and cell biology. In: Taussig LM, Landau LI, eds. *Pediatric Respiratory Medicine.* 2nd ed. Mosby Elsevier; 2008:791804.

72. Marra M, Sammarco R, Dr Lorenzo A, et al. Assessment of body composition in health and disease using bioelectrical impedance analysis (BIA) and dual energy x-ray absorptiometry (DXA): a critical overview. *Contrast Media Mol Imaging* 2019; 2548284. https://doi.org/10.1155/2019/3548284
73. Landau LI, Martinez FD. Asthma: Treatment. In: Taussig LM, Landau LI, eds. *Pediatric Respiratory Medicine.* 2nd ed. Mosby Elsevier; 2008:829–844.
74. Han X, Zhu Z, Xiao Q, et al. Obesity-related biomarkers underlie a shared genetic architecture between childhood body mass index and childhood asthma. *Commun Biol*. 2022;5(1):1098. https://doi.org/10.1038/s42003-022-04070-9
75. Wang Q, Ying Q, Zhu W, et al. Vitamin D and asthma occurrence in children: a systematic review and meta-analysis. *J Pediatr. Nurs*. 2022;62:e60−e68. https://doi.org/10.1016/j.pedn.2021.07.005
76. Alwarith J, Kahleova H, Crosby L, et al. The role of nutrition in asthma prevention and treatment. *Nutr Rev*. 2020;78(11):928−938. https://doi.org/10.1093/nutrit/nuaa005
77. Fernandez R, Safaenili N, Kurihara C, et al. Association of body mass index with lung transplantation survival in the United States following implementation of the lung allocation score. *J Thorac Cardiovasc Surg*. 2018;155(4):1871−1879. https://doi.org/10.1016/j.jtcvs.2017.11.031
78. Benden C, Ridout DA, Edwards LB, et al. Body mass index and its effect on outcome in children after lung transplantation. *J Heart Lung Transplant.* 2013;32:196–201. https://doi.org/10.1016/j.healun.2012.11.002
79. Ramos KJ, Smith PJ, McKone EF, et al. Lung transplant referral for individuals with cystic fibrosis: Cystic Fibrosis Foundation consensus guidelines. *J Cyst Fibros.* 2019;18(3):321−333. https://doi.org/10.1016/j.jcf.2019.03.002
80. Jomphe V, Lands L, Mailhot G. Nutritional requirements of lung transplant recipients: challenges and considerations. *Nutrients.* 2018;10:790. https://doi.org/10.3390/nu10060790
81. Hackman KL Snell GI, Bach LA. Prevalence and predictors of diabetes after lung transplantation: p prospective, longitudinal study. *Diabetes Care.* 2014;37:2919–2925. https://doi.org/10.2337/dc14-0663

82. Chesdachi S, Tangpricha V. Treatment of vitamin D deficiency in cystic fibrosis. *J Steroid Biochem Mol Biol*. 2017;164:36−39. https://doi.org/10.1016/j.jsbmb.2015.09.013
83. Lowery EM, Bemiss B, Cascino T, et al. Low vitamin D levels are associated with increased rejection and infections after lung transplantation. *J Heart Lung Transplant.* 2012;31:700–707. https://doi.org/10.1016/j.healun.2012.02.012
84. Ho T, Gupta S., Brotherwood M, et al. Increased serum vitamin A and E levels after lung transplantation. *Transplantation.* 2011;92:601606. https://doi.org/10.1097/tp.0b013e31822790e3

Test Your Knowledge Answers

1. The correct answer is **C**. Acidity in the GI tract may prevent or retard dissolution of enteric-coated pancreatic enzymes. If activation does not occur in the small intestine, then it may be difficult for a person with CF to absorb macronutrients and micronutrients.
2. The correct answer is **B**. Blood levels of fat-soluble vitamins should be measured to assure adequacy (vitamins A, E, D). Prothrombin time is not a sensitive measure of vitamin K deficiency in CF but is the only test that is currently clinically available. PIVKA II provides a better indicator of vitamin K nutrition but is not widely available.
3. The correct answer is **A**. All risk factors need to be evaluated. Treatment includes optimizing nutrition, increasing physical activity, controlling underlying inflammation, decreased corticosteroid use, and addressing hormone deficiencies.
4. The correct answer is **B**. Nutrition concerns regarding patients who require oral corticosteroids include growth failure, obesity, glucose intolerance, hypertension, and decreased bone density.

27

Pediatric Oncology and Hematopoietic Stem Cell Transplant Patients

Hannah Williams, RD, LDN, CSP, CSO; Bethany Squillante, MS, RD, CSP, LDN; Darielle Wilhelm, RD, LDN, CNSC; Karen Smith, MS, RD, CSO, LD/LDN; Erika May Murphy, PharmD, BCPPS; and Susan Rheingold, MD

Learning Objectives

1. Evaluate the nutrition status of the pediatric oncology patient and determine the caloric, macronutrient, and micronutrient needs of the patient.
2. Identify the common nutrition issues for children undergoing both general oncology treatment and hematopoietic stem cell transplantation.
3. Choose the most effective mode of nutrition support and monitor its tolerance in the pediatric oncology population.
4. Describe the types of medications used to alleviate gastrointestinal problems including chemotherapy-induced nausea, vomiting, and anorexia.
5. Explain the nutrition and activity goals for survivors of childhood cancer.

Introduction

Cancer is the most common cause of disease-related death in children and adolescents up to the age of 19 years in the United States. An estimated 15,500 children are diagnosed with cancer each year, affecting 2 to 3 children and teens per 100,000.[1] As a result of improved multimodal therapy and supportive care, the 5-year survival rates for this population have improved from <50% in the 1970s to approximately 85% today.[1,2] Unfortunately, the toxicity of cancer therapy has been shown to adversely impact nutrition status in the pediatric oncology population. Recent research has demonstrated that malnutrition (both undernutrition and overnutrition) can impact therapy-related toxicity and clinical outcomes including survival rate.[3–7] It is therefore essential to optimize nutrition status from the time of diagnosis, throughout therapy, and well into survivorship to improve outcomes and minimize long-term side effects.

The goal of nutrition intervention for a child with cancer is to provide adequate nutrients for growth and development and to prevent and/or reverse malnutrition. Up to 65% of children will present with acute malnutrition at diagnosis.[9–11] A higher incidence of malnutrition may be related to delay in diagnosis, specific diagnosis, stage of disease, and/or location of the tumor. Diagnoses associated with a higher risk of malnutrition include brain and head/neck tumors; advanced-stage solid tumors such as neuroblastoma, sarcomas, and Wilms' tumor; as well as any child with recurrent or refractory cancers.[3]

During therapy, malnutrition is observed in up to 46% of children. [9,11,12] Younger children may be at higher risk of acute malnutrition because of limited nutrient stores and increased caloric demand for growth.[10] Higher incidences of malnutrition have a direct correlation with more intensive courses of treatment, often including hematopoietic stem cell transplant (HSCT).[10] Optimal growth and weight gain in children with cancer are thus essential for maximizing tolerance to treatment and decreasing treatment delays.[3]

It is important to note that most published literature regarding the prevalence of malnutrition in the pediatric oncology population contains varied definitions of malnutrition rather than the Indicators Recommended

for the Identification and Documentation of Pediatric Malnutrition (Undernutrition) published in 2015, so results from these studies can be challenging to interpret.[8]

Multimodal Cancer Treatment Effects on Nutrition

Surgery

Cancers of the head and neck regions, such as nasopharyngeal sarcoma, are rare in children but have a significant impact on nutritional status before and after surgery because of the impact on swallowing. Malignancies involving the gastrointestinal (GI) tract, such as hepatoblastoma, neuroblastoma, renal tumors, sarcomas, and Burkitt's lymphoma, can cause changes in motility and nutrient delivery, and affect digestion and absorption before surgical resection.[14] Postoperative complications from GI tract or intraperitoneal organ surgery may include impaired swallowing function, decreased gastric capacity or emptying, ileus of the small bowel, and malabsorption from altered bowel length and integrity.

Radiation Therapy

Radiation therapy uses beams or particles of energy in high doses to destroy cancer cells and limit their ability to replicate.[18] Radiation can be used as an independent therapy but is often used in conjunction with surgery and chemotherapy.[19] Complications arise from radiation therapy because healthy cells within the radiation field are inevitably damaged during treatment. Newer radiation modalities, such as proton beam radiation, decrease radiation exposure to normal healthy cells thereby decreasing toxicity. Expected nutrition-related side effects, which are based on the location of the radiation field, can be found in Table 27-1.[21,22]

TABLE 27-1. Nutrition-Related Side Effects of Radiation Therapy[21,23]

Location	Adverse Reaction
Central nervous system Brain and spinal cord	Nausea/vomiting Fatigue Loss of appetite Alterations in pituitary functions Growth failure
Head and neck Tongue, larynx, pharynx Oropharynx, tonsils Salivary glands	Xerostomia Sore mouth/throat Dysphagia Mucositis Altered taste and smell Fatigue Loss of appetite
Abdomen and pelvis Gastrointestinal tract, reproductive organs Rectum, colon, testicles	Nausea/vomiting Diarrhea Abdominal cramping Bloating Gas Enteritis and colitis Lactose intolerance Fatigue Loss of appetite

The GI tract is the most susceptible to nutrition effects of radiation.[22] Mucositis, which is the inflammation of mucosal membranes lining the digestive tract, can range from moderate to severe and can occur anywhere from the mouth to the anus. It may result in malabsorption of nutrients, diarrhea, and severe pain both with and without oral intake. Diarrhea from abdominal/pelvic radiation results in decreased absorption of whatever nutrients the child does manage to consume. The effect of radiation on appetite depends on the radiation type, involved field, total radiation dose, and the number of fractions received.[20,23,24]

Additional oral complications of head and neck radiation and certain chemotherapy agents include dysgeusia, anosmia, and xerostomia, which can significantly alter oral intake because of decreased palatability or decreased tolerance of certain textures. Though these complications

generally subside, they can create long-standing food aversions.[16,25] Tooth development and integrity of existing teeth may also be compromised as a result of head and neck radiation.[26]

Acute side effects of radiation may begin as early as 1 week from initiation and last several weeks after the final fraction. When pediatric patients require general anesthesia for daily radiation therapy, fasting requirements may result in decreased enteral intake. In tube-fed patients, adjusted feeding schedules and calorically dense formulas are potential strategies that can be implemented to meet nutritional needs within the time constraints.

Chemotherapy/Immunotherapy/Targeted Therapy

Classic cytotoxic chemotherapy works by inhibiting the division of rapidly dividing cells.[27] Although cancer cells are the main target, rapidly dividing normal cells, including those of the mucosa of the GI tract, taste buds, hair, and bone marrow, are equally affected. The effect of chemotherapy on the patient's nutrition status is associated with the combination of chemotherapy and other therapies used, dose, administration route, and treatment duration (see Table 27-2).

TABLE 27-2. Complications of Select Chemotherapy and Targeted Therapies Agents[209,210]

Chemotherapy Agent	Nausea/ Vomiting[a]	Anorexia	Mucositis	Diarrhea	Constipation	Electrolyte Derangements	Xerostomia	Taste Alteration
Asparaginase	3							
Azacitidine	4	X	X	X	X			
Bendamustine	3	X	X	X	X			X
Bleomycin	1	X	X					
Brentuximab	2	X		X	X			
Carboplatin	5			X	X	↓ Ca, Mg, K, Na		X
Cisplatin	5	X	X	X		↓ Ca, K, Mg, P		X
Cyclophosphamide	3	X	X				X	
Cytarabine	4	X	X	X				
Dactinomycin	5	X	X	X	X	↓ Ca		
Daunorubicin	4	X	X	X				
Doxorubicin	3	X	X	X				
Etoposide	2	X	X	X	X			
Fluorouracil	2	X	X	X				
Gemcitabine	2	X	X	X	X			
Hydroxyurea	1			X	X	↓ Mg		
Idarubicin	3		X	X				
Ifosfamide	3							
Imatinib	3	X		X	X	↓ Ca, K		
Irinotecan	4	X	X	X	X			
Lomustine	4		X					
Mercaptopurine	2	X		X				
Methotrexate	3	X	X	X				
Mitoxantrone	3	X	X	X	X	↓ Ca, K, Na		
Nelarabine	2	X	X	X	X	↓ K, Ca, Mg		
Procarbazine	2	X	X	X			X	
Rituximab	1			X		↓ P		
Temozolomide	3	X		X	X			
Thioguanine	1	X	X					
Topotecan	2	X	X	X	X			
Venetoclax	2		X	X	X	↑ K; ↓ Ca, P, Na		
Vinblastine	3	X	X	X	X			
Vincristine	1	X	X	X	X			
Vinorelbine	2	X	X	X	X			

Ca, calcium; K, potassium; Na, sodium; P, phosphorus.

[a] Most emetogenic = 5; least emetogenic = 1

The most common nutrition-related side effect of cytotoxic drugs is nausea and vomiting, but with modern antiemetics, the degree of emesis is much less severe. Taste changes, along with anticipatory nausea, lead to anorexia with a loss of interest in eating and subsequent malnutrition. Chemotherapy can lead to mucositis, changes in digestion changes, and nutrient malabsorption.[3,28] Nutrition-related side effects of select

chemotherapies, immunotherapies, and targeted anti-cancer therapies can be found in Table 27-2.

Direct Effects of Cancer on Nutrition Status

Metabolic Effects

One of the most severe metabolic effects of cancer is cancer cachexia. The American Society of Clinical Oncology defines cancer *cachexia* as a multifactorial syndrome characterized by loss of appetite, weight, and skeletal muscle leading to fatigue, functional impairment, increased treatment-related toxicity, poor quality of life, and reduced survival.[33] There is concern regarding the lack of recent research on pediatric-specific criteria for cancer cachexia.[34] Metabolic alterations due to cachexia result in weight loss from diminished muscle and adipose tissue, which compounds the effects of inadequate intake and anorexia. Research has demonstrated that glucose, protein, and lipid metabolism changes in cancer patients cause weight loss even before they experience decreased appetite and oral intake.[36,37]

Psychosocial Effects

All pediatric cancer patients and their families should receive psychological support throughout treatment and survivorship partly due to the multifactorial impact on nutrition status. Cancer therapy can negatively impact emotional well-being, which can be associated with anxiety, depression, poor body image, and malaise.[43] Oral aversions are also common because of the negative experiences with eating and food resulting from therapy-related side effects.[44] A specialized feeding program may be necessary to help overcome food aversions and resume pretreatment eating habits and oral intake.

Evaluation of Nutrition Status and

Determination of Nutrient Requirements

Assessment of Nutrition Status

Determining nutrition status and recognizing the risk for or presence of malnutrition at diagnosis is essential for nutritional supportive care.[45] This task can be challenging to assess based on weight or appearance alone because large tumor burdens may disguise the loss of adipose and lean muscle mass. The nutrition status of the pediatric oncology patient was previously categorized using guidelines developed by the 2008 Children's Oncology Group, Cancer Control, Nutrition Sub-Committee.[46] These guidelines preceded the development of the consensus statement from the Academy of Nutrition and Dietetics and the American Society for Parenteral and Enteral Nutrition regarding pediatric malnutrition indicators.[8,47] Table 27-3 contains components of a nutrition assessment that are commonly used in children with cancer.

TABLE 27-3. Components of a Nutrition Assessment for Pediatric Oncology and HSCT Patients[211]

Category	Components
Medical history	Diagnosis stage and date Past medical history Medication history Anticipated therapy protocol Malnutrition history
Anthropometrics[a]	Weight history BMI/weight-for-age Height-for-age Recent growth trends % Ideal body weight % Usual body weight % Diagnosis weight Mid-arm circumference Malnutrition assessment
Food and nutrition-related history	Current intake (amounts, stage, feeding times) Usual intake Feeding behavior Modified oral intake Tube feeds (including enteral access) Parenteral nutrition Vitamin/mineral supplementation
Gastrointestinal symptoms/side effects	Nausea Vomiting Constipation Diarrhea Dry mouth Taste changes Mouth sores Difficulty swallowing Early satiety
Laboratory assessment	Electrolytes Blood glucose Serum proteins Absolute neutrophil count Complete blood count Liver function tests

Category	Components
Quality of life	Activity level Family support system Depression/anxiety Pain Treatment plan Resources

Various screening guidelines for nutritional status have been developed and tested in recent years, and currently, only the nutrition screening tool for childhood cancer (SCAN; see Appendix 27-1) has been validated for assessing malnutrition risk in the pediatric oncology population.[48–54] The Oncology Nutrition Practice Group of the Academy of Nutrition and Dietetics has also developed medical nutrition therapy guidance for adult medical, surgical, and radiation oncology patients that may serve as a resource for the pediatric population, and certainly for the adolescents and young adults frequently treated in pediatric oncology centers.[55]

Energy and Protein Needs

Calorie and protein needs can be difficult to assess in the pediatric oncology population as they are impacted by current nutrition status, disease state, and therapy protocol. Standard calculations used for nutritional assessment in pediatric patients are presented in Chapter 30, "Assessment of Nutrition Status by Age and Determining Nutrient Needs." An activity/stress factor may need to be utilized with these formulas, although weight loss tends to correlate with decreased oral intake rather than increased energy expenditure in this population.[56] Protein needs are increased to facilitate preservation and maintenance of lean body mass, and recommendations are not based on serum albumin and prealbumin levels. Nitrogen balance may be useful to assess protein status but is inaccurate in patients with vomiting, diarrhea, and renal insufficiency, and 24-hour urine collections may be difficult. Given these complexities, monitoring of protein intake is imperative to ensure patients are meeting their protein needs.

Outcome Measures

Biochemical Evaluation

Laboratory tests should be closely monitored from initial nutrition assessment through repletion. Basic electrolytes (sodium, potassium, chloride, bicarbonate), glucose, renal function (creatinine, blood urea nitrogen), minerals (calcium, phosphorus, magnesium), liver function tests (alkaline phosphatase, aspartate aminotransferase, alanine transaminase, γ-glutamyl transferase, total bilirubin), and lipids (triglycerides and cholesterol) should be assessed. Additional laboratory data can be obtained if the clinician suspects vitamin and/or mineral deficiencies such as vitamin D. Because of electrolyte wasting potential with certain chemotherapy agents, frequent lab monitoring may be indicated. Additional information about checking nutrition labs can be found in Chapter 26, "Evaluation and Monitoring of Pediatric Patients Receiving Specialized Nutrition Support."

Anthropometric

Physical examination is an important aspect of a nutrition evaluation. Promoting consistent growth along the chart curve z-scores is the goal, therefore monitoring linear growth (in addition to weight trends) is essential for long-term assessment and identification of malnutrition.[8,47,57] Growth should be plotted and monitored for each patient at least monthly on weight-for-age, length/height-for-age, body mass index (BMI) for age (>2 y), weight-for-length (< 2 y), and head circumference (<3 y) charts. Additionally, weight measurements may be impacted in children with large mediastinal or abdominal tumors (such as lymphoma, hepatoblastoma, Wilms' tumor, or neuroblastoma) at presentation or those with edema due to corticosteroid use.[3] In these cases, a mid-upper arm circumference measurement can be a valuable tool for assessing malnutrition and also for monitoring growth trends.[58] For patients who have undergone amputations, Appendix 27-2 provides standardized corrections.

Treatment Tolerance

Studies suggest a better tolerance of oncologic treatment with optimal nutrition status, while delays in treatment are seen more often in those with poor nutrition status.[3] The metabolism of chemotherapy is also affected by

fat and muscle mass, a reflection of nutrition status, which in turn can affect efficacy and tolerance of therapy.[3] Studies have shown negativ weight impacts at either extreme (underweight or obese) on treatment-related toxicity, event-free survival, and overall morbidity, particularly in acute lymphoblastic leukemia (ALL).[7,59]

Children with other complex medical diseases and malnutrition also tend to have longer hospital admissions.[60,61,12] A review of studies conducted on nutrition status and associated morbidities reported that intervention with intravenous (IV) nutrition support and enteral supplementation resulted in better adherence to radiation and chemotherapy treatment schedules.[62]

Nutrition Status and Outcome

Studies on children with cancer have shown a relationship between outcome and nutrition status.[63,64] Results have been published associating poor survival outcomes in both malnourished and children with obesity and adolescents specifically with leukemia.[6] Suboptimal nutrition status before or during therapy can negatively impact treatment tolerance, increase infection and hospitalization rates, and decrease quality of life and survival.[2,62,65]

Selection of Nutrition Support Route

Nutrition support should be individualized for each child, and a nutrition plan should be developed based on the patient's nutrition assessment, disease type and stage, treatment, and quality-of-life considerations. Studies have shown that pediatric patients who receive intervention from a registered dietitian during active treatment have improved weight and nutrition status throughout therapy.

Enteral Nutrition

Oral Nutrition

Oral nutrition is important to promote normalized and developmentally age-appropriate feeding in infants and children and should be encouraged when deemed medically safe. About one-third of patients receiving chemotherapy

and/or radiation demonstrate food aversion. Supportive care measures to improve oral intake include appetite stimulants, anti-emetics, management of electrolyte supplements, and behavioral therapy, which are discussed in more detail in the next section. Many pediatric patients on oral diet alone have significant weight loss and muscle wasting and need to be supported by other means, such as enteral tube feeding.

Enteral Tube Feeding

General information about enteral tube feeding (ETF) is described in Chapter 32, "Enteral Nutrition Support." For children with cancer, ETF is an effective method of maintaining nutritional status, preventing further weight loss, and reversing malnutrition.[68,69] Feeding the GI tract directly via oral or ETF should be used as the first-line treatment over intravenous parenteral nutrition whenever possible.[70] Formula selection is complex and should be based on standard nutritional assessment methods and may need to be modified throughout treatment. Education regarding the potential need for a feeding tube and the benefits for nutritional and treatment outcomes should be a priority during counseling and presented positively to facilitate better acceptance of nutrition intervention.[68] Clinicians should avoid presenting ETF as a negative consequence of poor oral intake as doing so may perpetuate stress and frustration.

Feeds can be provided enterally via nasogastric (NG), nasojejunal (NJ), gastrostomy tube (GT), gastro-jejunostomy (GJ), or jejunostomy tubes (JT). Gastric feeds, whether via NG or GT, are appropriate for most children with cancer. GT, GJ, or JT may have additional benefits for oncology patients as they bypass the issue of tube displacement with emesis and prevent needing tube replacement during periods of mucositis. Children undergoing cancer treatment may require additional feeding modifications such as a combination of bolus and continuous methods via a feeding pump, since a controlled rate can improve tolerance.[68]

Parenteral Nutrition

Parenteral nutrition (PN) is commonly used in children with cancer because of the high risk of gastrointestinal toxicity associated with disease and treatment side effects.[70] Reported benefits of PN include reversal or

prevention of malnutrition, restoration of immune competence, and enhanced tolerance of antineoplastic therapy.[71] Oncology patients with compromised nutrition status prior to PN initiation are at risk of refeeding syndrome when nutrition support is initiated, and advancement should be monitored closely.[72,73] When children are unable to consume adequate calories for multiple days because of uncontrollable vomiting, typhlitis, severe mucositis, or intestinal obstruction, PN may be necessary.[75]

Complementary and Alternative Medicine and Integrative Medicine

Patients with chronic diseases (including cancer) and their families often look to resources outside of conventional medicine during and after treatment.[76] Complementary medicine is used in conjunction with conventional medicine, while alternative medicine replaces the Western approach. Integrative medicine combines standard care with complementary and alternative medicine (CAM) with a holistic focus on wellness rather than on the treatment of disease.[77] The use of CAM in pediatric oncology has been reported in up to 84% of patients in recent years, and CAM has become much more mainstream.[76]

In 2017, the American Academy of Pediatrics (AAP) published a clinical report as an update to their 2008 policy statement on the use of CAM, noting its increasing popularity; delineating its many components; and identifying areas of concern related to safety, lack of scientific data, and ethical/legal issues.[78]

Complications of Cancer Treatment Affecting Nutrition Status

Children with cancer are at significant risk for complications that have direct and indirect impacts on nutrition status. Nutrition intervention strategies for specific treatment-related symptoms should be implemented for all patients as outlined in Table 27-4.[81]

TABLE 27-4. Nutrition Strategies for Treatment-Related Symptom Management[83]

Symptom	Dietary Intervention Strategies
Nausea/vomiting	Small frequent meals; carbohydrate-based foods; nonacidic beverages; cold clear foods and beverages; avoid extremely hot/cold and heavily seasoned foods; avoid high-fat content foods
Anorexia	Small frequent meals; nutrient-dense foods and supplements; carbohydrate and protein modulars; pleasant eating atmosphere; dine with the child; vary food colors/flavors/textures
Diarrhea	Low-fat, cold, or room temperature foods; avoid caffeine; encourage adequate fluid intake
Dysgeusia	Herbs, spices, and marinades; cold non-odorous foods; fruit-flavored beverages; good oral hygiene; mint (but not alcohol-based) mouthwashes; lemon-flavored beverages; sour candies
Mucositis	Soft diet; smooth, bland, moist foods; frozen slushes/ices/ice cream; high-calorie liquid beverages
Xerostomia	Moist foods; encourage liquids with meals; add sauces/gravy/butter/broth; add vinegar and lemon to stimulate saliva; good oral hygiene

Nausea and Vomiting

Two of the most common side effects of cancer treatment are nausea and vomiting.[82] These symptoms may result directly from tumor location (brain, GI tract), treatment (chemotherapy, radiation), and/or anxiety. Management involves various pharmacologic agents (see the section entitled "Gastrointestinal Supportive Medications") as well as dietary interventions, including small frequent meals, adequate hydration with electrolyte-containing beverages, avoidance of high fat or greasy foods, and inclusion of foods such as toast, crackers, and dry cereal.[83]

Taste and Smell Alteration

Changes in taste and smell are also common during pediatric cancer treatment because of tumor location and the effect of the therapy on tastebuds and mucosa.[67] Good oral care such as tooth brushing, oral rinses, and antiseptic mouthwashes can help counteract these changes.[67] In

general, using plastic utensils and keeping foods cool or at room temperature can reduce unpleasant tastes and odors.[67]

Infection

Most cancer and HSCT therapy results in suppression or ablation of the bone marrow, causing a decrease in white blood cells, platelets, and red blood cells for days to weeks, thus poor nutrition and increased infection risk have been reported in children with cancer.[65,85] Infections affecting the GI tract, such as *Clostridium difficile*, and GI viruses can lead to severe diarrhea, intolerance of oral intake, and ETF. Antiviral, antifungal, and antibiotic medications used for treatment can cause loss of appetite, nausea, vomiting, diarrhea, and malabsorption.[89]

Mucositis

Mucositis is inflammation and breakdown of the mucosal lining that can occur anywhere along the GI tract and is a side effect of many chemotherapy agents and radiation. It is particularly common during HSCT because of the conditioning regimens used, with incidence estimated at 75%–100% of patients undergoing transplantation.[90] Severity ranges from mild erythema to extensive mucosal sloughing causing enteritis-related malabsorption.[90] Oral intake is also nearly impossible, thus requiring alternate modalities for nutrition support until the patient can meet their energy and hydration needs by mouth.[91,92]

Pancreatic Insufficiency

Acute pancreatitis is a known side effect of certain chemotherapy agents, such as asparaginase, but is also seen in approximately 5% of children undergoing HSCT.[86,94,95] Pancreatic insufficiency can result in compromised exocrine and endocrine function, creating a need for pancreatic enzymes and/or insulin.

Anorexia

Anorexia, or loss of appetite, is a common side effect of cytotoxic therapy, and may be perpetuated by multiple cycles of chemotherapy and other

treatments.[3,96] Although typically seen as an independent symptom, many variables can cause anorexia in children, such as weight loss, dehydration, persistent vomiting, early satiety, and depression.

Bacterial Overgrowth

Bacterial overgrowth is the malabsorptive state that results from a disruption in the normal microbiome of the small intestine due to an overgrowth of opportunistic bacteria.[97] Studies have shown altered gut microbiota during HSCT associated with long-term use of antibiotics, prolonged periods of NPO (nil per os or "nothing by mouth"), and minimal enteral stimulation, among other factors.[97,98] Bacterial overgrowth can present as abdominal pain, diarrhea, and feeding intolerance.

Diarrhea

Diarrhea causes a loss of fluids and electrolytes as well as nutrient malabsorption and can be linked directly to specific chemotherapies, radiation to the abdominal and pelvic areas, and abdominal surgery.[3,99] Other potential causes of diarrhea during therapy include infections, antibiotics, adverse drug effects, and stress.

Gastroesophageal Reflux

Gastroesophageal reflux (GER) can be caused by specific oncology treatment modalities (eg, steroids, radiation) as well as significant psychosocial stressors. Management may involve feeding adjustments as well as pharmacological intervention.

Hematopoietic Stem Cell Transplant

Hematopoietic stem cell transplantation (HSCT) is performed to replace diseased and defective bone marrow and restore hematopoietic and immunologic function following ultra-high-dose chemotherapy and/or radiation.[102] HSCT is a broad category that encompasses bone marrow transplantation, peripheral blood stem cell transplantation, umbilical cord blood transplantation (named for the source of hematopoietic stem cells), as well as newer cellular or genetic therapies.[103] HSCT is a treatment option

for children with a variety of potentially fatal malignant and nonmalignant diseases including many types of cancers, immunodeficiency syndromes, severe aplastic anemia, sickle cell anemia, hemophagocytic lymphohistiocytosis, and inherited metabolic disorders like Krabbe's disease and Hurler's syndrome, among many others. Examples of diseases treated by an autologous transplant (when patients receive their own stem cells) include solid tumors like high-risk neuroblastoma and brain tumors. Diagnoses such as acute leukemia, Hodgkin's and non-Hodgkin's lymphoma, myelodysplastic syndrome, and immunodeficiencies are treated with an allogeneic transplant (where the patient receives stem cells from another person). The donor can be a sibling, parent (haploidentical), or unrelated person.

Nutrition Evaluation and Assessment

Children undergoing HSCT are at increased risk of malnutrition, and it is critical to assess their needs, anticipate problems, and institute appropriate preventive nutrition support in a timely manner. The toxicity of the conditioning regimen affects the integrity of the GI tract, causing mucositis, nausea, vomiting, and diarrhea.[106] Table 27-5 details drugs commonly used during HSCT and their side effects. These symptoms may be further exacerbated by post-transplant complications including graft versus host disease (GVHD), infection, engraftment, or cytokine release syndrome, as well as the standard use of multiple antibiotics and immunosuppressive medications.[106] The nutrition status in some patients coming to HSCT may already be suboptimal due to symptomology associated with disease, previous treatment, prolonged hospitalizations, and other problems that have affected their ability to maintain adequate nutritional intake.

TABLE 27-5. Side Effects of Some of the Drugs Commonly Used During HSCT[100]

Drug	Usage	Side Effect
Steroids	Immunosuppressive	Adrenal suppression, CNS/psychiatric behavioral changes, cushingoid features, GI effects (ulcers, gastritis, abdominal distention), hyperglycemia, increased risk of infection, weight gain, osteoporosis, fluid and sodium retention, cardiomyopathy, hypercholesterolemia, hypertriglyceridemia, gut infection
Methotrexate	Immunosuppressive	Mucositis, nausea, vomiting, diarrhea, hepatotoxicity, nephrotoxicity, fatigue, myelosuppression, hepatic and renal toxicities
Cyclosporine	Immunosuppressive	Hepatotoxicity, diabetes mellitus, low blood counts, nephrotoxicity, significant hyperkalemia, hypomagnesemia, hepatotoxicity, hyperglycemia, hyperlipidemia, hypercholesterolemia, nausea, vomiting
Tacrolimus	Immunosuppressive	Diabetes mellitus, low blood counts, nephrotoxicity, electrolyte derangements (most notably hypomagnesemia), hypercholesterolemia, hyperglycemia, hyperlipidemia, elevated hepatic enzymes, nausea/vomiting, anorexia, diarrhea
Sirolimus	Immunosuppressive	Edema, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, hypokalemia, constipation, nausea, abdominal pain, low blood counts,
Cellcept	Immunosuppressive	Nausea, vomiting, diarrhea, anorexia, renal impairment, neutropenia, low blood counts, edema, hypercholesterolemia, hyperglycemia, hyperlipidemia, hypocalcemia, hypokalemia, hypomagnesemia,

Drug	Usage	Side Effect
		hypophosphatemia, constipation, hepatoxicity
Antithymocyte globulin	Immunosuppressive	Nausea, vomiting, constipation, diarrhea, abdominal pain, low blood counts, hyperkalemia, hypokalemia
Busulfan	Immunosuppressive	Edema, hypomagnesemia, hypokalemia, hypocalcemia, hyperglycemia, nausea, vomiting, mucositis/stomatitis, anorexia, constipation, diarrhea, abdominal pain, xerostomia, low blood counts, hepatotoxicity, nephrotoxicity, increased risk of GVHD and infection
Fludarabine	Immunosuppressive	Edema, nausea, vomiting, anorexia, diarrhea, low blood counts
Rituximab	Immunosuppressive	Hypophosphatemia, weight gain, diarrhea, nausea, low blood counts, hepatotoxicity,
Thiotepa	Immunosuppressive	Mucositis, low blood counts, hepatotoxicity
Alemtuzumab	Immunosuppressive	Thyroid abnormalities, diarrhea, nausea, low white blood counts
Carboplatin	Immunosuppressive	Hypocalcemia, hypomagnesemia, hypokalemia, hyponatremia, GI upset, nausea, vomiting, low blood counts, hepatoxicity, nephrotoxicity
Cytarabine	Immunosuppressive	Abdominal pain, anorexia, diarrhea, nausea, vomiting, mucositis, low blood counts, hepatotoxicity, nephrotoxicity
Carmustine	Immunosuppressive	Nausea, vomiting, constipation,
Clofarabine	Immunosuppressive	Edema, abdominal pain, anorexia, diarrhea, mucositis, nausea, vomiting, low blood counts, hepatotoxicity, nephrotoxicity
Etoposide	Immunosuppressive	Nausea, vomiting, anorexia, diarrhea, hepatotoxicity, metabolic acidosis, low blood counts

Drug	Usage	Side Effect
Melphalan	Immunosuppressive	Peripheral edema, hypokalemia, hypophosphatemia, abdominal pain, diarrhea, constipation, anorexia, nausea, vomiting, low blood counts
Treosulfan	Immunosuppressive	Peripheral edema, abdominal pain, constipation, diarrhea, nausea, vomiting, decreased blood counts, hepatotoxicity
Acyclovir/Valacyclovir	Antiviral	Nephrotoxicity, decreased blood counts, malaise, anorexia, nausea, vomiting, diarrhea, elevated hepatic enzymes, hyperbilirubinemia
Cefepime	Antibiotic	Increased risk of C. diff, nausea, vomiting, diarrhea
Voriconazole/Azole class	Antifungal	AKI, hyperkalemia, hypokalemia, diarrhea, nausea/vomiting, hepatotoxicity
Amphotericin	Antifungal	Hypokalemia, hypocalcemia, hypomagnesemia, hyponatremia, anorexia, diarrhea, nausea/vomiting, nephrotoxicity
Caspofungin/ Micafungin	Antifungal	Edema, diarrhea, nausea/vomiting, decreased blood counts, increased risk of nephrotoxicity, hepatotoxicity

Abbreviations: AKI, acute kidney injury; C. diff, Clostridioides difficile; CNS, central nervous system; GI, gastrointestinal; GVHD, graft-vs-host disease.

A complete nutrition assessment should be performed at the beginning of transplant consultation and coordination. The interval between consultation and admission for transplant may span many weeks to months and can be used as an opportunity to educate and improve or maintain adequate nutrition status to best prepare the patient for transplant. Assessment and evaluation are important before, during, and after the transplant process because nutrition status and nutrient needs continually change. A detailed list of components for assessment of the general oncology and HSCT patient can be found in Table 27-3.

Anthropometric Assessment

Weight, height, and BMI should be assessed at the time of admission and throughout the transplant and recovery process. Care must be taken when evaluating anthropometric data, as body weight and BMI are easily affected by hydration, edema, and sinusoidal obstruction syndrome (SOS) which may occur in the early posttransplant period. A baseline mid-upper arm circumference (MUAC) should be obtained and monitored, as fluid shifts will not affect this measurement.[108]

Nutrition Requirements of the Pediatric HSCT Patient

Energy and Protein Needs

Patients undergoing HSCT show changes in energy requirements throughout the process.[109,110] During the initial period, patients are in a hypermetabolic state with increased catabolism due to mucositis, fever, tissue repair, and marrow regeneration. An increase in the metabolic rate can also be caused by the conditioning regimen, fevers, and post-transplant complications.[111] As a result, the caloric needs of the HSCT patient have been reported to be as high as 150% of the basal metabolic rate (BMR) of non-stressed, well-nourished patients and 180%–200% of the BMR of malnourished patients.[71,74,96] Conversely, a study observed significant decreases in resting energy expenditure (REE) following allogeneic stem cell transplant in patients with leukemia and aplastic anemia, with the return of energy expenditure to pretransplant levels after engraftment.[110] Studies assessing energy requirement in HSCT are limited, and further research is needed to better determine the caloric needs of children during and post-transplant. Using indirect calorimetry to assess caloric requirement is the gold standard; however, access to a metabolic cart is often limited. Protein requirements are increased to minimize loss of lean body mass and promote tissue repair. Refer to Table 27-6 for the calorie and protein requirements of the HSCT pediatric patient.

TABLE 27-6. Calorie and Protein Requirements of Pediatric Patients Undergoing HSCT[71,74,81,113]

Age	Calories	Protein (g/kg/d)
0–12 mo	BMR × 1.6–1.8	3
1–6 y	BMR × 1.6–1.8	2.5–3
7–10 y	BMR × 1.4–1.6	2.4
11–14 y	BMR × 1.4–1.6	2
15–18 y	BMR × 1.5–1.6	1.8
>19 y	Refer to adult energy equations	

Fluid Needs

In general, daily fluid needs can be assessed using the Holiday-Segar method, taking into consideration the various medical factors that impact daily fluid balance during HSCT.[112] Fluid needs are increased with fever, GI losses (eg, vomiting, diarrhea), mucositis, open skin wounds, and other factors.[74] Liver and kidney dysfunction may lead to fluid retention and require fluid restriction. In addition to PN and enteral (oral or ETF) intake, patients can receive significant additional fluid with medication administration and blood products which may contribute to total volume intake. Close monitoring of fluid status is very important with awareness that fluid shifts may result in weight changes that do not reflect nutrition status.

Vitamin and Mineral Needs

Specific vitamin and mineral requirements for patients undergoing HSCT have not been determined. The nutrition support regimen should meet 100% of the dietary reference intake of vitamins and minerals or 100% of the age-appropriate injectable multivitamin for patients receiving PN. If oral intake or ETF does not meet the vitamin and mineral needs, then an iron-free multivitamin and mineral supplement(s) should be provided. Generally, iron supplementation is contraindicated during HSCT due to frequent blood transfusions and the associated iron overload. The risk of vitamin and mineral deficiencies is higher if patients have diarrhea, vomiting, and malabsorption. Thiamine, vitamin C, vitamin K, vitamin D, calcium, and

zinc deficiency have been noted in children undergoing HSCT. Bone metabolism may also be compromised by various treatment modalities; therefore, serum vitamin D and calcium levels should be monitored and repleted as needed.

Provision of Nutrition Support for the HSCT Patient

The provision of nutrition support is complex for the HSCT patient. The selection of the best route for nutrition support is discussed in greater detail in the general oncology section of this chapter and should be paired with the following considerations that are unique to HSCT.

Oral Route

The HSCT process poses many barriers to adequate oral intake. Patients experience side effects associated with high-dose chemotherapy as discussed earlier, and post-transplant complications can further exacerbate challenges to meet nutritional needs via oral route alone.

Oral intake and appetite in the HSCT patient do not return to a normal state until 4–6 weeks post-transplant. In adults, severity of oral mucositis and GVHD are the most significant factors affecting return of oral intake.[114,115] Use of appetite stimulants may be useful to help boost appetite in patients who have engrafted and do not have GVHD.

Sometimes even after return of oral intake, nutrition status may be compromised due to malabsorption. Feeding, speech, and occupational therapies should be considered for those who have developed avoidance. Reintroduction and reliance on energy intake via the oral route after HSCT is a slow process and needs careful monitoring of symptoms and ongoing assessment of nutrition status.

Diet Restrictions

Various iterations of diet restrictions have been recommended for HSCT patients due to their immunocompromised status. Neutropenic diets, a historic standard during HSCT, aim to restrict foods that are believed to contain large amounts of potentially pathogenic bacteria which can cause infections in the immunocompromised patient. Studies have shown inconsistent results regarding the effect of dietary modification on the

incidence of foodborne illness during HSCT.[116,117] For this reason, some centers use a more liberal approach to dietary restrictions, emphasizing safe food handling and allowing patients to eat a greater variety of foods (such as well-washed fresh fruits and vegetables) not traditionally included in a neutropenic diet.[118,119] A recent trial investigating the role of restrictive diet after adult HSCT found no significant differences in infection rates, acute GVHD, or feeding outcomes.[120]

Enteral Tube Feeding

The benefits of enteral nutrition (oral and ETF) are well known for the oncology patient's nutritional status. Evidence that ETF nutrition is an effective modality to support the HSCT patient has been lacking until recent years. Adult HSCT guidelines now recommend ETF as the first-line nutrition support modality (over PN) during HSCT; however, no specific pediatric guidelines exist.[121] Previously, ETF during transplant was not preferred for many reasons, including concerns for intolerance, malabsorption of nutrients, and complexities associated with nasoenteric tube placement in the presence of pancytopenia and mucositis.[115,122] If GI tolerance to full nutrition needs via ETF is impaired, trophic rates of ETF can be used in conjunction with PN to meet nutritional needs, provide the benefit of protecting gut integrity, and reduce the risk of bacterial translocation.

Several studies have shown ETF to be feasible and cost effective. It can also be as successful as PN in preserving the nutrition status of children undergoing allogeneic HSCT.[121,123–125] Enteral tube feeding may provide favorable benefits regarding non-nutritionally related considerations such as GVHD and platelet engraftment for allogenic transplant patients when compared to the use of PN alone.[121,126,127] Studies comparing ETF to PN in the heterogenous pediatric transplant population are lacking; however, this is an area of current study. Enteral tube feeding prescriptions unique to HSCT have not been defined. For patients without pre-existing enteral access, successful tube placement has been achieved between days –2 and +2.[121]

Parenteral Nutrition

In the setting of GI toxicities leading to poor oral intake and intolerance to ETF, PN has traditionally been used to support pediatric patients during the transplant process. While PN is associated with several risks, it is often transiently required for the HSCT patient who cannot tolerate adequate nutrition via the oral or enteral route.

Limited standardized criteria exist as to when PN should be initiated since most studies have been done on heterogeneous HSCT patient populations and have small sample sizes. This is an area of active research, and clinicians are again encouraged to continue to review the literature in conjunction with ETF during HSCT.

Nutrition Monitoring During HSCT

Monitoring and evaluating the efficacy of nutrition support in patients undergoing HSCT is very important and involves a complex process. Unfortunately, data are scarce to support the use of a single specific test or a battery of tests that could be used broadly in most clinical situations. Clinical judgment should be paired with the following considerations and published data.

Fluid and Electrolytes

Multiple factors, including the type and quantity of feeding, impact fluid and electrolyte status. Decisions about the volume and composition of ETF or PN must be based on the state of fluid and electrolyte balance, which must be monitored daily. Mucositis, diarrhea, vomiting, excessive salivation, fever, and other factors increase fluid loss. Fluid retention and electrolyte abnormalities can be seen at the time of engraftment, with toxicities such as SOS and renal insufficiency and as side effects of HSCT-specific medications. Severe inflammatory reactions in the post-transplant or cellular therapy period may lead to cytokine release or capillary leak syndrome and third-spacing of fluids. In these situations, the weight may be increased, but the intravascular compartment is depleted. Frequency of electrolyte monitoring, standing provisions, and repletion needs will change throughout the transplant period in response to conditioning agents and

clinical course. See Table 27-7 for the suggested schedule for monitoring of biochemical indices.

TABLE 27-7. Suggested Schedule for Monitoring Blood Biochemical and Other Indices During Early Stages of HSCT

Laboratory Test	Frequency
Sodium, potassium, chloride, carbonate, BUN, creatinine, calcium, magnesium, phosphorus	Every day until stable on PN, then 3 times per week while on long-term PN
Ionized calcium	With consistent low-serum calcium
LFTs, albumin, total bilirubin	3 times per week until day +30, then weekly while on PN
Prothrombin time	Weekly while on multiple antibiotics
Vitamin D (25OH)	Pretransplant; then every 3 months until 1 year
Zinc	When increased losses suspected
Zinc, copper, selenium	Monthly when on long-term PN (4–6 wk)
Triglycerides	Weekly while on intravenous lipid emulsion
Weights	Daily while inpatient, then with every outpatient visit

Abbreviations: BUN, blood urea nitrogen; LFT, liver function tests; PN, parenteral nutrition

Triglycerides and Liver Function Tests

Fasting triglyceride levels should be obtained before administering intravenous fat emulsion (ILE), and non-fasting levels should be taken weekly for the duration of the ILE therapy. Serum triglyceride levels should be monitored weekly if a patient is receiving PN, cyclosporine, corticosteroids, tacrolimus, or sirolimus, all of which can affect levels.[74,113,122] Liver function tests should also be monitored 2 to 3 times per week because they may fluctuate significantly during transplant due to hepatotoxic drugs and associated complications. Careful assessment of

nutritional and non-nutritional etiology of altered values should be considered prior to modifying nutrition support prescriptions.

Micronutrients and Other Biochemical Indices

Patients receiving trace element provisions from PN should have lab values monitored, including copper, ceruloplasmin, selenium, and zinc. Hyperbilirubinemia may also dictate trace element monitoring.[74,113] Zinc is a negative-acute phase reactant causing blood levels to be adversely affected by inflammation or infection, therefore levels do not accurately reflect tissue stores. Interpretation of certain biochemical indices such as low serum albumin, calcium, iron, copper, and retinol-binding protein (vitamin A), must also be evaluated with consideration of the acute-phase response.[128,129]

Growth

Weight trends should be monitored daily with consistent parameters (ie, same time of day, device consistency) throughout the entire transplant period with consideration of fluid shifts.[74] Length or height should be monitored monthly, but one should be mindful that critically ill transplant patients will likely not attain age-expected linear velocity despite the provision of optimal nutrition support. BMI values will be skewed if weights are elevated in the setting of fluid accumulation. BMI has also been reported to be a poor predictor of nutrition status when compared with body cell mass.[107] MUAC has been found to better reflect nutrition status because of limited impact of weight fluctuations.[58] Anthropometric data trends combined with the assessment of caloric and protein intake and fluid balance are critically important and useful for interpreting growth.

HSCT-Specific Complications Impacting Nutrition

Graft-vs-Host Disease

Graft-vs-host disease (GVHD) is caused by an immunologic reaction in allogeneic transplants in which donor-derived T cells recognize the host cells as foreign and attack them. The organs most commonly affected in acute GVHD are the skin (81%), GI tract (54%), and liver (50%).[106]

Skin GVHD usually presents as a rash first which may be misattributed to nutritional deficiencies because of appearance. Symptoms of acute upper GI GVHD include nausea, vomiting, and anorexia, while signs of lower gut GVHD usually include vomiting, abdominal pain, and secretory diarrhea associated with bleeding and cramping.[139] Gut GVHD leads to mucosal degeneration, malabsorption, and protein loss, thus a diet low in fiber, lactose, and greasy/fatty foods may be beneficial.[140] Recent studies suggest reduced rates of gut GVHD with early use of ETF following an allogeneic transplant.[121] Liver GVHD is characterized by cholestasis, though it can be challenging to differentiate from other causes of impaired liver function.[139,141]

Chronic GVHD may involve the skin, GI tract, liver, lungs, eyes, mouth, or bone marrow. Symptoms of chronic gut GVHD may be similar to acute GVHD or may be more subtle (eg, early satiety, strictures). In addition to the previously mentioned risk factors, history of acute GVHD is linked with development of chronic GVHD.[135] Treatment and nutritional interventions, including dietary modifications or PN use, will depend on the severity of the symptoms and the organs involved.

Hepatic Sinusoidal Obstructive Syndrome

Sinusoidal obstructive syndrome (SOS), historically referred to as hepatic veno-occlusive disease is an unpredictable and potentially life-threatening complication of HSCT that impacts both children and adults. Preexisting liver dysfunction, prior transplantation, abdominal radiation, and certain types of conditioning regimens are among the factors that increase the risk for SOS. Severe SOS leading to liver failure, hepatorenal syndrome, and multiorgan failure is associated with a high mortality rate. This damage causes hepatic congestion and portal hypertension.[143,144] The clinical presentation of SOS may peak around day +12 and can include hepatomegaly, ascites, right upper quadrant pain, and weight gain.[142,143] Nutrition support considerations may include manipulation of salt and water balance to minimize extracellular fluid overload.[149]

Gastrointestinal Supportive Care Medications

Gastroesophageal Reflux/Gastrointestinal Dysmotility

GERD and motility disorders may be a manifestation of the malignancy or as an adverse effect of treatment, including chemotherapy, surgery, radiation, and opioid use for pain. Symptoms of GERD and GI dysmotility include the following:

- heartburn
- regurgitation
- chest pain
- rapid or slow gut transit time
- motor or sensory abnormality
- functional obstruction

Such symptoms are non-specific and often overlap with cancer itself and may be acute, chronic, or appear in later years post-cancer treatment. Treatment for GERD and GI dysmotility are discussed in detail later.

Gastrointestinal Motility Medications

Prior to the development of serotonin receptor antagonists to mitigate chemotherapy-induced nausea and vomiting (CINV), motility agents were commonly used in oncology patients. Metoclopramide improves forward motility and increases gastric emptying, but studies have indicated that children are more sensitive to extrapyramidal side effects of metoclopramide, particularly with higher doses used for CINV.[158,159]

Erythromycin, a macrolide antibiotic, has prokinetic effects at low doses compared with higher doses used for antimicrobial effects.[161,162] Typical complications with erythromycin include GI upset (ie, diarrhea, abdominal pain), but these are less likely at the lower dose used for motility. Rare adverse effects of erythromycin include hepatotoxicity, ototoxicity, cardiac arrhythmias, and pyloric stenosis (reported in infants <2 mo old). Use is also limited by tachyphylaxis.

Chemotherapy-Induced Nausea and Vomiting Medications

Antiemetic Guidelines

Antiemetic use in children undergoing cancer treatment is essential because of the high rates of nausea and vomiting from chemotherapy, radiation, and surgery/anesthesia. Multiple national organizations publish guidelines with suggestions and recommendations regarding CINV in the oncology population. The American Society of Clinical Oncology antiemetic guidelines include suggestions regarding radiation-induced emesis.[158] For the pediatric population, the Pediatric Oncology Group of Ontario publishes recommendations related to CINV (see https://www.pogo.ca/healthcare/practiceguidelines/chemotherapy-induced-nausea-and-vomiting/).[163] Those that are endorsed by the Children's Oncology Group are available online (https://www.childrensoncologygroup.org/cog-supportive-care-endorsed-guidelines).[164] These guidelines classify chemotherapy based on its emetogenic potential: high, moderate, low, or minimal. Emetogenic ratings by drug are listed in Table 27-2.

Serotonin Receptor Antagonists

Serotonin receptor (5-HT3) antagonists are the single most effective class of antiemetics for acute chemotherapy-induced nausea and vomiting.[165] All 5-HT3 antagonists come with Food and Drug Administration (FDA)-required labeling of possible QTc prolongation which is important to monitor when used with other medications that also cause QTc prolongation and in patients with history of QTc prolongation.

Neurokinin-1 Receptor Antagonists

Neurokinin-1 (NK-1) receptor antagonists inhibit substance P/NK1 receptor and augment antiemetic activity of 5-HT3 antagonists. Aprepitant (Emend) and fosaprepitant (IV Emend) are NK-1 antagonists that have been found to produce a small reduction in acute nausea and vomiting and a larger reduction in delayed nausea and vomiting. Aprepitant and fosaprepitant are FDA-approved for use in both adults and pediatrics (6 months of age or older and greater than or equal to 6kg) for CINV of highly and moderately emetogenic chemotherapy.

Glucocorticoids

Steroids are often used in combination with 5-HT3 ± NK-1 antagonists for moderately to highly emetogenic chemotherapy and are often used as single-agent therapy for low emetogenic chemotherapy. In hematologic malignancies, steroids are used less frequently for CINV as they are part of the chemotherapeutic regimen.

Phenothiazines

Phenothiazines (prochlorperazine, promethazine) block dopamine receptors in the vomiting center and chemotherapy receptor trigger zone. Though no longer preferred as first- or second-line treatment for CINV, phenothiazines are occasionally useful for breakthrough or refractory CINV. Like metoclopramide, phenothiazines also have an unfavorable side effect profile including extrapyramidal symptoms, dystonia, and drowsiness.

Atypical Antipsychotics

Olanzapine is an atypical antipsychotic that antagonizes dopamine and serotonin receptors but is less likely to cause extrapyramidal side effects. National Comprehensive Cancer Network (NCCN) guidelines recommend its use in acute, delayed, and breakthrough CINV. Fatigue is the main side effect seen at drug initiation with weight gain and increased risk of metabolic syndrome reported with longer use.[169]

Cannabinoids

Cannabinoids (dronabinol) are currently approved for patients with refractory CINV and not responding to the other treatment options mentioned above. The limited data available report promising results in the prevention of CINV when used in children as monotherapy or adjunctive therapy.[170,171] Adverse effects include euphoria or dysphoria, hypotension, tachycardia, increased appetite, dry mouth, and occasional hallucinations with dizziness and drowsiness. A secondary indication that is beneficial in the cancer population is the use of dronabinol for appetite stimulation (for more information, see “Appetite Stimulants” section).

Antihistamines and Benzodiazepines

Antihistamines (diphenhydramine) and benzodiazepines (lorazepam) have been used as adjunctive agents for chemotherapy-induced nausea and vomiting. Independently, neither has great antiemetic activity but the side effect of sedation may help patients sleep through nausea and vomiting symptoms.

Miscellaneous Agents

Other agents used to combat CINV are transdermal patches, such as scopolamine, and integrative non-pharmacological options such as wrist pressure bands, acupuncture, aromatherapy, and mind-body work. Scopolamine antagonizes serotonin and histamine receptors and is only available as a transdermal patch which is placed behind the patient's ear and changed every three days. Typically, scopolamine transdermal patches are used in conjunction with the above options to prevent or treat CINV. Due to its anticholinergic activity, side effects include dry mouth, drowsiness, confusion, and blurry vision.[155]

Appetite Stimulants

Appetite stimulants have been used to prevent weight loss in cancer patients and have been used successfully to increase oral intake and nutrition status in the general pediatric population. While studies in the adult population have shown notable weight improvement, limited data in the pediatric oncology population exist regarding optimal medication, dose, duration, and timing of initiation.[173]

Megestrol Acetate

Megestrol acetate (Megace) is a derivative of progesterone which has an effect of increasing appetite thereby causing weight gain. A recent small randomized, double-blind, placebo-controlled trial of megestrol acetate in pediatric cancer patients showed a mean weight gain of 20%; however, the data also suggested fat body mass increased more reliably than lean body mass.

Cyproheptadine

Cyproheptadine (Periactin) is a serotonin antagonist and a first-generation antihistamine that has been studied as an appetite stimulant in cancer patients. It is currently approved in children for allergic conditions, prevention of cyclic vomiting syndrome, prevention of migraines, and spasticity associated with spinal cord damage, in addition to appetite stimulation.[155] A study in children with cancer found that many had an increase in weight with drowsiness as the only common side effect, although the study was limited because of unclear timing of initiation and limited duration of use.

Cannabinoids

Dronabinol (Marinol) is FDA-approved in adults for treating anorexia in patients with acquired immunodeficiency syndrome and in both adults and children for breakthrough/refractory CINV.[174] Limited data are available for use in pediatric cancer patients with anorexia, although the few available studies noted weight gain.[172]

Tricyclic Antidepressants/Atypical Antipsychotics

In situations where poor appetite appears to be associated with depression or anxiety, the use of antidepressants may improve appetite. The only studied antidepressant that showed weight gain is amitriptyline in females with anorexia nervosa. Studies of atypical antipsychotics, such as mirtazapine and olanzapine, have indicated weight gain and the development of metabolic syndrome is a known side effect. Because of a lack of research and reports of sedating side effects in the pediatric population, the use of these agents has been limited but is growing.[177]

Mucositis

A sub-analysis paper of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology clinical practice guidelines for the management of mucositis reviewed available evidence for managing mucositis in children undergoing cancer treatment.[178] Unfortunately,

because of the diverse pediatric cancer population, the evidence gathered was not as robust as the evidence in the adult population.

Medications for mucositis fit into 2 categories: symptom control or prevention. Most medications have little, if any, effect on the healing rate of the mucositis. Medications used to treat symptoms of mucositis are categorized as basic oral care/mucosal coating agents, analgesics, growth factors, and natural agents (glutamine).

Vitamin and Mineral Supplements

Vitamin and mineral deficiencies in the pediatric oncology population are a concern and small studies have documented deficiencies of vitamins A, C, D, and zinc. If vitamin and mineral deficiencies are suspected based on symptoms and dietary recall, levels should be checked and repletion is advised.[184]

Certain chemotherapy agents work by depriving cancer cells of specific essential vitamins such as methotrexate blocking folate metabolism. Using high-dose supplements (eg, vitamin C) while receiving these agents may affect chemotherapy efficacy. Over-the-counter vitamin and mineral supplements need to be scrutinized for oncology patients. When looking for a brand of supplement, care should be taken when examining the label, as products are not reviewed by the FDA prior to being on the market. The United States Pharmacopeia, National Sanitation Foundation, Underwriters Laboratories, Labdoor, and Consumer Labs are all third-party agencies that certify supplements and test for purity and accuracy in labeling. Additional attention is needed when examining nutritional supplement facts labels, as some brands list the total weight of a mineral salt, not the amount of elemental mineral being supplemented.

Late Effects of Treatment for Survivors

The overall 5-year survival rate for childhood cancer is approximately 85%, and for some cancer diagnoses the 5-year survival rate is >95%.[2,53] Based on these statistics, the United States has approximately 465,000 childhood cancer survivors.[185] The Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult

Cancers extensively review the long-term effects of the treatments used (see www.survivorshipguidelines.org).[186] These guidelines are appropriate for survivors of childhood, adolescent, or young adult cancers 2 or more years following the completion of cancer therapy and provide a variety of recommendations for healthy lifestyle practices post-cancer treatment. The guidelines also include references and patient education materials on a variety of topics.[186]

Gastrointestinal Problems in Survivors

Treatment of childhood cancer can result in chronic problems of the GI system including bowel obstruction, gallstones, pancreatic insufficiency, esophageal stricture, hepatic fibrosis, colorectal cancer, chronic enterocolitis, dysmotility, and dental abnormalities.[189] Symptoms of GI problems can include chronic nausea, vomiting, acid reflux, constipation or diarrhea, dysphagia, pain (eg, swallowing, abdominal), change in appetite, weight loss, blood in the stool, abdominal distention, and jaundice. Radiation doses of 30 Gy (3000 cGy/rads) or higher to the head, chest, neck, pelvis, spine, or abdomen, and surgery in the pelvis or abdomen increase the risk of having late GI complications.[186] Other risk factors include family history of gallstones or colorectal or esophageal cancer, patient history of bowel adhesions (scarring) or bowel obstruction (blockage), use of tobacco, or chronic GVHD.

Endocrine System

Bone Health

Bone is a living growing tissue that comprises the body's skeleton. During treatment for childhood cancer, survivors may not be able to obtain normal peak bone mass and may experience increased calcium loss from the bones, which increases fracture risk.[191] Survivors are also at increased risk for osteopenia and osteoporosis, a result of too little bone formation or too much bone loss, respectively. Current clinical practice guidelines advise a DEXA upon entry into long-term follow-up, typically 2 to 5 years after treatment is completed.[186] If the DEXA is normal, follow-up surveillance can be completed again at 25 years of age when peak bone mass would be established.

General risk factors for osteoporosis and osteopenia include the following:

- Being female, Caucasian, or Asian
- Having a family history of osteoporosis
- Having a small/thin frame
- Smoking
- Having a diet low in calcium or high in salt
- Drinking increased amounts of alcohol, caffeine, or soda
- Lacking weight-bearing exercise

Osteoporosis risk also increases with age. More specific risk factors in survivors of childhood cancer treatment include receipt of methotrexate or corticosteroids or a history of radiation to weight-bearing bones. Drugs including anticonvulsants (barbiturates and phenytoin), estrogen used to suppress menorrhagia during therapy, aluminum-containing antacids, cholesterol-lowering medication, and high-dose heparin for prolonged periods are additional risk factors. Recommendations for decreasing the risk of osteoporosis, both during and after completion of cancer therapy, include weight-bearing activity (eg, walking, dancing, jogging) and resistance (light weight-lifting) exercises.[186]

Vitamin D is needed to absorb calcium and is generally found in dairy products that are fortified and can be synthesized through sun exposure. Excessive sun exposure or exposure without sunscreen is discouraged in cancer survivors due to their increased risk for the development of secondary skin cancers due to their exposure to chemotherapy and radiation.[195] There is currently no international consensus on optimal doses for Vitamin D supplementation.[193] The amount of vitamin D prescribed should be individualized based on vitamin D level and adjusted as needed.

Obesity and Metabolic Syndrome

Childhood cancer survivors are at increased risk for obesity.[196] It most commonly occurs after treatment for ALL and brain tumors, which combined account for over 40% of childhood cancer diagnoses.[197]

Metabolic syndrome is a combination of symptoms that include obesity, insulin resistance, hyperglycemia, and dyslipidemia, and has been seen in

survivors, especially those treated with cranial radiation or prolonged corticosteroid use.[199] Metabolic syndrome is often a precursor to the onset of Type 2 diabetes even in young adults. It is therefore extremely important that childhood cancer survivors maintain a healthy weight and participate in aerobic activity.

Heart Health After Treatment for Childhood Cancer

Treatment for a childhood cancer elevates the risk for cardiac disease.[186,200] Specific treatments associated with increased risk include regimens containing anthracyclines and mitoxantrone. Chest-directed radiotherapy has also been associated with a higher risk of cardiac disease in survivors of childhood cancer but has been somewhat mitigated by proton beam radiation which has a more focused radiation beam and less scatter to tissue surrounding the malignancy.

Diet and Physical Activity for Survivors

Once treatment has ended, cancer survivors should adopt the American Institute for Cancer Research Recommendations for Cancer Prevention, which include the following:[190,203]

1. Be a healthy weight. Keep your weight within the healthy range and avoid weight gain in adult life.
2. Be active. Make physical activity part of everyday life.
3. Eat a diet rich in whole grains, vegetables, fruits, and beans. Make whole grains, vegetables, fruits, and pulses (legumes) such as beans and lentils a major part of your normal diet.
4. Limit consumption of “fast foods” and other processed foods that are high in fat, starches, or sugars. Limiting these products helps you control your calorie intake and makes it easier to maintain a healthy weight.
5. Limit consumption of red and processed meat. Eat no more than moderate amounts (12–18 oz/wk of red meat, such as beef, pork, and lamb). Eat limited, if any, processed meat.
6. Limit consumption of sugar-sweetened drinks. Drink mostly water and unsweetened drinks.

7. Limit alcohol to reduce cancer risk. For cancer prevention, it is best not to drink alcohol.
8. Do not use supplements for cancer prevention. Aim to meet your nutritional needs through diet alone.

These recommendations are also compatible with the American Cancer Society nutrition and physical activity guideline for cancer survivors.[204]

Test Your Knowledge Questions

1. Mucositis is one of the complications affecting the nutrition status of pediatric oncology patients. Which chemotherapy agent is most likely to lead to the development of mucositis?
   A. Methotrexate
   B. Cyclophosphamide
   C. Vincristine
   D. Carboplatin
2. The use of EN during HSCT is commonly discouraged because of
   A. The need for frequent tube replacement
   B. Excessive bleeding risk with tube placement because of mucositis
   C. Dislodgement of the feeding tube
   D. All of the above
3. Which is true regarding agents used to enhance gut motility?
   A. Use of erythromycin to enhance gut motility increases resistance among susceptible bacteria.
   B. Children are more susceptible to the extrapyramidal side effects of metoclopramide and erythromycin than adults.
   C. Case reports of tardive dyskinesias with the use of metoclopramide are too infrequent to be considered clinically important.
   D. Motility-enhancing agents may increase or decrease the absorption of other drugs.
4. Survivors of childhood cancer can be at greater risk for osteoporosis because of which of the following?
   A. History of corticosteroid use
   B. History of methotrexate-containing regimen
   C. Inadequate calcium and vitamin D intake

D. All of the above

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA: a cancer journal for clinicians*. 2021;71(1):7–33. https://doi.org/10.3322/caac.21654
2. Howlader N, Noone A, Krapcho M, et al. SEER cancer statistics review, 1975–2017. National Cancer Institute. 2020;4. https://seer.cancer.gov/csr/1975_2017/
3. Bauer J, Jürgens H, Frühwald MC. Important aspects of nutrition in children with cancer. *Advances in Nutrition*. 2011;2(2):67–77. https://doi.org/10.3945/an.110.000141
4. White JV, Guenter P, Jensen G, et al. Consensus statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). *Journal of the Academy of Nutrition and Dietetics*. 2012;112(5):730–738. https://doi.org/10.1016/j.jand.2012.03.012
5. Orgel E, Framson C, Buxton R, et al. Caloric and nutrient restriction to augment chemotherapy efficacy for acute lymphoblastic leukemia: the IDEAL trial. *Blood Adv*. Apr 13 2021;5(7):1853–1861. https://doi.org/10.1182/bloodadvances.2020004018
6. Lange BJ, Gerbing RB, Feusner J, et al. Mortality in overweight and underweight children with acute myeloid leukemia. *Jama*. 2005;293(2):203–211. https://doi.org/10.1001/jama.293.2.203
7. Orgel E, Sposto R, Malvar J, et al. Impact on survival and toxicity by duration of weight extremes during treatment for pediatric acute lymphoblastic leukemia: A report from the Children's Oncology Group. *J Clin Oncol*. May 1 2014;32(13):1331–7. https://doi.org/10.1200/jco.2013.52.6962
8. Becker P, Carney LN, Corkins MR, et al. Consensus Statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: Indicators Recommended for the Identification and Documentation of Pediatric Malnutrition (Undernutrition). *Nutr*

Clin Pract. 2015; 30(1):147–61. https://doi.org/10.1177/0884533614557642
9. Brinksma A, Huizinga G, Sulkers E, et al. Malnutrition in childhood cancer patients: a review on its prevalence and possible causes. *Crit Rev Oncol Hematol*. 2012;83(2):249–75. https://doi.org/10.1016/j.critrevonc.2011.12.003
10. Runco DV, Wasilewski-Masker K, McCracken CE, et al. Normalized measures and patient characteristics to identify undernutrition in infants and young children treated for cancer. *Clin Nutr ESPEN*. 2020;38:185–191. https://doi.org/10.1016/j.clnesp.2020.05.005
11. Zimmermann K, Ammann RA, Kuehni CE, et al. Malnutrition in pediatric patients with cancer at diagnosis and throughout therapy: A multicenter cohort study. *Pediatr Blood Cancer*. 2013;60(4):642–9. https://doi.org/10.1002/pbc.24409
12. Runco DV, Stanek JR, Yeager ND, Belsky JA. Malnutrition identification and management variability: An administrative database study of children with solid tumors. *JPEN J Parenter Enteral Nutr*. 2022;46(7):1559–1567. https://doi.org/10.1002/jpen.2329
13. LaQuaglia MP, Gerstle JT. Advances in the treatment of pediatric solid tumors: A 50-year perspective. *J Surg Oncol*. 2022;126(5):933–942. https://doi.org/10.1002/jso.27038
14. Ladd AP, Grosfeld JL. Gastrointestinal tumors in children and adolescents. *Seminars in pediatric surgery*. 2006;15(1):37. https://doi.org/10.1053/j.sempedsurg.2005.11.007
15. Barrera R. Nutritional support in cancer patients. *Journal of Parenteral and Enteral Nutrition*. 2002;26:S63–S71. https://doi.org/10.1177/014860710202600516
16. Ladas EJ, Sacks N, Meacham L, et al. A multidisciplinary review of nutrition considerations in the pediatric oncology population: a perspective from children's oncology group. *Nutrition in clinical practice*. 2005;20(4):377–393. https://doi.org/10.1177/0115426505020004377
17. National Cancer Institute. Nutrition in Cancer Care (PDQ*). National Cancer Institute. Updated December 9 2022. Accessed January 21, 2023. https://www.cancer.gov/about-cancer/treatment/side-effects/appetite-loss/nutrition-pdq#section/all

18. National Cancer Institute. Dictionary of Cancer Terms: Radiation Therapy. National Cancer Institute. Accessed January 21, 2023. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/radiation-therapy?redirect=true
19. National Cancer Institute. Radiation Therapy to Treat Cancer National Cancer Institute. Updated January 8 2019. Accessed January 21, 2023. https://www.cancer.gov/about-cancer/treatment/types/radiation-therapy#HRTWAC
20. Baggott C, Fochtman D, Foley G, Kelly K. Nursing care of children and adolescents with cancer and blood disorders, 4th Edition. APHON, 2011.
21. National Cancer Intitute. Radiation Therapy Side Effects. National Cancer Institute. Updated January 11 2022. Accessed January 21, 2023. https://www.cancer.gov/about-cancer/treatment/types/radiation-therapy/side-effects
22. Unsal D, Mentes B, Akmansu M, et al. Evaluation of nutritional status in cancer patients receiving radiotherapy: a prospective study. *American journal of clinical oncology*. 2006;29(2):183–188. https://doi.org/10.1097/01.coc.0000198745.94757.ee
23. Ogama N, Suzuki S, Umeshita K, et al. Appetite and adverse effects associated with radiation therapy in patients with head and neck cancer. *European Journal of Oncology Nursing*. 2010;14(1):3–10. https://doi.org/10.1016/j.ejon.2009.07.004
24. Suneja G, Poorvu PD, Hill-Kayser C, Lustig RA. Acute toxicity of proton beam radiation for pediatric central nervous system malignancies. *Pediatric blood & cancer*. 2013;60(9):1431–1436. https://doi.org/10.1002/pbc.24554
25. Grant M, Kravits K. Symptoms and their impact on nutrition. Elsevier; 2000:113–121. https://doi.org/10.1053/on.2000.5738
26. Barbería E, Hernandez C, Miralles V, Maroto M. Paediatric patients receiving oncology therapy: review of the literature and oral management guidelines. *Eur J Paediatr Dent*. 2008;9(4):188–94. https://pubmed.ncbi.nlm.nih.gov/19072007/
27. National Cancer Institute. Chemotherapy To Treat Cancer National Cancer Institute. Updated August 23 2022. Accessed January 21, 2023. https://www.cancer.gov/about-

cancer/treatment/types/chemotherapy#chemotherapy-can-cause-side-effects
28. Hooke MC BC, Robinson D, et al. Management of disease and treatment-related complications. In: Baggott C FG, Fotchman D, Patterson K, ed. *Nursing Care of Children and Adolescents with Cancer and Blood Disorders*. Association of Pediatric Hematology/Oncology Nurses; 2011:510–584.
29. National Cancer Institute. Pediatric Chimeric Antigen Receptor (CAR) T-Cell Therapy (PDQ®)–Health Professional Version. National Cancer Institute. Updated February 4 2022. Accessed February 4, 2023. https://www.cancer.gov/types/childhood-cancers/hp-stem-cell-transplant/car-t-cell-therapy#_646_toc
30. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144(5):646–74. https://doi.org/10.1016/j.cell.2011.02.013
31. Vazquez A, Kamphorst JJ, Markert EK, et al. Cancer metabolism at a glance. *J Cell Sci*. 2016;129(18):3367–73. https://doi.org/10.1242/jcs.181016
32. Warburg O. The metabolism of carcinoma cells. *The Journal of Cancer Research*. 1925;9(1):148–163.
33. Roeland EJ, Bohlke K, Baracos VE, et al. Management of cancer cachexia: ASCO guideline. *Journal of Clinical Oncology*. 2020;38(21):2438–2453. https://doi.org/10.1200/jco.20.00611
34. Runco DV, Zimmers TA, Bonetto A. The urgent need to improve childhood cancer cachexia. *Trends Cancer*. 2022;8(12):976–979. https://doi.org/10.1016/j.trecan.2022.07.005
35. Biswas AK, Acharyya S. Cancer-associated cachexia: A systemic consequence of cancer progression. *Annual Review of Cancer Biology*. 2020;4:391–411. https://doi.org/10.1146/annurev-cancerbio-030419-033642
36. Moschovi M, Trimis G, Vounatsou M, et al. Serial plasma concentrations of PYY and ghrelin during chemotherapy in children with acute lymphoblastic leukemia. *Journal of Pediatric Hematology/Oncology*. 2008;30(10):733–737. https://doi.org/10.1097/mph.0b013e318179a1d8
37. Cravo M, Gloria L, Claro I. Metabolic responses to tumour disease and progression: tumour–host interaction. *Clinical nutrition*.

2000;19(6):459–465. https://doi.org/10.1054/clnu.2000.0140
38. Bosaeus I, Daneryd P, Lundholm K. Dietary intake, resting energy expenditure, weight loss and survival in cancer patients. *The Journal of nutrition*. 2002;132(11):3465S-3466S. https://doi.org/10.1093/jn/132.11.3465s
39. Keller U. Nutritional laboratory markers in malnutrition. *Journal of clinical medicine*. 2019;8(6):775. https://doi.org/10.3390/jcm8060775
40. Fuhrman MP, Charney P, Mueller CM. Hepatic proteins and nutrition assessment. *Journal of the American Dietetic Association*. 2004;104(8):1258–1264. https://doi.org/10.1016/j.jada.2004.05.213
41. Mosby TT, Barr RD, Pencharz PB. Nutritional assessment of children with cancer. *Journal of pediatric oncology nursing*. 2009;26(4):186–197. https://doi.org/10.1177/1043454209340326
42. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *New England journal of medicine*. 1999;340(6):448–454. https://doi.org/10.1056/nejm199902113400607
43. Steele AC, Mullins LL, Mullins AJ, Muriel AC. Psychosocial Interventions and Therapeutic Support as a Standard of Care in Pediatric Oncology. *Pediatr Blood Cancer*. 2015;62 Suppl 5:S585-618. https://doi.org/10.1002/pbc.25701
44. Brinksma A, Sulkers E, IJpma I, et al. Eating and feeding problems in children with cancer: Prevalence, related factors, and consequences. *Clinical Nutrition*. 2020;39(10):3072–3079. https://doi.org/10.1016/j.clnu.2020.01.012
45. İlhan İ E, Sarı N, Yeşil Ş, et al. Anthropometric and Biochemical Assessment of Nutritional Status in Pediatric Cancer Patients. *Pediatr Hematol Oncol*. 2015;32(6):415–22. https://pubmed.ncbi.nlm.nih.gov/26237587/
46. Rogers PC, Melnick SJ, Ladas EJ, et al. Children's Oncology Group (COG) Nutrition Committee. *Pediatr Blood Cancer*. 2008;50(2 Suppl):447–50. discussion 451. https://doi.org/10.1002/pbc.21414
47. Becker P, Carney LN, Corkins MR, et al. Consensus statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: indicators recommended for the identification and documentation of pediatric malnutrition (undernutrition). *Nutr*

Clin Pract. 2015;30(1):147–61. https://doi.org/10.1177/0884533614557642
48. Glatt D, Hughes C, McCarthy O, et al. Nutritional screening and assessment of paediatric cancer patients: A quality improvement project (baseline results). *Clin Nutr ESPEN*. 2020;38:242–252. https://doi.org/10.1016/j.clnesp.2020.04.003
49. Murphy AJ, White M, Viani K, Mosby TT. Evaluation of the nutrition screening tool for childhood cancer (SCAN). *Clin Nutr*. 2016;35(1):219–224. https://doi.org/10.1016/j.clnu.2015.02.009
50. Gallo N, Horvath K, Czuppon K, et al. Different nutritional screening tools and recommended screening algorithm for pediatric oncology patients. *Clin Nutr*. 2021;40(6):3836–3841. https://doi.org/10.1016/j.clnu.2021.05.013
51. Hulst JM, Zwart H, Hop WC, Joosten KF. Dutch national survey to test the STRONGkids nutritional risk screening tool in hospitalized children. *Clin Nutr*. 2010;29(1):106–11. https://doi.org/10.1016/j.clnu.2009.07.006
52. Ladas EJ, Sacks N, Brophy P, Rogers PC. Standards of nutritional care in pediatric oncology: results from a nationwide survey on the standards of practice in pediatric oncology. A Children's Oncology Group study. *Pediatric blood & cancer*. 2006;46(3):339–344. https://doi.org/10.1002/pbc.20435
53. Hill R SN, Ringwald-Smith K, Caceres J. Nutritional Management of the Pediatric Oncology Patient. In: Voss A WV, ed. *Oncology Nutrition for Clinical Practice*. 2nd ed. Academy of Nutrition and Dietetics; 2021:250–277.chap 13.
54. Ringwald-Smith K, Hill R, Evanoff L, et al. When Reality and Research Collide: Guidelines Are Essential for Optimal Nutrition Care in Pediatric Oncology. *Journal of Pediatric Hematology/Oncology*. 2022;44(1):e144–e151. https://doi.org/10.1097/mph.0000000000002200
55. Voss AC, Williams V. *Oncology Nutrition for Clinical Practice*. Academy of Nutrition and Dietetics; 2021.
56. Green GJ, Weitzman SS, Pencharz PB. Resting energy expenditure in children newly diagnosed with stage IV neuroblastoma. *Pediatric*

research. 2008;63(3):332–336. https://doi.org/10.1203/pdr.0b013e318163a2d4
57. Isanaka S, Villamor E, Shepherd S, Grais RF. Assessing the impact of the introduction of the WHO growth standards and weight-for-height Z score criterion on the response to treatment of severe acute malnutrition in children: secondary data analysis. *Pediatrics*. 2009;123(1):e54. https://doi.org/10.1542/peds.2008-1375
58. Yaprak DS, Yalçın B, Pınar AA, Büyükpamukçu M. Assessment of nutritional status in children with cancer: Significance of arm anthropometry and serum visceral proteins. *Pediatric Blood & Cancer*. 2021;68(1):e28752. https://doi.org/10.1002/pbc.28752
59. Co-Reyes E, Li R, Huh W, Chandra J. Malnutrition and obesity in pediatric oncology patients: causes, consequences, and interventions. *Pediatr Blood Cancer*. 2012;59(7):1160–7. doi:10.1002/pbc.24272. https://doi.org/10.1002/pbc.24272
60. Guenter P, Abdelhadi R, Anthony P, et al. Malnutrition diagnoses and associated outcomes in hospitalized patients: United States, 2018. *Nutr Clin Pract*. 2021;36(5):957–969. https://doi.org/10.1002/ncp.10771
61. Niseteo T, Hojsak I, Kolaček S. Malnourished children acquire nosocomial infections more often and have significantly increased length of hospital stay. *Clinical Nutrition*. 2020;39(5):1560–1563. https://doi.org/10.1016/j.clnu.2019.06.022
62. Sala A, Pencharz P, Barr RD. Children, cancer, and nutrition—a dynamic triangle in review. *Cancer*. 2004;100(4):677–687. https://doi.org/10.1002/cncr.11833
63. Joffe L, Dwyer S, Glade Bender JL, et al. Nutritional status and clinical outcomes in pediatric patients with solid tumors: a systematic review of the literature. *Semin Oncol*. 2019;46(1):48–56. doi:10.1053/j.seminoncol.2018.11.005. https://doi.org/10.1053/j.seminoncol.2018.11.005
64. Joffe L, Ladas EJ. Nutrition during childhood cancer treatment: current understanding and a path for future research. *Lancet Child Adolesc Health*. 2020;4(6):465–475. https://doi.org/10.1016/s2352-4642(19)30407-9

65. Loeffen EA, Brinksma A, Miedema KG, et al. Clinical implications of malnutrition in childhood cancer patients—infections and mortality. *Support Care Cancer*. 2015;23(1):143–50. https://doi.org/10.1007/s00520-014-2350-9
66. Capra S, Ferguson M, Ried K. Cancer: impact of nutrition intervention outcome—nutrition issues for patients. *Nutrition*. 2001;17(9):769–772. https://doi.org/10.1016/s0899-9007(01)00632-3
67. Van Den Brink M, Ter Hedde MM, van den Heuvel E, et al The impact of changes in taste, smell, and eating behavior in children with cancer undergoing chemotherapy: A qualitative study. *Frontiers in nutrition*. 2022:2310. https://doi.org/10.3389/fnut.2022.984101
68. Trehan A, Viani K, da Cruz LB, et al. The importance of enteral nutrition to prevent or treat undernutrition in children undergoing treatment for cancer. *Pediatric Blood & Cancer*. 2020;67:e28378. https://doi.org/10.1002/pbc.28378
69. Sacks N, Hwang WT, Lange BJ, et al. Proactive enteral tube feeding in pediatric patients undergoing chemotherapy. *Pediatric blood & cancer*. 2014;61(2):281–285. https://doi.org/10.1002/pbc.24759
70. McGrath KH, Evans V, Yap J. Indications and patterns of use for parenteral nutrition in pediatric oncology. *Journal of Parenteral and Enteral Nutrition*. 2020;44(4):632–638. https://doi.org/10.1002/jpen.1685
71. Charuhas PM. Nutrition management of oncology and marrow/hematopoietic stem cell transplantation. In: Amore-Spalding K NL, ed. *Pediatric Manual of Clinical Dietetics*. 2nd ed. American Dietetic Association; 2008:175–184.
72. Dunn RL, Stettler N, Mascarenhas MR. Refeeding syndrome in hospitalized pediatric patients. *Nutrition in clinical practice*. 2003;18(4):327–332. https://doi.org/10.1177/0115426503018004327
73. Tresley J, Sheean PM. Refeeding syndrome: recognition is the key to prevention and management. *Journal of the American Dietetic Association*. 2008;108(12):2105–2108. https://doi.org/10.1016/j.jada.2008.09.015
74. Charuhas P LA, Lessen P, McMillen K. Hematopoietic stem cell transplantation. In: Merritt RJ DM, Holcombe B, et al. (eds.) *The*

ASPEN Nutrition Support Practice Manual. American Society for Parenteral and Enteral Nutrition. 2005:187–199.
75. Bozzetti F. Nutritional support of the oncology patient. *Critical reviews in oncology/hematology*. 2013;87(2):172–200.
76. Diorio C, Lam CG, Ladas EJ, et al. Global Use of Traditional and Complementary Medicine in Childhood Cancer: A Systematic Review. *J Glob Oncol*. 2017;3(6):791–800. https://doi.org/10.1200/jgo.2016.005587
77. National Center for Complementary and Integrative Health. Complementary, alternative, or integrative health: what's in a name? National Instituites of Health. Updated April 2021. Accessed January 22, 2023. https://www.nccih.nih.gov/health/complementary-alternative-or-integrative-health-whats-in-a-name
78. Kemper K, Vohra S, Walls R. Task Force on Complementary and Alternative Medicine; Provisional Section on Complementary, Holistic, and Integrative Medicine. *American Academy of Pediatrics The use of complementary and alternative medicine in pediatrics Pediatric*. 2008. https://doi.org/10.1542/peds.2008-2173
79. Diorio C, Kelly KM, Afungchwi GM, et al. Nutritional traditional and complementary medicine strategies in pediatric cancer: A narrative review. *Pediatric Blood & Cancer*. 2020;67:e28324. https://doi.org/10.1002/pbc.28324
80. Lawenda BD, Kelly KM, Ladas EJ, et al. Should supplemental antioxidant administration be avoided during chemotherapy and radiation therapy? *Journal of the national cancer institute*. 2008;100(11):773–783. https://doi.org/10.1093/jnci/djn148
81. Academy of Nutrition and Dietetics. Pediatric Nutrition Care Manual. Academy of Nutrition and Dietetics Accessed January 30, 2023. https://www.nutritioncaremanual.org/topic.cfm?ncm_category_id=13&lv1=144629&lv2=273757&ncm_toc_id=273757&ncm_heading=Nutrition%20Care%20home%20page
82. Bryant R. Managing side effects of childhood cancer treatment. *Journal of pediatric nursing*. 2003;18(2):113–125. https://doi.org/10.1053/jpdn.2003.11
83. Academy of Nutrition and Dietetics. Managing Side Effects of Cancer and Treatment. Academy of Nutrition and Dietetics Updated 2018.

Accessed January 31, 2023. https://www.nutritioncaremanual.org/client_ed.cfm?ncm_client_ed_id=436
84. Martindale R, Shikora S, Nishikawa R, Siepler J. The metabolic response to stress and alterations in nutrient metabolism. *Nutritional Considerations in the Intensive Care Unit—Science, Rationale and Practice Dubuque: Kendall/Hunt*. 2002:11–20.
85. Triarico S, Rinninella E, Cintoni M, et al. Impact of malnutrition on survival and infections among pediatric patients with cancer: a retrospective study. *Eur Rev Med Pharmacol Sci*. 2019;23(3):1165–1175. https://doi.org/10.26355/eurrev_201901_17009
86. Barker C, Anderson R, Sauve R, Butzner J. GI complications in pediatric patients post-BMT. *Bone marrow transplantation*. 2005;36(1):51–58. https://doi.org/10.1038/sj.bmt.1705004
87. Mhaissen MN, Rodriguez A, Gu Z, et al. Epidemiology of Diarrheal Illness in Pediatric Oncology Patients. *Journal of the Pediatric Infectious Diseases Society*. 2016;6(3):275–280. https://doi.org/10.1093/jpids/piw050
88. Chakrabarti S, Collingham K, Stevens R, et al. Isolation of viruses from stools in stem cell transplant recipients: a prospective surveillance study. *Bone marrow transplantation*. 2000;25(3):277–282. https://doi.org/10.1038/sj.bmt.1702164
89. Burgunder MR DB. Hematopoietic stem cell transplantation. In: Kogut VJ LS, ed. *Nutritional Issues in Cancer Care*. Oncology Nursing Society; 2005:253–263.
90. Alhussain A, Alkhayal Z, Ayas M, Abed H. Prevalence and risk factors of oral mucositis in paediatric patients undergoing haematopoietic stem cell transplantation. *Oral Diseases*. 2022;28(3):657–669. https://doi.org/10.1111%2Fodi.13777
91. Valeh M, Kargar M, Mansouri A, et al. Factors Affecting the Incidence and Severity of Oral Mucositis Following Hematopoietic Stem Cell Transplantation. *Int J Hematol Oncol Stem Cell Res*. 2018;12(2):142–152.
92. Miller MM, Donald DV, Hagemann TM. Prevention and treatment of oral mucositis in children with cancer. *The Journal of Pediatric*

Pharmacology and Therapeutics. 2012;17(4):340–350. https://doi.org/10.5863/1551-6776-17.4.340
93. Peng T-R, Lin H-H, Yang L-J, Wu T-W. Effectiveness of glutamine in the management of oral mucositis in cancer patients: a meta-analysis of randomized controlled trials. *Supportive Care in Cancer*. 2021;29(8):4885–4892. https://doi.org/10.1007/s00520-021-06060-9
94. Akpek G, Valladares J, Lee L, et al. Pancreatic insufficiency in patients with chronic graft-versus-host disease. *Bone marrow transplantation*. 2001;27(2):163–166. https://doi.org/10.1038/sj.bmt.1702769
95. Brook OR, Mullan CP, Mendiratta-Lala M, et al. Pancreatic atrophy in patients with chronic graft-versus-host disease. *Abdom Imaging*. 2014;39(2):342–7. https://doi.org/10.1007/s00261-013-0072-y
96. Bechard LJ EA, Jaksic T, Duggan C. Nutritional Supportive Care. In: Pizzo PA PD, ed. *Principles and Practice of Pediatric Oncology*. 4th ed. Lippincott, Williams & Wilkins; 2002:1285–1300.
97. Ginnebaugh B, Chey WD, Saad R. Small Intestinal Bacterial Overgrowth: How to Diagnose and Treat (and Then Treat Again). *Gastroenterol Clin North Am*. 2020;49(3):571–587. https://doi.org/10.1016/j.gtc.2020.04.010
98. Masetti R, Zama D, Leardini D, et al. The gut microbiome in pediatric patients undergoing allogeneic hematopoietic stem cell transplantation. *Pediatr Blood Cancer*. 2020;67(12):e28711. https://doi.org/10.1002/pbc.28711
99. Cunningham RS, Bell R. Nutrition in cancer: an overview. Elsevier; 2000:90–98.
100. Lexicomp Online. Pediatric and Neonatal Lexi-Drugs Online. UpToDate Inc. Updated October 15 2019. Accessed January 20, 2023. https://online.lexi.com
101. Heidelbaugh JJ. Proton pump inhibitors and risk of vitamin and mineral deficiency: evidence and clinical implications. *Therapeutic advances in drug safety*. 2013;4(3):125–133. https://doi.org/10.1177/2042098613482484
102. National Cancer Institute. Blood Forming Stem Cell Transplants. National Cancer Institute. Updated August 12, 2013. Accessed January 22, 2023. https://www.cancer.gov/about-

cancer/treatment/types/stem-cell-transplant/stem-cell-fact-sheet#how-are-the-donors-stem-cells-matched-to-the-patients-stem-cells-in-allogeneic-or-syngeneic-transplantation
103. Laetsch TW, Yanik GA, Boyer MW, Rheingold SR. An owner's manual for CD19 "CAR"-T cell therapy in managing pediatric and young adult B-cell acute lymphoblastic leukemia. *Blood Reviews*. 2021;50:1–11.
104. Abikoff CM, Cairo MS. Reduced intensity conditioning and hematopoietic stem cell transplantation in pediatric nonmalignant disease: a new therapeutic paradigm. *The Journal of Pediatrics*. 2014;164(5):952–953. e2. https://doi.org/10.1016/j.jpeds.2014.01.061
105. Souza MM, Coutinho-Camillo CM, de Paula FM, et al. Relevant proteins for the monitoring of engraftment phases after allogeneic hematopoietic stem cell transplantation. *Clinics*. 2022;77:100134. https://doi.org/10.1016/j.clinsp.2022.100134
106. Pulsipher M NS, Heslop H. General Principles of Hematopoietic Stem Cell Transplantation. In: Blaney S AP, Helman L, ed. *Pizzo and Poplack's Pediatric Oncology*. 8th ed. Wolters Kluwer; 2021:chap 13.
107. White M, Murphy A, Hastings Y, et al. Nutritional status and energy expenditure in children pre-bone-marrow-transplant. *Bone marrow transplantation*. 2005;35(8):775–779. https://doi.org/10.1038/sj.bmt.1704891
108. Rodgers C, Wills-Alcoser P, Monroe R, et al. Growth patterns and gastrointestinal symptoms in pediatric patients after hematopoietic stem cell transplantation. Oncol Nurs Forum. May 2008;35(3):443–8. https://doi.org/10.1188/08.ONF.443-448
109. Duggan C, Bechard L, Donovan K, et al. Changes in resting energy expenditure among children undergoing allogeneic stem cell transplantation. *The American journal of clinical nutrition*. 2003;78(1):104–109. https://doi.org/10.1093/ajcn/78.1.104
110. Duro D, Bechard LJ, Feldman HA, et al. Weekly measurements accurately represent trends in resting energy expenditure in children undergoing hematopoietic stem cell transplantation. *Journal of Parenteral and Enteral Nutrition*. 2008;32(4):427–432. https://doi.org/10.1177/0148607108319804

111. Ringwald-Smith K, Williams R, Horwitz E, Schmidt M. Determination of energy expenditure in the bone marrow transplant patient. *Nutrition in clinical practice*. 1998;13(5):215–218.
112. Hospital TCs. *Texas Children's Hospital Pediatric Nutrition Reference Guide*. 13th ed. Texas Children's Hospital 2022.
113. Charuhas P GS. Parenteral Nutrition in Pediatric Oncology. In: Chernoff R BR, Baker SS, Davis AM, ed. *Pediatric Parenteral Nutrition*. Chapman and Hall; 1997.
114. Roberts S, Thompson J. Graft-vs-host disease: Nutrition therapy in a challenging condition. *Nutrition in clinical practice*. 2005;20(4):440–450.https://doi.org/10.1177/0115426505020004440
115. LJ B. Oncology and Stem Cell Transplantation. In: Baker SS BR, Davis AM, ed. *Pediatric Nutrition Support*. Jones and Bartlett; 2007:433–445.
116. Moody K, Finlay J, Mancuso C, Charlson M. Feasibility and safety of a pilot randomized trial of infection rate: neutropenic diet versus standard food safety guidelines. *Journal of Pediatric Hematology/Oncology*. 2006;28(3):126–133. https://doi.org/10.1097/01.mph.0000210412.33630.fb
117. Van Tiel F, Harbers M, Terporten P, et al. Normal hospital and low-bacterial diet in patients with cytopenia after intensive chemotherapy for hematological malignancy: a study of safety. *Annals of oncology*. 2007;18(6):1080–1084. https://doi.org/10.1093/annonc/mdm082
118. Jubelirer SJ. The benefit of the neutropenic diet: fact or fiction? *The oncologist*. 2011;16(5):704–707. https://doi.org/10.1634/theoncologist.2011-0001
119. Trifilio S, Helenowski I, Giel M, et al. Questioning the role of a neutropenic diet following hematopoetic stem cell transplantation. *Biology of Blood and Marrow Transplantation*. 2012;18(9):1385–1390. https://doi.org/10.1016/j.bbmt.2012.02.015
120. Stella F, Marasco V, Levati GV, et al. Non-Restrictive Diet Does Not Increase Infections in Patients with Neutropenia after Stem Cell Transplantation: Final Analysis of the Neutrodiet Multicenter, Randomized Trial. *Blood*. 2022;140(Supplement 1):417–419.
121. Zama D, Gori D, Muratore E, et al. Enteral versus Parenteral Nutrition as Nutritional Support after Allogeneic Hematopoietic Stem Cell

Transplantation: a Systematic Review and Meta-Analysis. *Transplant Cell Ther*. 2021;27(2):180.e1–180.e8. https://doi.org/10.1016/j.jtct.2020.11.006.

122. De Santas K VA. Care of the Hematopoietic stem cell transplant patient after leaving the transplant center. In: AJ A, ed. *Suppotive Care of Children with Cancer: Current Therapy and Guidelines from the Children's Oncology Group*. 3rd ed. The Johns Hopkins University Press; 2004:286–333.
123. Hopman G, Pena E, Le Cessie S, et al. Tube feeding and bone marrow transplantation. *Medical and Pediatric Oncology: The Official Journal of SIOP—International Society of Pediatric Oncology (Societé Internationale d'Oncologie Pédiatrique*. 2003;40(6):375–379. https://doi.org/10.1002/mpo.10284
124. Hastings Y, White M, Young J. Enteral nutrition and bone marrow transplantation. *Journal of Pediatric Oncology Nursing*. 2006;23(2):103–110. https://doi.org/10.1177/1043454205285866
125. Garófolo A. Enteral nutrition during bone marrow transplantation in patients with pediatric cancer: a prospective cohort study. *Sao Paulo Medical Journal*. 2012;130:159–166. https://doi.org/10.1590/s1516-31802012000300005
126. Evans JC, Hirani SP, Needle JJ. Nutritional and Post-Transplantation Outcomes of Enteral versus Parenteral Nutrition in Pediatric Hematopoietic Stem Cell Transplantation: A Systematic Review of Randomized and Nonrandomized Studies. *Biol Blood Marrow Transplant*. 2019;25(8):e252–e259. https://doi.org/10.1016/j.bbmt.2019.02.023
127. Kvammen JA, Thomassen RA, Buechner J, et al. Impact of Allogeneic Hematopoietic Stem Cell Transplantation on Nutritional Status and Intake in Children. *J Pediatr Gastroenterol Nutr*. 2022;75(5):675–682. https://doi.org/10.1097/mpg.0000000000003592
128. McMillan DC, Maguire D, Talwar D. Relationship between nutritional status and the systemic inflammatory response: micronutrients. *Proc Nutr Soc*. 2019;78(1):56–67. https://doi.org/10.1017/s0029665118002501
129. Galloway P, McMillan DC, Sattar N. Effect of the inflammatory response on trace element and vitamin status. *Ann Clin Biochem*.

2000;37 (Pt 3):289–97. https://doi.org/10.1258/0004563001899429
130. Cheney CL, Abson KG, Aker SN, et al. Body composition changes in marrow transplant recipients receiving total parenteral nutrition. *Cancer*. 1987;59(8):1515–1519. https://doi.org/10.1002/1097-0142(19870415)59:8<1515::aid-cncr2820590821>3.0.co;2-d
131. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant*. 2015;21(3):389–401.e1. https://doi.org/10.1016/j.bbmt.2014.12.001
132. Flowers ME, Inamoto Y, Carpenter PA, et al. Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria. *Blood*. 2011;117(11):3214–9. https://doi.org/10.1182/blood-2010-08-302109
133. MacMillan ML, Weisdorf DJ, Wagner JE, et al. Response of 443 patients to steroids as primary therapy for acute graft-versus-host disease: comparison of grading systems. *Biology of Blood and Marrow Transplantation*. 2002;8(7):387–394. https://doi.org/10.1053/bbmt.2002.v8.pm12171485
134. Hahn T, McCarthy Jr PL, Zhang M-J, et al. Risk factors for acute graft-versus-host disease after human leukocyte antigen–identical sibling transplants for adults with leukemia. *Journal of Clinical Oncology*. 2008;26(35):5728. https://doi.org/10.1200/jco.2008.17.6545
135. Zecca M, Prete A, Rondelli R, et al. Chronic graft-versus-host disease in children: incidence, risk factors, and impact on outcome. *Blood, The Journal of the American Society of Hematology*. 2002;100(4):1192–1200.
136. Koc S, Leisenring W, Flowers ME, et al. Therapy for chronic graft-versus-host disease: a randomized trial comparing cyclosporine plus prednisone versus prednisone alone. *Blood, The Journal of the American Society of Hematology*. 2002;100(1):48–51. https://doi.org/10.1182/blood.v100.1.48
137. Berger M, Barone M, Carnevale-Schianca F, et al. HSCT with Mismatched Unrelated Donors (MMUD): A Comparison of Different

Platforms for GvHD Prophylaxis. *Transplantology*. 2022;3(1):51–67. https://doi.org/10.3390/transplantology3010006
138. Gatza E, Reddy P, Choi SW. Prevention and Treatment of Acute Graft-versus-Host Disease in Children, Adolescents, and Young Adults. *Biol Blood Marrow Transplant*. 2020;26(5):e101–e112. https://doi.org/10.1016/j.bbmt.2020.01.004
139. Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. *The Lancet*. 2009;373(9674):1550–1561.
140. Academy of Nutrition and Dietetics. GVHD Nutrition Therapy. Academy of Nutrition and Dietetics. Accessed January 31 2023, https://www.nutritioncaremanual.org/client_ed.cfm?ncm_client_ed_id=255
141. Lee SJ. Classification systems for chronic graft-versus-host disease. *Blood*. 2017;129(1):30–37. https://doi.org/10.1182/blood-2016-07-686642
142. Corbacioglu S, Carreras E, Ansari M, et al. Diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in pediatric patients: a new classification from the European society for blood and marrow transplantation. *Bone Marrow Transplant*. 2018;53(2):138–145. https://doi.org/10.1038/bmt.2017.161
143. Kumar S, DeLeve LD, Kamath PS, Tefferi A. *Hepatic veno-occlusive disease (sinusoidal obstruction syndrome) after hematopoietic stem cell transplantation*. Elsevier; 2003:589–598.
144. Cesaro S, Pillon M, Talenti E, et al. A prospective survey on incidence, risk factors and therapy of hepatic veno-occlusive disease in children after hematopoietic stem cell transplantation. *haematologica*. 2005;90(10):1396–1404.
145. Schiavetti A, Matrunola M, Varrasso G, et al. Ultrasound in the management of hepatic veno-occlusive disease in three children treated with dactinomycin and vincristine. *Pediatric hematology and oncology*. 1996;13(6):521–529. https://doi.org/10.3109/08880019609030867
146. Kotecha RS, Buckland A, Phillips MB, et al. Hepatic sinusoidal obstruction syndrome during chemotherapy for childhood medulloblastoma: report of a case and review of the literature. *Journal of Pediatric Hematology/Oncology*. 2014;36(1):76.

147. Tang C, Lindsay J, Gill A, Kerridge I. Defibrotide use in vincristine-induced hepatic sinusoidal obstruction syndrome. *Clinical Lymphoma Myeloma and Leukemia*. 2017;17(8):539–541. https://doi.org/10.1016/j.clml.2017.06.032
148. Kizilocak H, Dikme G, Özdemir N, et al. Sinusoidal obstruction syndrome during chemotherapy of pediatric cancers and its successful management with defibrotide. *Journal of Pediatric Hematology/Oncology*. 2017;39(7):e373–e376. https://doi.org/10.1097/mph.0000000000000958
149. Nabarrete JM, Pereira AZ, Garófolo A, et al. Brazilian Nutritional Consensus in Hematopoietic Stem Cell Transplantation: children and adolescents. *Einstein (Sao Paulo)*. 2021;19:eAE5254. https://doi.org/10.31744/einstein_journal/2021AE5254
150. Shafi MA. Gastrointestinal motility issues in cancer patients. *Current gastroenterology reports*. 2019;21:1–8.
151. Savarino V, Marabotto E, Zentilin P, Demarzo MG, de Bortoli N, Savarino E. Pharmacological management of gastro-esophageal reflux disease: an update of the state-of-the-art. *Drug Design, Development and Therapy*. 2021:1609–1621. https://doi.org/10.2147/dddt.s306371
152. Boruta M, Boruta R, Li J. Acid suppression therapy and symptom improvement (or lack thereof) in children. *Pediatrics*. 2019;144(1) https://doi.org/10.1542/peds.2019-0909
153. Orel R, Benninga MA, Broekaert IJ, et al. Drugs in focus: proton pump inhibitors. *J Pediatr Gastroenterol Nutr*. 2021;72(5):645–653. https://doi.org/10.1097/mpg.0000000000003063
154. Suzuki K, Doki K, Homma M, et al. Co-administration of proton pump inhibitors delays elimination of plasma methotrexate in high-dose methotrexate therapy. *Br J Clin Pharmacol*. 2009;67(1):44–9. https://doi.org/10.1111/j.1365-2125.2008.03303.x
155. Lexicomp Online PaNL-DO. UpToDate, Inc. Updated July 30 2021. Accessed January 20, 2023. https://online.lexi.com/lco/action/home
156. Hatlebakk JG, Katz PO, Camacho-Lobato L, Castell DO. Proton pump inhibitors: better acid suppression when taken before a meal than without a meal. *Aliment Pharmacol Ther*. 2000;14(10):1267–72. https://doi.org/10.1046/j.1365-2036.2000.00829.x

157. Olabisi A, Chen J, Garala M. Evaluation of different lansoprazole formulations for nasogastric or orogastric administration. *Hospital Pharmacy*. 2007;42(6):537–542.
158. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: ASCO Guideline update. *J Clin Oncol*. 2020;38(24):2782–2797. https://doi.org/10.1200/jco.20.01296
159. Camilleri M, Atieh J. New developments in prokinetic therapy for gastric motility disorders. *Front Pharmacol*. 2021;12:711500. https://doi.org/10.3389/fphar.2021.711500
160. US Food and Drug Administration. FDA Requests Removal of All Ranitidine Products (Zantac) from the Market. Food and Drug Administration. Updated April 1 2020. Accessed January 22, 2023. https://www.fda.gov/news-events/press-announcements/fda-requests-removal-all-ranitidine-products-zantac-market
161. Chicella MF, Batres LA, Heesters MS, Dice JE. Prokinetic drug therapy in children: a review of current options. *Ann Pharmacother*. 2005;39(4):706–11. https://doi.org/10.1345/aph.1E411
162. Kovacic K, Elfar W, Rosen JM, et al. Update on pediatric gastroparesis: A review of the published literature and recommendations for future research. *Neurogastroenterol Motil*. 2020;32(3):e13780. https://doi.org/10.1111/nmo.13780
163. Pediatric Oncology Group of Ontario. Healthcare Practice; Chemotherapy-Induced Nausea and Vomiting. Accessed February 7, 2023. https://www.pogo.ca/healthcare/practiceguidelines/chemotherapy-induced-nausea-and-vomiting/
164. Children's Oncology Group. Guidelines on Chemotherapy-induced Nausea and Vomiting in Pediatric Cancer Patients. Updated July 15 2022. Accessed December 30, 2022. Children's Oncology Group https://www.childrensoncologygroup.org/cog-supportive-care-endorsed-guidelines
165. Sherani F, Boston C, Mba N. Latest Update on Prevention of Acute Chemotherapy-Induced Nausea and Vomiting in Pediatric Cancer Patients. *Curr Oncol Rep*. 2019;21(10):89. https://doi.org/10.1007/s11912-019-0840-0

166. Tricco AC, Blondal E, Veroniki AA, et al. Comparative safety and effectiveness of serotonin receptor antagonists in patients undergoing chemotherapy: a systematic review and network meta-analysis. *BMC Med*. 2016;14(1):216. https://doi.org/10.1186/s12916-016-0761-9
167. Southard BT, Al Khalili Y. Promethazine. *StatPearls [Internet]*. StatPearls Publishing; 2022.
168. National Comprehensive Cancer Network. Antiemesis guidelines. Accessed December 29, 2022. https://www.nccn.org/guidelines/category_1#antiemesis.
169. Naik RD, V S, Singh V, Pillai AS, et al. Olanzapine for prevention of vomiting in children and adolescents receiving highly emetogenic chemotherapy: investigator-initiated, randomized, open-label trial. *J Clin Oncol*. 2020;38(32):3785–3793. https://doi.org/10.1200/jco.20.00871
170. Simonian J, Varanasi S, Richards G, et al. A critical narrative review of medical cannabis in pediatrics beyond epilepsy, part III: chemotherapy-induced nausea and vomiting and inflammatory bowel disease. *Pediatric Medicine*. 2020;3
171. Rower JE, King AD, Wilkins D, et al. Dronabinol prescribing and exposure among children and young adults diagnosed with cancer. *Journal of Adolescent and Young Adult Oncology*. 2021;10(2):175–184. https://doi.org/10.1089/jayao.2020.0021
172. Ullrich C DJ, Joselow M. Pediatric palliative care. In: Kliegman RM SGJ, ed. *Nelson Textbook of Pediatrics*. 21st ed. Elsevier; 2020:chap 7.
173. Hawes C, Gomes A, Byham-Gray L, Henderson S. The effect of oral nutrition supplements and appetite stimulants on weight status among pediatric cancer patients: a systematic review. *Nutrition in Clinical Practice*. 2022. https://doi.org/10.1002/ncp.10919
174. Yavuzsen T, Davis MP, Walsh D, et al. Systematic review of the treatment of cancer-associated anorexia and weight loss. *Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]*. 2005. https://doi.org/10.1200/jco.2005.01.8010
175. Childs DS, Jatoi A. A hunger for hunger: a review of palliative therapies for cancer-associated anorexia. *Annals of palliative medicine*. 2019;8(1):50. https://doi.org/10.21037/apm.2018.05.08

176. Strasser F, Luftner D, Possinger K, et al. Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-In-Cachexia-Study-Group. *Journal of Clinical Oncology*. 2006;24(21):3394–3400. https://doi.org/10.1200/jco.2005.05.1847
177. Gura K, Ciccone R. Drugs and appetite: an overview of appetite stimulants in the pediatric patient. *ICAN: Infant, Child, & Adolescent Nutrition*. 2010;2(6):358–369. https://doi.org/10.1177/1941406410387925
178. Miranda-Silva W, Gomes-Silva W, Zadik Y, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis: sub-analysis of current interventions for the management of oral mucositis in pediatric cancer patients. *Support Care Cancer*. 2021;29(7):3539–3562. https://doi.org/10.1007/s00520-020-05803-4
179. Brown TJ, Gupta A. Management of cancer therapy–associated oral mucositis. *JCO oncology practice*. 2020;16(3):103–109. https://doi.org/10.1200/jop.19.00652
180. Patel P, Robinson PD, Baggott C, et al. Clinical practice guideline for the prevention of oral and oropharyngeal mucositis in pediatric cancer and hematopoietic stem cell transplant patients: 2021 update. *Eur J Cancer*. 2021;154:92–101. https://doi.org/10.1016/j.ejca.2021.05.013
181. Elad S, Cheng KKF, Lalla RV, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer*. 2020;126(19):4423–4431. https://doi.org/10.1002/cncr.33100
182. Keefe DM, Schubert MM, Elting LS, et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer: Interdisciplinary International Journal of the American Cancer Society*. 2007;109(5):820–831. https://doi.org/10.1002/cncr.22484
183. Sencer SF, Zhou T, Freedman LS, et al. Traumeel S in preventing and treating mucositis in young patients undergoing SCT: a report of the Children's Oncology Group. *Bone Marrow Transplant*. 2012;47(11):1409–14. https://doi.org/10.1038/bmt.2012.30

184. Morrell MB, Baker R, Johnson A, et al. Dietary intake and micronutrient deficiency in children with cancer. *Pediatric blood & cancer*. 2019;66(10):e27895. https://doi.org/10.1002/pbc.27895
185. Ward E, DeSantis C, Robbins A, et al. Childhood and adolescent cancer statistics, 2014. *CA Cancer J Clin*. 2014;64(2):83–103. https://doi.org/10.3322/caac.21219
186. Children's Oncology Group. Long-term follow-up guidelines for survivors of childhoood, adolescent, and young adult cancer. Version 5.0. Children's Oncology Group. Updated October 2018. Accessed January 23, 2023. http://www.survivorshipguidelines.org/pdf/2018/cog_ltfu_guidelines_v5.pdf
187. Arroyave WD, Clipp EC, Miller PE, et al. Childhood cancer survivors' perceived barriers to improving exercise and dietary behaviors. 2008. https://doi.org/10.1188/08.onf.121-130
188. Demark-Wahnefried W, Werner C, Clipp EC, et al. Survivors of childhood cancer and their guardians: current health behaviors and receptivity to health promotion programs. *Cancer: Interdisciplinary International Journal of the American Cancer Society*. 2005;103(10):2171–2180. https://doi.org/10.1002/cncr.21009
189. Castellino S SS. Gastrointestinal Health. Children's Oncology Group. Updated October 2018.
190. S F. Staying Healthy Through Diet and Physical Activity. Children's Oncology Group. Updated October 2018. Accessed December 12, 2022.
191. Marcucci G, Beltrami G, Tamburini A, et al. Bone health in childhood cancer: review of the literature and recommendations for the management of bone health in childhood cancer survivors. *Annals of Oncology*. 2019;30(6):908–920. https://doi.org/10.1093/annonc/mdz120
192. van Atteveld JE, Mulder RL, van den Heuvel-Eibrink MM, et al. Bone mineral density surveillance for childhood, adolescent, and young adult cancer survivors: evidence-based recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Diabetes Endocrinol*. 2021;9(9):622–637. https://doi.org/10.1016/s2213-8587(21)00173-x

193. Institute of Medicine Committee to Review Dietary Reference Intakes for Vitamin D, Calcium. The National Academies Collection: Reports funded by National Institutes of Health. In: Ross AC, Taylor CL, Yaktine AL, Del Valle HB, eds. *Dietary Reference Intakes for Calcium and Vitamin D*. National Academies Press (US), National Academy of Sciences; 2011.
194. Consumer Lab. Calcium and Bone Health Supplements Review. Consumer Lab. Updated January 5 2023. Accessed January 23, 2023. https://www.consumerlab.com/reviews/bone-supplements-calcium-with-vitamin-d-k-magnesium/calcium/
195. Meadows AT, Friedman DL, Neglia JP, et al. Second neoplasms in survivors of childhood cancer: findings from the Childhood Cancer Survivor Study cohort. *J Clin Oncol*. 2009;27(14):2356–62. https://doi.org/10.1200/jco.2008.21.1920
196. Zhang FF, Parsons SK. Obesity in Childhood Cancer Survivors: Call for Early Weight Management. *Adv Nutr*. 2015;6(5):611–9. https://doi.org/10.3945/an.115.008946
197. CureSearch. Number of Diagnoses. CureSearch. Accessed January 23, 2023. https://curesearch.org/number-of-diagnoses
198. Walters M, Mowbray C, Jubelirer T, et al. A bilingual dietary intervention early in treatment is feasible and prevents weight gain in childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2021;68(5):e28910. https://doi.org/10.1002/pbc.28910
199. Friedman DN, Tonorezos ES, Cohen P. Diabetes and metabolic syndrome in survivors of childhood cancer. *Horm Res Paediatr*. 2019;91(2):118–127. https://doi.org/10.1159/000495698
200. Mulrooney DA, Yeazel MW, Kawashima T, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *BMJ*. 2009;339:b4606. https://doi.org/10.1136/bmj.b4606
201. Asselin BL, Devidas M, Chen L, et al. Cardioprotection and safety of dexrazoxane in patients treated for newly diagnosed T-cell acute lymphoblastic leukemia or advanced-stage lymphoblastic non-Hodgkin lymphoma: a report of the Children's Oncology Group Randomized Trial Pediatric Oncology Group 9404. *J of clinical oncology*. 2016;34(8):854. https://doi.org/10.1200/jco.2015.60.8851

202. Guida F, Masetti R, Andreozzi L, et al. The role of nutrition in primary and secondary prevention of cardiovascular damage in childhood cancer survivors. *Nutrients*. 2022;14(16). https://doi.org/10.3390/nu14163279
203. American Institute for Cancer Research. Committed to Cancer Prevention. Amerian Institute for Cancer Research. https://www.aicr.org/cancer-prevention/
204. Rock CL, Thomson CA, Sullivan KR, et al. American Cancer Society nutrition and physical activity guideline for cancer survivors. *CA Cancer J Clin*. 2022;72(3):230–262. https://doi.org/10.3322/caac.21719
205. Phillips S, Edlbeck A, Kirby M, Goday P. Ideal body weight in children. *Nutr in clinical practice*. 2007;22(2):240. https://doi.org/10.1177/0115426507022002240
206. Hamwi GJ. Therapy: changing dietary concepts. *Diabetes mellitus: diagnosis and treatment*. 1964;1:73–78.
207. Energy. In: Otten JJ, Hellwig JP, Meyers LD, ed. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements.* The National Academies Press; 2006:82–93.
208. Protein and Amino Acids. In: Otten JJ, Hellwig JP, Meyers LD, ed. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. The National Academies Press; 2006:144–155.
209. Tables of Possible Side Effects for Commonly-Used Oncology Drugs. National Cancer Institute. Updated January 18, 2023. Accessed January 31, 2023. https://ctep.cancer.gov/protocoldevelopment/sideeffects/drugs.htm
210. van den Boogaard WM, Komninos DS, Vermeij WP. Chemotherapy side-effects: not all DNA damage is equal. *Cancers*. 2022;14(3):627. https://doi.org/10.3390/cancers14030627
211. Academy of Nutrition and Dietetics. Nutrition Assessment. Pediatric Nutrition Care Manual. Accessed February 5, 2023. https://www.nutritioncaremanual.org/topic.cfm?ncm_category_id=13&lv1=144629&lv2=273748&ncm_toc_id=273748&ncm_heading=Nutrition%20Care%20home%20page
212. Rowlings PA, Przepiorka D, Klein JP, et al. IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with

Glucksberg grade. *Br J Haematol*. 1997;97(4):855–64. https://doi.org/10.1046/j.1365-2141.1997.1112925.x

213. Cahn J-Y, Klein JP, Lee SJ, et al. Prospective evaluation of 2 acute graft-versus-host (GVHD) grading systems: a joint Societe Francaise de Greffe de Moelle et Therapie Cellulaire (SFGM-TC), Dana Farber Cancer Institute (DFCI), and International Bone Marrow Transplant Registry (IBMTR) prospective study. *Blood*. 2005;106(4):1495–1500. https://doi.org/10.1182/blood-2004-11-4557

Test Your Knowledge Answers

1. The correct answer is **A**. Methotrexate leads to the development of mucositis, which severely compromises oral intake.
2. The correct answer is **D**. EN through the use of feeding tubes is often discouraged in pediatric patients receiving hematopoietic transplant because of frequent tube replacement resulting from vomiting, bleeding risk in the presence of thrombocytopenia and pancytopenia with mucositis, feeding tube dislodgement, delayed gastric emptying, and malabsorption of nutrients.
3. The correct answer is **D**. The absorption of other drugs is increased or decreased.
4. The correct answer is **D**. All the factors listed can contribute to osteoporosis in cancer survivors.

APPENDIX 27-1. SCAN Tool for Assessing Malnutrition Risk in the Pediatric Oncology Patient[53]

Question	Points
Does the patient have a high-risk cancer?	**1**
Is the patient currently undergoing intensive treatment?	**1**
Does the patient have any symptoms relating to the gastrointestinal tract?	**2**
Has the patient had poor intake over the past week?	**2**
Has the patient had any weight loss over the past month?	**2**
Does the patient show signs of undernutrition?	**2**
Total	

3 points or greater indicates malnutrition risk; patient should be referred to a dietitian for assessment.

APPENDIX 27-2. Correction for Amputation Type and % Body Weight Lost Based on Segmental Weights[53]

Level of Amputation	Estimated % of Total Body Weight
Hand	0.7
Below the elbow	1.45
Above the elbow	3.55
Shoulder disarticulation	5.00
Hemipelvectomy or hip disarticulation	11.83
Above the knee	9.96
Below the knee	1.30

Equations for adjusting body weight for amputations:

A. Adjusted weight (kg) = [actual weight (kg) × 100] / (100 − % body weight of amputated limb)

B. Adjusted Body Mass Index (BMI, in kg/m^2) = adjusted weight (kg)/height (m^2)

C. Adjusted Ideal Body Weight (IBW, in kg) = [IBW (kg) × 100] / (100 − % body weight of amputated limb)

28

Trauma and Burns

Arlet G. Kurkchubasche, MD

Learning Objectives

1. Understand the components of the stress response and how these contribute to hypermetabolism in trauma and burn patients.
2. Identify childhood conditions that place patients at risk for trauma and child abuse, as well as nutrition impairment.
3. Understand the injury pattern seen in blunt trauma and how it impacts the ability to use enteral nutrition.
4. Understand the limitations of methods for predicting energy needs in pediatric patients with significant burn injuries.

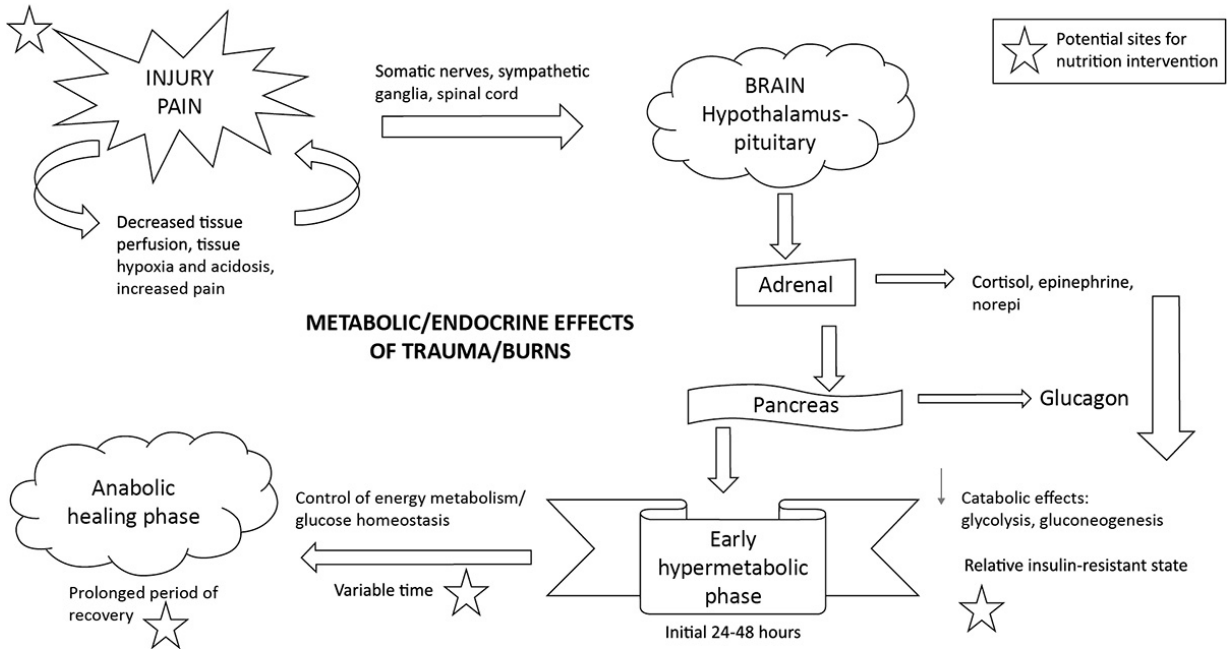
Introduction

This chapter introduces readers to the core of pediatric trauma and burn injuries to provide a basis for nutritional assessment in these specific yet unique circumstances, especially when multisystem injuries are present. While most pediatric trauma patients have low-grade injuries and recover to baseline rapidly without significant nutritional intervention, it is more challenging with multiply injured and critical trauma patients. Compared to non-surgical pediatric intensive care unit (ICU) patients with sepsis or respiratory failure, who have been the subject of randomized controlled

studies in nutrition support, these trauma patients present a smaller, less homogenous population as evidenced by the paucity of data from strong clinical trials and meta-analyses. It is therefore important for practitioners to understand the fundamental goals of trauma care in an organ-based manner and develop a functional nutrition support plan given the child's specific impairments and potential operative needs.

Trauma, burn injury, and surgery are known stressors resulting in hormonal, metabolic, and immune derangements. The initial physiological response to these events is well studied and is generally described in terms of the hormonal and cytokine responses (see Figure 28-1). These responses include the centrally mediated release of adrenocorticotropic hormone (ACTH), which stimulates cortisol release from the adrenal glands. This augments the action of epinephrine and norepinephrine, which are released from the adrenal medulla via sympathetic stimulation and impact cardiovascular response.

FIGURE 28-1. Metabolic/Endocrine Effects of Trauma and Burns



Glucagon is responsible for mobilizing glucose availability via glycogenolysis and gluconeogenesis. During the initial resuscitation, tissue

perfusion is reduced and there is an overall (transient) reduction in metabolic rate. This is promptly followed by the hypermetabolic/catabolic phase of injury, which is mediated by the hypothalamic-pituitary axis and the proinflammatory cytokines (ie, tumor necrosis factor, interleukin-6). This phase is characterized by changes in glucose homeostasis, with insulin promoting lipolysis and proteolysis to generate glucose, while relative insulin resistance contributes to elevated serum glucose levels during this acute phase.[1]

Trauma and burn injury have provided good clinical models for studying these responses because they are quantifiable injuries in terms of trauma scores and extent of burn injury. The physiological responses in pediatric patients are fundamentally no different than in adults. The focus of nutrition management is aligned with the fundamentals of critical care, which attempt to optimize all organ functions by ensuring adequate perfusion and tissue oxygenation. Support of this hypermetabolic state, aiming to control the resultant hyperglycemia and limit the extent of proteolysis, becomes the focus of nutrition interventions. The specific nutrient requirements, and whether certain micronutrients either become conditionally essential or can impact the elaboration of proinflammatory and anti-inflammatory cytokines and other agents such as nitric oxide, have been the subject of intense research.

The premise of this chapter is that the nutrition support of the child in the critical care unit follows clinical guidelines that parallel those for shock and sepsis or respiratory failure. What distinguishes this surgical scenario, however, is that appropriate consideration must be given to the actual physical and physiological insults and therapies employed to treat them. Pain management plays a significant role in the treatment of injured patients. While the use of narcotic and non-narcotic medications contributes to an amelioration of metabolic demands, it also promotes intestinal dysmotility and ileus and thereby impacts enteral feeding tolerance. The use of sedating agents (eg, propofol), which are solubilized in a lipid solution, should be considered carefully with patients requiring parenteral nutrition (PN) support to avoid excess dosing of lipids.

Traditionally, the goals of energy provision were estimated to be 130% to 160% of resting energy expenditure (REE) with an expectation to initiate

this by day 3 and consistently deliver this by 7 days post-injury. Considerations for timing, extent, and route of energy provision[2–4] will be re-evaluated in the context of changes such as those in the management of neurotrauma and burn injury.

General Background on Trauma in Childhood

Trauma accounts for significant morbidity, mortality, and long-term disability in children. The patterns of pediatric trauma are both age- and gender-related. Mechanisms for injury in children in the first 3 years of life include falls, poisoning (including caustic ingestions), transportation-related injuries, foreign body aspiration or ingestion, burn injuries, assault/neglect, and submersion/drowning mechanisms. With older children, falls and bicycle/pedestrian and other transportation-related injuries occur at a greater frequency. These primarily blunt mechanisms are accompanied later in adolescence by an increasing number of penetrating injuries. The specific organ injuries are broadly classified as neurotrauma (closed head injury/traumatic brain injury, spinal cord injury), thoracic trauma (chest wall, pulmonary, cardiac), abdominal-pelvic trauma (solid and hollow visceral, genitourinary), and musculoskeletal (long bone and pelvic fractures, craniofacial injuries). An anatomical classification system allows for injury severity scoring (ISS), which has a strong relationship with outcomes including morbidity, mortality, and length of stay and provides a valuable basis for trauma registries and databases.[5]

Most children are generally healthy prior to their acute injury; however, others may have underlying diagnoses such as neurocognitive disorders including autism or attention-deficit/hyperactivity. These conditions not only modify their risk-taking behaviors and place them at risk for injury, but also potentially contribute factors that may result in nutrition depletion over a shorter period than expected. On the opposite end of the spectrum, children injured as passive bystanders/occupants of a vehicle may also present with significant issues related to overweight/obesity.[6] These issues may complicate their acute surgical management and impact their nutrition support in the acute phase. The effect of excess weight on outcomes of

critically ill children has been evaluated, but not in a specific surgical cohort.[7]

The following sections provide brief descriptions of the most common forms of pediatric trauma and perspectives on when enteral nutrition (EN) is feasible and when there should be an anticipation of prolonged non-enteral nutrition.

Closed Head Injuries/Traumatic Brain Injury

The brain has an inordinately high metabolic demand, and under normal circumstances, brain metabolism and cerebral blood flow are generally tightly regulated. When there is a traumatic brain injury, there is often a change in cerebral perfusion resulting from intracranial pressure changes.[8] Despite this, the brain remains critically dependent on the uninterrupted delivery of both oxygen and glucose. Failure to support the brain adequately during this period likely impacts long-term outcomes. Current brain protective strategies may also affect the actual metabolic demand and alter the extent of caloric support.[9–11]

Hypothermia protocols in pediatric traumatic brain injury aim to reduce metabolic needs during periods of relative hypoperfusion. The nutrition support of such a severely injured patient will require assurance of glucose provision; however, the concomitant use of medications such as glucocorticoids and development of diabetes insipidus (DI) place this patient at risk for hyperglycemia. Furthermore, sodium and water balance are affected by the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and DI, as well as by the administration of resuscitative fluids that may include hypertonic saline. These electrolyte and fluid balance issues may impact the ability to provide proteins, which along with lipids remain essential during the catabolic phase. Management guidelines for these complex patients from multidisciplinary teams have been published and are updated regularly.[12,13] Once neurologic recovery is underway, maintenance of muscular tone for adequate respiratory function and physical rehabilitation is critical. The use of immune-enhancing diets containing omega-3 fatty acids, branched-chain amino acids, and

nucleotides has been evaluated in head injury patients and has not shown benefits over standard nutritional formulations.[14]

With a transition into rehabilitation facilities, adaptive nutrition management is still critical because these patients often have impaired swallowing and airway protection. Estimating caloric needs is difficult, and there are many studies documenting a difference between the calculated needs of the predictive equations and actual needs based on nitrogen balance studies.[15,16] The undesirable effects of chronic hyperglycemia and elevated respiratory quotient are evident.

Spine and Spinal Cord Trauma

This constellation of injuries most often affects adolescents in the context of sports injuries, diving accidents, and motor vehicle crashes. Injuries to the cervical and thoracolumbar spine are a common immediate concern in the trauma room, although the incidence is lower than in adults and compromises <2% of all fractures in children. Options for stabilization are based on the instability of the vertebral column, and these injuries can typically be managed nonoperatively. The primary concern is protection of the spinal cord and preservation of neurologic function. Secondary concerns relate to the normal ongoing growth and development of the axial skeleton to prevent progressive spinal deformity.

Spinal injuries often do not occur in isolation. There are reciprocal paradigms that ensure full imaging of the thoracolumbar spine when significant abdominal injuries occur that require emergent exploration and, conversely, require spine imaging because of findings such as the “seatbelt sign” from lap restraints that can cause Chance fractures (flexion/distraction injury to the lumbar spine), which are associated with small bowel injuries.[17] Both orthopedic surgeons specializing in pediatric spine disorders and neurosurgeons may be involved in the care of these patients. When a spinal cord injury has occurred, particularly in the cervical spine, patient support may require chronic ventilator and nutritional support based on the extent of the neurologic deficit. In both closed head injury (CHI) and severe spinal cord injury, early consideration of tracheostomy and

gastrostomy or gastro-jejunostomy may facilitate recovery and transfer to a rehabilitation center.

The peri-injury protection of the spinal cord remains a topic of active research and controversy and includes the acute use of steroids in those with “incomplete” injury as well as hypothermia protocols. The nutrition assessment of these patients is very individualized because of variability in neuromuscular deficit and metabolic demand despite ongoing perfusion.[18,19]

Blunt Abdominal Trauma/Solid Visceral Injuries

Solid organ injuries (ie, to the liver/spleen) are some of the most frequent injuries encountered in pediatric patients. In contrast to the adult population, these injuries are frequently isolated and can be managed nonoperatively. Despite their prevalence, there has been no universally accepted algorithm for their management. While radiographic parameters permit injury grading to indicate the severity level, it is the physiologic response that determines the immediate course of action. Operative intervention is reserved for those with profound or persistent hemodynamic instability. Simple immobilization with bed rest may be sufficient in most patients to permit intrinsic mechanisms for hemostasis to result in the formation of a stable hematoma. Since the stomach is intricately associated with the spleen via the short gastric vessels, it is usually decompressed, or enteral feedings are at least withheld for 24 hours to avoid gastric distention and retching. If there is a significant amount of blood in the abdomen, this not only creates abdominal pain but also is responsible for a transient ileus. The period of observation with bed rest is variable and typically depends on the degree of injury, but in general, these algorithms have become much less restrictive.

Hemodynamic instability despite transfusion is the predominant factor in determining whether nonoperative management will be successful. With hemodynamically unstable splenic injuries, splenic salvage can be attempted operatively, or splenectomy may become necessary. The use of embolization techniques for those with evidence of contrast extravasation

on imaging, but not hemodynamically unstable has been employed as well. Given the role of the spleen in the immunocompetency of the child, every effort is made to avoid splenectomy.[20]

Hepatic injuries rarely require operative intervention. In the most severe instances, an avulsion of the liver off the retrohepatic vena cava occurs, and these injuries are generally immediately fatal. Parenchymal injuries are best managed nonoperatively, especially if Glisson's capsule is intact. The abdominal wall provides some compression and containment, which is lost with laparotomy. When hemodynamic instability mandates exploration, the liver is packed with laparotomy sponges to compress the injured tissues, arterial inflow can be reduced by occluding the hepatic artery manually, and injured segments can either be compressed with large sutures or resected. Control of hemorrhage is as much a surgical event as it is a medical event in that hypothermia and coagulopathy can rapidly obviate any surgical advances. In the patient who is or becomes stable, postoperative management will assess bilirubin levels, which may become elevated for several reasons (ie, shed blood, biloma formation, biliary ascites). Intestinal bleeding may be from hemobilia, in which a fistula forms from the vascular system into the biliary ductal system. Depending on the degree of shock, the liver parenchyma may exhibit some degree of hepatic dysfunction, which should be considered when selecting medications. With restoration of adequate perfusion, this is usually only a transient phenomenon. These solid organ injuries are rarely associated with significant gastrointestinal dysfunction, and oral diets are resumed within several days of injury. Depending on the severity of the injury and whether there are additional injuries, these patients may benefit from caloric supplementation. This is because these children may not demonstrate a normal appetite and may develop constipation due to the lack of physical activity.

Pancreatic Trauma

Injury to the pancreas typically occurs from a compression force to the mid-abdomen, such as a bicycle handlebar or another object striking the epigastrium, or the result of a deceleration injury from a seatbelt, for example. Child abuse must always be considered when the injury

mechanism is otherwise not obvious. Complete fractures of the pancreas occur over the neck of the organ where it crosses the spinal column. Initial laboratory assessment in the trauma room is often inadequate for the detection of this injury. Amylase and lipase levels typically rise 8 hours after injury.

Computed tomography (CT) scanning of the abdomen is a method that often raises concern, and it may not be sufficiently sensitive. While adult trauma protocols would mandate operative exploration, there are case series in pediatric patients in which the injury is managed nonoperatively with the use of endoscopic retrograde cholangiopancreatography (ERCP) for stenting of the ampulla to provide a low-pressure system for pancreatic secretions to drain into the gastrointestinal (GI) tract rather than forming a pseudocyst.[21] These cases are controversial, and the most *conservative* approach may indeed be exploration with resection of the tail of the pancreas, thereby eliminating the ongoing leak of pancreatic enzymes and avoiding prolonged dependency on PN.[22] Resections at this level of the pancreas are not expected to affect glucose homeostasis, although there are some reports of late pancreatic exocrine insufficiency, which present with malabsorption as evidenced by diarrheal stools.

The patient who develops a pancreatic pseudocyst from the trauma can be managed with laparoscopic, open, or endoscopic cyst gastrostomy, which is usually delayed for 4 to 6 weeks to allow the cyst wall to mature. This allows the cyst content of pancreatic secretions to drain into the intestinal tract with the ultimate expectation that the ductal defect will heal and the pseudocyst involutes.

The extent of nutrition support depends on the physiologic impact of this traumatic pancreatitis. When jejunal access can be safely established, it is reasonable to use this route once there is evidence of return of intestinal motility. In the most severely injured, with ongoing pancreatitis and perhaps complications such as pancreatic necrosis and infection, PN is likely essential in the early postinjury period despite caution of adverse outcomes and prolonged hospitalization in pancreatic trauma.[23]

Renal Trauma

Injuries to the kidneys are typically unilateral, and assessment must include evaluation of the ureter and bladder. Typically, delayed-phase images on CT scans will identify urinary extravasation. In the absence of urine extravasation, renal injuries are primarily managed nonoperatively. Patients remain on bed rest until the hematuria subsides. If urinary extravasation occurs, it is classified as contained or free. The former may permit ongoing nonoperative management, although placement of a ureteral stent or percutaneous drainage would be advised in the latter. In rare cases, a primary nephrectomy is performed. Late consequences of renal injury include the development of renovascular hypertension. These patients generally experience transient ileus and then can resume an enteral diet. There are rarely concerns of renal insufficiency that would lead to a consideration of special diets.

Adrenal Hemorrhage

The adrenal glands have an exuberant blood supply from multiple sources. While generally protected in the retroperitoneum, they are at risk for direct injury, but rarely as an isolated organ. Injury is generally evident as adrenal hemorrhage but does not necessarily portend adrenal insufficiency, even when bilateral. When isolated, these injuries have minimal impact on the overall nutrition management of the patient.

Blunt Abdominal Trauma/Hollow Visceral Injuries

Duodenal Injuries

Duodenal hematoma and perforation are not infrequently encountered in pediatric trauma and result from blunt force trauma to the epigastrium (ie, bicycle handlebar injury, nonaccidental trauma). While most duodenal hematomas are dealt with nonoperatively, duodenal perforation is a significant injury that demands prompt operative intervention to avoid morbidity and even mortality. Duodenal hematomas become symptomatic

when extraluminal blood impacts on the luminal caliber, resulting in gastric outlet obstruction. Passage of a transduodenal feeding tube is almost always possible, either by radiographic guidance or endoscopically. This allows the patient to receive enteral nutrition despite the proximal obstruction, which may require decompression with a concomitant nasogastric tube. Operative intervention is rarely indicated in this injury. Pancreatic injury may be concomitant, so it is wise to check for chemical pancreatitis before initiating feeding. Resolution of the obstruction can occur within 10 to 14 days of injury as evidenced by improved gastric emptying.

Duodenal perforation is a much more significant injury that will require either primary repair with drain placement or sometimes more complicated surgical solutions to protect the duodenal repair from leakage (ie, pyloric exclusion with gastrojejunostomy). Typically, the pyloric channel will open 4 to 6 weeks later, which prompts the gastrojejunostomy to close spontaneously. These patients will often require PN support in the early postoperative phase until the gastrojejunal anastomosis becomes functional.

Small Intestine and Colon Injuries

Jejunoileal perforations or mesenteric injuries resulting in devascularized segments of the small intestine are frequently associated with seatbelt injuries and other mechanisms resulting in deceleration forces on the abdomen. The presence of a Chance fracture, a flexion-distraction fracture of the midlumbar region, was considered a hallmark of potential bowel injury.[24] These fractures may not be evident on initial CT imaging and may present within the first 24 hours, requiring repeated surgical examination of these patients while *nil per os* (NPO). Unless there is an extensive delay in diagnosis (24 h), most of these injuries can be treated with resection and anastomosis and should allow for resumption of oral alimentation within 5 days. Missed injuries are likely from vascular insufficiency resulting in stricture and may present 4 to 6 weeks after the traumatic event with symptoms of enteral intolerance.

Colon injuries in young children often occur from a penetrating mechanism such as falling onto a sharp object, rather than the missile injuries experienced by teenagers and young adults. Exploration is indicated in hemodynamically unstable patients and those with peritoneal findings.

The use of a triple-contrast CT involves administration of intravenous, enteral, and rectal contrast and has become a reliable exam in patients with a penetrating injury without the aforementioned parameters for exploration. In the absence of massive contamination, primary repair of colon injuries is attempted, in lieu of diversion. A return to oral alimentation should be possible after the resolution of postoperative ileus and should not require interval nutritional intervention.

Thoracic Injuries

Thoracic injuries in children may be remarkably unassociated with chest wall signs of trauma. The bony thoracic cage is sufficiently pliable in the young child to permit complete transduction of the impact energy to the lung parenchyma, resulting in pulmonary injury that most often consists of contusion rather than overt tissue disruption. Similarly, the pliability of the intrathoracic vessels results in fewer great vessel injuries than seen in the adult population. Blunt cardiac trauma is also well compensated with the capacity to offset compromised contractility with an increased heart rate response. When intrathoracic injuries occur that require operative intervention, recovery is supported by the generally healthy state of these organs.

Often these injuries occur in the setting of multiple traumas and require mechanical pulmonary support. When in isolation, they are usually of minimal consequence to nutrition management. Notable exceptions include direct esophageal injuries and chylothorax. Esophageal injuries may be the consequence of penetrating trauma, caustic ingestion, or ingestion of batteries. Batteries, particularly disk batteries, are ingested by young children and become lodged in the upper esophagus where they discharge their energy, may leak content, and create pressure-induced mucosal changes from the resultant contraction of the esophagus. With minimal mucosal damage, the patient can frequently return to a normal diet. Depending on the nature and severity of the injury, there may be an indication for gastrostomy or gastrojejunostomy placement for distal enteral feedings.[25]

The development of traumatic chylothorax is most often associated with a diaphragm injury. Depending on the amount of output via chest tubes, this may require initial enteral rest with progression to enteral nutrients with medium-chain triglycerides to reduce lymphatic flow and leakage. These injuries may require a prolonged period of nonoperative management and consequent parenteral or enteral nutrition.[26]

Pelvis and Extremity Trauma

When long bone fractures and pelvic fractures occur in multiply injured trauma patients, these injuries contribute to the injury severity score and consequently to the nutrition and metabolic demands of the patient. When these bony injuries are associated with overlying open soft tissue wounds, the risk for infection is increased. Operative management for limiting the extent of contamination and fixation of the fracture are routine measures. Even simple immobilization of a long bone fracture or the pelvis has metabolic consequences for the patient.

Current literature emphasizes the importance of providing adequate vitamin D and calcium. The American Academy of Pediatrics consortium on calcium focused on prevention to limit the fracture risk for young children and adolescents.[27,28] The prevalence of sports-related injuries in otherwise healthy young adolescents has led to studies on bone health, including vitamin D status.[29]

In skeletally immature pediatric patients, it is critical to address the consequences of growth plate fractures, nonunion of fractures, and subsequent growth impairment. In the absence of multiple-organ injury involving the abdomen, these patients rapidly resume enteral intake. Caloric intake targets should account for activity levels.

Facial trauma constitutes a specific subset of musculoskeletal trauma and is often associated with CHI. It has the added concerns for impacting enteral alimentation when the mandible and maxilla are involved. The passage of nasal tubes may be contraindicated in the presence of a basilar skull fracture, and depending on the patient's mental status, alimentation may be accessible via straw through a wire-stabilized jaw, or more extreme

measures such as gastrostomy may need to be considered early in the course.

Summary of Pediatric Trauma

While much pediatric trauma is minor and ambulatory, children with major single-system injuries or multiply injured trauma patients require early and intense evaluation for nutrition support. After restoration of vital organ perfusion, consistent nutrition support is a critical intervention to ensure the child is appropriately meeting the metabolic demands imposed by injury.[30]

Pediatric Burns

Burn trauma encompasses injuries from flames, thermal and chemical exposure, inhalation of smoke, and electrical contact. These continue to inflict significant morbidity and mortality on patients of all ages. Young children are particularly vulnerable to both accidental and nonaccidental burn injuries. Burn management has evolved dramatically in the past 30 years with centralization of care for the more severely injured patients. This has allowed for more concentrated experiences as well as focused clinical trials, resulting in significantly improved outcomes, with decreased mortality attributable to shock and wound sepsis. These patients, however, require extensive and chronic support from a multidisciplinary team to return to optimal functional status. With a better understanding of the metabolic consequences of burn injury in both animal and clinical research, the consistent emphasis on the importance of nutrition support has persisted as one of the hallmarks of burn care.[31–33]

Features Specific to the Pediatric Patient

Children have deeper burn injuries than adults because of their thinner dermal structure and architecture. Thermal injury in children occurs from contact with hot liquids in 70% of cases, in contrast with flame burn, which is more common among adult patients. In second-degree and third-degree burns, the percentage of total body surface area (TBSA) involved is a critical determinant of mortality. An understanding of individualized burn

resuscitation, guided by %TBSA involvement, has virtually eliminated burn shock as a cause of immediate death. In injuries involving >20% of TBSA, an associated stress response leads to the hypermetabolic state that has been well described with burn injury. It is less clear how TBSA impacts the severity of the stress response invoked when greater areas are involved,[34] although TBSA >30%to 40% results in tenfold elevations of urinary catecholamines.[35] Attempts to modulate the severity of this response have been diverse, including wound management strategies, enteral feeding strategies, and the use of pharmacologic agents. Current therapies using early burn wound excision and grafting have significantly reduced wound infections, thus reducing transdermal losses of fluid and protein, and achieving earlier healing and rehabilitation. The improved technologies for coverage of burn wounds with reduced frequency of painful dressing changes will also reduce metabolic demands.[36,37]

The use of the intestinal tract for alimentation has been specifically promoted for burn injuries. Concerns about mucosal atrophy and impairment of the gut-associated immune defenses because of nonuse have been key motivators. While enteral feeding may frequently require administration via nasoenteric tubes, often oral supplementation is well-received by young children. At times, simple nighttime nasogastric supplementation to reach target caloric goals is sufficient. Formula selection is typically based on calculated caloric needs with special emphasis on protein content.

Early enteral feeding has not shown the same benefit as delayed enteral feeding, and risks using an underperfused intestinal tract, thereby subjecting the patient to additional morbidity.[38,39] The use of pharmacologic agents such as growth hormone, oxandrolone (a testosterone analog), and insulin-like growth factor results in decreased catabolism, but it is unclear how this will ultimately affect clinical course and outcomes. The use of low-dose insulin has been described as a useful intervention, which may be a consequence of controlling hyperglycemia in a state of relative insulin resistance.[40] Vitamin D supplementation remains controversial because pediatric burn patients have consistently low serum values, but supplementation did not appear to affect bone health and other outcomes.[41]

One persistent problem in the management of pediatric burn injury is the frequency of potentially painful interventions and the consequent interruption of enteral alimentation. While the use of coverage substrates with reduced frequency of dressing changes has improved the situation, another option is to allow for ongoing enteral nutrition during intraoperative interventions under sedation or general anesthesia.[42,43] Despite the reluctance to use PN in burn injury, there are reports of benefits from cautious use with hypocaloric goals.[44]

Inhalation injury also has a greater potential for complications in the young child because of the decreased luminal diameter of the trachea and bronchi with a propensity for formation of obstructive casts and secretion plugs. Early intubation and respiratory toilet are important, especially in those with associated facial burn injury, given the rapid and dramatic swelling associated with third-space extravasation of resuscitative fluids. These patients remain at risk for prolonged respiratory support and ventilator-associated pneumonias, which further impact their hypermetabolic state.[45] Recent studies document that the highest mortality is encountered in children under 4 years of age with TBSA >30% and inhalation injury.[46]

Energy Estimates in Burn Injury

Children start with greater metabolic and specific nutrient demands (greater caloric demand per kilogram) compared with their adolescent and young adult counterparts, a demand that is amplified by the injury. They generally have lower energy stores, which are more rapidly depleted. Their propensity toward fevers, despite the absence of infection, further compounds their energy demands. Despite the ubiquitous use of the Harris-Benedict equation and other variants to estimate caloric needs for these patients, these remain very rudimentary tools and there are data that they do not accurately reflect actual needs as measured by indirect calorimetry.[47] Providing excess calories will not obviate the proteolysis accompanying the hypermetabolic response, but likely contributes to hyperglycemia. How hyperglycemia specifically impacts the incidence of wound infection in burn patients is not known; however, there is enough suggestive evidence from other models of critical illness to avoid blatant overnutrition. On the opposite end, we know

that undernutrition negatively impacts wound healing and maintenance of lean body mass. Muscle catabolism, particularly involving the muscles of respiration, leads to functional debilitation that can be measured in terms of prolonged respiratory support; however, physical rehabilitation of the core muscles and extremities is similarly impacted in the later stages of therapy. Despite the consistent recommendation to assess these patients with indirect calorimetry, in general, a target of 120% to 130% of REE is believed to be appropriate.[48]

The composition of the energy sources is primarily carbohydrates (up to 60% of calories) but with a maximum glucose load limited to 7 mg/kg/min. This is to avoid hyperglycemia and to limit lipogenesis, resulting in increased oxygen consumption and carbon dioxide elaboration, which raises the respiratory quotient (RQ). Lipids should initially deliver between 12% and 15% of total nonprotein calories. This lower proportion has been associated with improved clinical outcomes as compared with the higher lipid-containing diets (35% calories from fat) in a randomized clinical trial.[49] The use of omega-3-containing fatty acids is theoretically beneficial from the standpoint of reducing the precursors for prostaglandin E2 and leukotrienes, thereby limiting further immunosuppression. The protein needs are exacerbated in burn patients because of the additional losses via the open wounds in addition to the standard urine losses and the gluconeogenesis as seen in other instances of hypermetabolism. Daily intake of 2.5 g/kg/d and up to 4 g/kg/d may be necessary and is limited by the patient's state of hydration and renal function. Specific "immune-enhancing" diets that contain high protein loads, omega-3 fatty acids, and branched-chain amino acids and nucleotides have not been shown to be superior to standard high-protein diets.[50,51]

Enteral feedings remain as the preferred nutrition support route and should be instituted as soon as it is deemed safe to use the intestinal tract. In some institutions, the early use of postpyloric feedings is encouraged, and techniques have been developed to safely place these devices at the bedside.[52] Although initial studies suggested that early feeding would be beneficial, no clear benefit has been demonstrated in terms of decreased length of stay, morbidity, or mortality.[53] As with any other invasive procedure, the risks and benefits must be considered when initiating enteral

feeds. There are case reports of early aggressive enteral feeding leading to luminal obstruction and perforation.[54] PN support retains a critical role in those patients with a prolonged ileus or persistent systemic and visceral hypoperfusion.

Laboratory evaluation using the standard visceral proteins is limited in the immediate/acute injury period and may be more useful as a predictor of outcomes, rather than as a measure of visceral protein status. The degree of hypoalbuminemia observed in early burn injury is attributable to the losses via the burn wound. Further complicating their interpretation is that albumin therapy is prevalent in burn resuscitation and does not reflect intrinsic production. Weight and other anthropometrics are also invalidated in the early resuscitative phase given the rapid expansion of the extravascular space. Trends in prealbumin and other visceral proteins, as well as weight changes once the acute resuscitative phase is complete, are reasonable to monitor.

Clinical Example 1

A 14-year-old female with morbid obesity is transported to the trauma center after being involved in a multi-vehicle collision as a restrained passenger. Although alert and oriented, she is dyspneic and is found to have a pneumothorax. She has a significant air leak, suggesting a bronchial injury. She is intubated and undergoes bronchoscopy with subsequent thoracotomy for repair of a proximal airway injury. Her initial abdominal exam was unremarkable but limited by obesity. A focused assessment with sonography for trauma (FAST) exam was not possible, and the urgent intervention for her airway delayed further evaluation. She develops abdominal tenderness, which prompts CT evaluation and subsequent laparotomy for a left hepatic duct avulsion with ischemia to the left lobe of the liver. What are her requirements for energy support in this phase of her acute illness? How are they best met?

Answer/Considerations

The energy assessment of the teenager with overweight and morbid obesity who requires critical care support is extraordinarily difficult. In this time of

metabolic stress, the goal should not be weight management, but preservation of protein status. Estimates for caloric intake are best derived from the assessment of metabolically active tissues, and these are more closely related to ideal body weight than actual. Not only will this patient need to heal her traumatic injuries, but she now has 2 additional wounds (thoracotomy and laparotomy) to heal. Indirect calorimetry will likely provide the best guidance in this scenario. Given the intra-abdominal injuries, one would expect a period of ileus to follow, and thus provision of nutrients should not be delayed and can initially occur via parenteral route.

Clinical Example 2

A 12-year-old female equestrian sustained a kick to her stomach while grooming her horse. Her initial abdominal CT shows a hematoma over the neck of the pancreas. There is no free fluid in the abdomen. She is nauseated and a nasogastric tube evacuates bilious fluid. Over the next 24 hours, she continues to complain of abdominal pain and her amylase rises to 950. Do you advise nutritional supplementation at this point?

Five days later, an ERCP was done, and there is no major ductal injury. Her abdominal pain has improved, and amylase is 200. What do you expect her ability to eat will be within the next 48 hours?

Answer/Considerations

Pancreatic injuries, despite nonoperative management, can lead to significant metabolic stress because of the inflammatory nature of the retroperitoneal injury (hematoma), which is further exacerbated by the release of pancreatic enzymes. While we can expect this patient to have been active and healthy from a nutrition standpoint, we would anticipate a return to GI function within approximately 5 days. The information related to the ERCP would suggest that cautious introduction of enteral feeds would be acceptable and that her response to enteral stimulation of pancreatic secretions must be monitored. Should she develop recurrent pain and pancreatitis with oral intake, the institution of PN until a jejunal feeding tube can be placed would be appropriate.

Clinical Example 3

A 2-year-old boy is brought to the trauma/burn unit with 35% TBSA injury from a hot oil burn to his face, trunk, and lower extremities. Within 24 hours, he has developed anasarca, but is hemodynamically stable and making urine at 1 mL/kg/h. He is scheduled to undergo burn wound excision on the following day. When do you consider starting nutrition support? How do you best determine his caloric needs? How do you initiate caloric intake?

Answer/Considerations

This child has sustained a significant injury and is expected to exhibit a stress response leading to catabolism. Nutrition support will become essential for re-establishing a positive nitrogen balance. Given the extent of injury, this child will likely have central venous access, and provision of glucose and protein can be started early via this route. At the time of the operation, it would be ideal to have a nasoenteral tube placed for subsequent enteral feeding access. Energy requirements are notoriously difficult to predict, and indirect calorimetry remains the most accurate tool.

Test Your Knowledge Questions

1. Blunt abdominal trauma with injury to the liver requires which of the following?
   A. Prolonged support on PN
   B. Specialized formulas to account for hepatic insufficiency
   C. Rarely requires operative intervention
   D. Is rare in the pediatric patient
2. Which of the following is NOT a result of pancreatic trauma?
   A. Chemical pancreatitis
   B. Prolonged intestinal ileus
   C. Clinical features of pancreatic insufficiency
   D. Diabetes mellitus
3. Closed-head injury patients unequivocally benefit from the provision of immunonutrients. True or False?
4. Total burn surface area is most predictive of which of the following?

A. Mortality
B. Metabolic stress
C. Energy needs
D. None of the above

References

1. Simsek T, Simsek HU, Canturk NZ. Response to trauma and metabolic changes: posttraumatic metabolism. *Ulusal Cer Derg*. 2014;30:153–9. https://doi.org/10.5152/UCD.2014.2653
2. Martinez-Ortega AJ, Pinar-Gutierrez A, Serrano-Aguayo P, et al. Perioperative nutritional support: a review of current literature. *Nutrients*. 2022:14(8):1601. https://doi.org/10.3390/nu14081601
3. Fivez T, Kerklaan D, Mesotten D, et al. Early versus late parenteral nutrition in critically ill children. *N Engl J Med*. 2016;374(12):1111–22. https://doi.org/10.1056/nejmoa1514762
4. Houschyar M, Borrelli MR, Tapking C, et al. Burns: modified metabolism and the nuances of nutrition therapy. *J Wound Care*. 2020;29(3):184–191. https://doi.org/10.12968/jowc.2020.29.3.184
5. Brown JB, Gestring ML, Leeper CM, et al. The value of the injury severity score in pediatric trauma: time for a new definition of severe injury? *J Trauma Acute Care Surg*. 2017;82(6):995–1001. https://doi.org/10.1097/ta.0000000000001440
6. Rana AR, Michalsky MP, Teich S, et al. Childhood obesity: a risk factor for injuries observed at a level-1 trauma center. *J Pediatr Surg*. 2009;44(8):1601–1605. https://doi.org/10.1016/j.jpedsurg.2008.11.060
7. Goh VL, Wakeham MK, Brazauskas R, et al. Obesity is not associated with increased mortality and morbidity in critically ill children. *JPEN J Parenter Enteral Nutr*. 2013;37(1):102–108. https://doi.org/10.1177/0148607112441801
8. Philip S, Udomphorn Y, Kirkham F, Vavilala M. Cerebrovascular pathophysiology in pediatric traumatic brain injury. *J Trauma*. 2009;67(suppl 2):S128. https://doi.org/10.1097/ta.0b013e3181ad32c7
9. Elliott E, Shoykhet M, Bell MJ, Wai K. Nutritional Support for Pediatric Severe Traumatic Brain Injury. *Front Pediatr*.

2022;10:904654. https://doi.org/10.3389/ped.2022.904654
10. Mtaweh H, Smith R, Kochanek PM, et al. Energy expenditure in children after severe traumatic brain injury. *Pediatr Crit Care Med*. 2014;15(3):242–249. https://doi.org/10.1097PCC.0000000000000041
11. Bowman CE, Scafidi J, Scafidi S. Metabolic perturbations after pediatric TBI: it's not just about glucose. *Exp Neurol*. 2019;316:74–84. https://doi.org/10.1016/j.expneurol.2019.03.018
12. Reuter-Rice K, Christoferson E. Critical update on the third edition of the Guidelines for Managing Severe Traumatic Brain Injury in Children. *Am J Crit Care*. 2020;29(1):e13–e18. https://doi.org/10.4037/ajcc2020228
13. Kochanek PM, Tasker RC, Carney N, et al. Guidelines for the management of pediatric severe TBI, third edition: update of the Brain Trauma Foundation guidelines, executive Summary. *Neurosurg*. 2019;84(6):1169–1178. https://doi.org/10.1093/neuros/nyz051
14. Briassoulis G, Filippou O, Kanariou M, et al. Temporal nutritional and inflammatory changes in children with severe head injury fed a regular or an immune-enhancing diet: a randomized, controlled trial. *Pediatr Crit Care Med*. 2006;7(1):56. https://doi.org/10.1097/01.pcc.0000192339.44871.26
15. Havalad S, Quaid M, Sapiega V. Energy expenditure in children with severe head injury: lack of agreement between measured and estimated energy expenditure. *Nutr Clin Pract*. 2006;21(2):175. https://doi.org/10.1177/0115426506021002175
16. Joffe A, Anton N, Lequier L, et al. Nutritional support for critically ill children. *Cochrane Database Syst Rev*. 2009;(2):CD005144. https://doi.org/10.1002/14651858.cd005144.pub2
17. Daniels AH, Sobel AD, Eberson CP. Pediatric thoracolumbar spine trauma. *J Am Acad Orthop Surg*. 2013;21:707–716. https://doi.org/10.5435/jaaos-21-12-707
18. Patt P, Agena S, Vogel L, et al. Estimation of resting energy expenditure in children with spinal cord injuries. *J Spinal Cord Med*. 2007;30(suppl 1):S83. https://doi.org/10.1080/10790268.2007.11754610
19. Brown RL, Brunn MA, Garcia VF. Cervical spine injuries in children: a review of 103 patients treated consecutively at a level 1 pediatric

trauma center. *J Pediatr Surg*. 2001;36(8):1107. https://doi.org/10.1053/jpsu.2001.25665
20. Shinn K, Gilyard S, Chahine A, et al. Contemporary management of pediatric blunt splenic trauma: a national trauma databank analysis. *J Vasc Interv Radiol*. 2021;32(5):692–702. https://doi.org/10.1016/j.jvir.2020.11.024
21. Maeda K, Ono S, Baba K, Kawahara I. Management of blunt pancreatic trauma in children. *Pediatr Surg Int.* 2013;29(10):1019–1022. https://doi.org/10.1007/s00383-013-3402-9
22. Beres AL, Wales PW, Christison-Lagay ER, et al. Non-operative management of high-grade pancreatic trauma: is it worth the wait? *Pediatr Surg.* 2013;48(5):1060–1064. https://doi.org/10.1016/j.jpedsurg.2013.02.027
23. McLaughlin C, Park C, Lane CJ, et al. Parenteral nutrition prolongs hospital stay in children with nonoperative blunt pancreatic injury: a propensity score weighted analysis. *J Pediatr Surg*. 2020;55(7):1249–1254. https://doi.org/10.1016/j.jpedsurg.2019.06.015
24. Achildi O, Betz RR, Grewal H. Lapbelt injuries and the seatbelt syndrome in pediatric spinal cord injury. *J Spinal Cord Med*. 2007;30:S21–S24. https://doi.org/10.1080/10790268.2007.11753964
25. Fuentes S, Cano I, Benavent MI, Gomez A. Severe esophageal injuries caused by accidental ingestion of button batteries in children. *J Emerg Trauma Shock*. 2014;7(4):316–321. https://doi.org/10.4103/0974-2700.142773
26. Seitelman E, Arellano JJ, Takabe K, et al. Chylothorax after blunt trauma. *J Thorac Dis*. 2012;4(3):327–330. https://doi.org/10.3978/j.issn.2072-1439.2011.09.03
27. Baker SS, Cochran WJ, Flores CA et al. American Academy of Pediatrics. Committee on Nutrition. Calcium requirements of infants, children, and adolescents. *Pediatrics*. 1999;104(5):1152. https://doi.org/10.1542/peds.104.5.1152
28. Goulding A. Risk factors for fractures in normally active children and adolescents. *Med Sport Sci*. 2007;51:102. https://doi.org/10.1159/000103007
29. James JR, Massey PA, Hollister AM, Greber EM. Prevalence of hypovitaminosis D among children with upper extremity fractures. *J*

Pediatr Orthop. 2013;33(2):159–162. https://doi.org/10.1097/bpo.0b013e3182770bf7
30. Hasenboehler E, Williams A, Leinhase I et al. Metabolic changes after polytrauma: an imperative for early nutritional support. *World J Emerg Surg*. 2006;1:29. https://doi.org/10.1186/1749-7922-1-29
31. Purdue G. American Burn Association presidential address 2006 on nutrition: yesterday, today, and tomorrow. *J Burn Care Res*. 2007;28(1):1. https://doi.org/10.1097/bcr.0b013e31802c8995
32. Valentini M, Seganfredo FB, Fernandes SA. Pediatric enteral nutrition therapy for burn victims: when should it be initiated? *Rev Bras Ter Intensiva*. 2019 Oct 14;31(3):393–402. https://doi.org/10.5935/0103-507x.20190062
33. Houschyar M, Borrelli MR, Tapking C et al. Burns: modified metabolism and the nuances of nutrition therapy. *J Wound Care*. 2020 Mar 2;29(3):184–191. https://doi.org/10.12968/jowc.2020.29.3.184
34. Atiyeh B, Gunn SWA, Dibo S. Metabolic implications of severe burn injuries and their management: a systematic review of the literature. *World J Surg*. 2008;32(8):1857. https://doi.org/10.1007/s00268-008-9587-8
35. Chan M, Chan G. Nutritional therapy for burns in children and adults. *Nutrition*. 2009;25(3):261. https://doi.org/10.1016/j.nut.2008.10.011
36. Saba S, Tsai R, Glat P. Clinical evaluation comparing the efficacy of aquacel ag hydrofiber dressing versus petrolatum gauze with antibiotic ointment in partial-thickness burns in a pediatric burn center. *J Burn Care Res*. 2009;30(3):380. https://doi.org/10.1097/bcr.0b013e3181a2898f
37. Saffle JR. Closure of the excised burn wound: temporary skin substitutes. *Clin Plast Surg*. 2009;10;36(4):627–641. https://doi.org/10.1016/j.cps.2009.05.005
38. Venter M, Rode H, Sive A, Visser M. Enteral resuscitation and early enteral feeding in children with major burns—effect on McFarlane response to stress. *Burns*. 2007;33(4):464–471. https://doi.org/10.1016/j.burns.2006.08.008
39. Peck M, Kessler M, Cairns B, et al. Early enteral nutrition does not decrease hypermetabolism associated with burn injury. *J Trauma*. 2004;57(6):1143. https://doi.org/10.1097/01.ta.0000145826.84657.38

40. Schulman C, Ivascu F. Nutritional and metabolic consequences in the pediatric burn patient. *J Craniofac Surg*. 2008;19(4):891. https://doi.org/10.1097/scs.0b013e318175b5cc
41. Rech MA, Colon Hidalgo D, Larson J, et al. Vitamin D in burn injured patients. *Burns*. 2019;45(1):32–41. https://doi.org/10.1016/j.burns.2018.04.015
42. Sunderman CA, Gottschlich MM, Allgeier C, et al. Safety and tolerance of intraoperative enteral nutrition support in pediatric burn patients. *Nutr Clin Pract*. 2019;34(5):728–734. https://doi.org/10.1002/ncp.10399
43. Hudson AS, Morzycki AD, Wong J. Safety and benefits of intraoperative enteral nutrition in critically ill pediatric burn patients: a systematic review and pooled analysis. *J Burn Res*. 2022;43(6):1343–1350. https://doi.org/10.1093/jbcr/irac036
44. Dylewksi ML, Baker M, Prelack K et al. The safety and efficacy of parenteral nutrition among pediatric patients with burn injuries. *Pediatr Crit Care Med*. 2013;14(3):e120–e125. https://doi.org/10.1097/pcc.0b013e3182712b2b
45. Palmieri T, Warner P, Mlcak R et al. Inhalation injury in children: a 10 year experience at Shriners Hospitals for Children. *J Burn Care Res*. 2009;30(1):206. https://doi.org/10.1097/bcr.0b013e3181923ea4
46. Sheridan RL, Schnitzer JJ. Management of the high-risk pediatric burn patient. *J Pediatr Surg*. 2001;36(8):1308–1312. https://doi.org/10.1053/jpsu.2001.25805
47. Suman OE, Mlcak RP, Chinkes DL, Herndon DN. Resting energy expenditure in severely burned children: analysis of agreement between indirect calorimetry and prediction equations using the Bland-Altman method. *Burns*. 2006;32(3):335–342. https://doi.org/10.1016/j.burns.2005.10.023
48. Chan MM, Chan GM. Nutritional therapy for burns in children and adults. *Nutrition*. 2009;25(3):261–269. https://doi.org/10.1016/j.nut.2008.10.011
49. Garrel DR, Razi M, Larivire F, et al. Improved clinical status and length of care with low-fat nutrition support in burn patients. *JPEN J Parenter Enteral Nutr*. 1995;19(6):482. https://doi.org/10.1177/0148607195019006482

50. Saffle JR, Wiebke G, Jennings K, et al. Randomized trial of immune-enhancing enteral nutrition in burn patients. *J Trauma*. 1997;42(5):793–800. https://doi.org/10.1097/00005373-199705000-00008
51. Marin V, Rodriguez-Osiac L, Schlessinger L, et al. Controlled study of enteral arginine supplementation in burned children: impact on immunologic and metabolic status. *Nutrition*. 2006;22(7–8):705. https://doi.org/10.1016/j.nut.2006.03.009
52. Cone L, Gilligan M, Kagan R, et al. Enhancing patient safety: the effect of process improvement on bedside fluoroscopy time related to nasoduodenal feeding tube placement in pediatric burn patients. *J Burn Care Res*. 2009;30(4):606. https://doi.org/10.1097/bcr.0b013e3181abffa3
53. Dylewksi ML, Baker M, Prelack K, et al. The safety and efficacy of parenteral nutrition among pediatric patients with burn injuries. *Pediatr Crit Care Med*. 2013;14(3):e120–e125. https://doi.org/10.1097/pcc.0b013e3182712b2b
54. Scaife CL, Saffle JR, Morris SE. Intestinal obstruction secondary to enteral feedings in burn trauma patients. *J Trauma*. 1999;47(5):859. https://doi.org/10.1097/00005373-199911000-00007

Test Your Knowledge Answers

1. The correct answer is **C**. Solid organ injuries are common in the child due to the exposure of the liver and spleen in the upper abdomen. Unless there is hemodynamic instability, these rarely require operative intervention and can be managed with physical limitations. Nutrition support generally consists of resumption of an age-appropriate diet with caloric supplementation when caloric intake is inadequate.
2. The correct answer is **D**. While the extent of pancreatic trauma is quite variable, it is often accompanied by chemical pancreatitis and ileus. When resection occurs, it is usually over the neck of the pancreas and leaves sufficient endocrine tissue for normal glucose control but may impact exocrine function as evidenced by steatorrhea.
3. The correct answer is **B**. While the concept of immunonutrition is appealing in this population of patients, randomized clinical studies

have failed to show benefit.

4. The correct answer is **A**. TBSA remains a predictor of mortality. In children under 4 years of age, inhalation injury combined with a TBSA injury of >30% defines the highest mortality risk group. It is not clearly proportional to the extent of the stress response, which is mediated by multiple additional factors. Estimates of energy needs based on TBSA are consistently inaccurate in their targets.

29

Surgery

Arlet G. Kurkchubasche, MD

Learning Objectives

1. Identify factors that impact nutrition requirements associated with acute metabolic changes in neonatal and pediatric surgical patients.
2. Identify methods for optimizing nutrition support throughout the perioperative period by using clinical assessment, laboratory analysis, and bedside calorimetry.
3. Provide a basis for determining when to initiate and progress enteral feeding in a core group of neonatal surgical conditions.
4. Delineate strategies to limit the progression of cholestatic jaundice in the postoperative infant with intestinal dysfunction.

Introduction

The metabolic consequences of surgical stress have been extensively studied and show a characteristic/stereotypic response in terms of hormone and cytokine elaboration. The resultant hypermetabolic state during the phase of injury and recovery has been the focus of nutrition support. In pediatrics, the challenge is not only to provide nutrients to support immediate metabolic needs but also to avert catabolism of limited protein and fat stores while providing substrate for growth and development.

Wound failure, infection, and mortality are primary outcome measures related to perioperative nutritional status. The discipline of surgical nutrition progressed at a time when critical care advancements allowed us to support infants with more complex conditions, and the institution of parenteral nutrition (PN) changed the face of postoperative care for this subset of patients. With time, however, an awareness of potentially adverse effects has become apparent, specifically the unique problem of cholestasis in the pediatric population.

With further advances in the science of intestinal physiology, the complexity of the intestinal tract and its role in fluid, electrolyte, and nutrient assimilation, as well as in immune sampling functions, became evident. The provision of appropriate nutrition held the promise of enhanced immune function, fewer complications related to catabolism, and overall improved outcomes. Studies on immunomodulatory agents provided either parenterally or enterally in clinical sepsis have been conducted on adult and pediatric patients alike.[1,2] The neonatal literature focuses on the components of human milk, which appears to be beneficial in averting gut-derived sepsis.[3]

The limitations of clinical research in pediatrics are evident when it comes to studies requiring repeated blood sampling and invasive procedures; however, there is reason to believe that the findings from adult clinical trials can be applied to pediatric patients. There is a wealth of knowledge from observational studies in pediatrics about growth needs for all age groups and many with congenital conditions, but they exclude more complex surgical patients. The best quantitative neonatal and pediatric data related to the metabolic response to stress are derived from studies of a relatively homogeneous group of infants who undergo cardiopulmonary bypass for repair of congenital cardiac disease or who require extracorporeal membrane oxygenation (ECMO) for pulmonary support.[4,5] These infants, however, cannot represent the entire spectrum of pediatric surgical conditions, and much work remains to be done.

Nutrition assessment and support of pediatric surgical patients require consideration of the acute impact of the surgical intervention and the more chronic consequences of intestinal resection or reconstruction. Potential postoperative complications and underlying congenital disorders may

further contribute to persistent impairment of intestinal function. Cholestasis, regardless of etiology, is an additional morbidity that may impact recovery. While hyperbilirubinemia associated with a primary disorder may not be preventable, efforts should be made to limit PN-related cholestasis.[6]

The first section of this chapter focuses on perioperative nutrition support and the general concept of adjustments in nutrition considerations for neonatal and pediatric patients in response to altered metabolic demands resulting from surgery. Recent publications also indicate the complex relationship between patients with underlying intestinal problems who are on PN and their propensity for a systemic inflammatory response syndrome-like reaction affecting their morbidity and mortality.[7] Patients who experience stress from trauma or burn injury are discussed in Chapter 28, "Trauma and Burns." The second section focuses on nutrition support strategies specific to some of the congenital gastrointestinal (GI) disorders encountered in neonatal pediatric surgery patients.

Pediatric surgical care of newborns to mature adolescents requires fundamental knowledge of the physiological changes that occur with growth and maturation. Depending on the underlying condition, patients will have variable impairments of GI function that may be related to intestinal motility, mucosal absorptive capacity, and immune function. The perioperative state is a dynamic period; as the patient's clinical status evolves, reassessment and redirection of nutrition care are necessary. Because these patients also represent a spectrum of acute and chronic disease, it is difficult to generate a uniform set of nutrition care standards.

The principles upon which guidelines are established should focus on and correspond to the general American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines for nutrition assessment in pediatrics, which include the following:

1. Individualized assessment of nutrition status to determine the urgency and extent of patient support needs.
2. Consideration of the timing of onset of postoperative nutrition support and the appropriate use of PN when the alimentary tract is compromised, with consideration for provision of either enteral nutrition (EN) or PN support within 3 days of hospitalization.

3. Provision of nutrition in a manner (enteral or parenteral) most consistent with safe clinical practice.
4. Avoidance of potential complications by continuous reassessment of individual risk/benefit ratios, including optimal timing for alimentary tract challenges.
5. Methods for determining the adequacy of nutrition support.

General Nutrition Considerations in Neonatal Surgery

Neonatal Assessment, Nutrient Composition, and Targets for Nutrition Support in the Early Postoperative Period

Infants with congenital disorders of the abdomen, especially the intestinal tract, have fluid and nutrition needs requiring frequent reassessment in the immediate perioperative period. The excess fluids required to restore or maintain vital organ perfusion are not necessarily accompanied by a greater demand for caloric provision.[8–10] It is important to consider these requirements separately and avoid the potential for overfeeding and hyperglycemia. Many factors in the postoperative patient impact energy estimates, including the use of mechanical ventilation, the provision of external heat support, and the use of sedating agents and neuromuscular blockers. Pain control has a tremendous impact on perioperative hormonal stress response. Preemptive analgesia using local and regional anesthesia helps to reduce the stress response and is part of current surgical practice; for instance, in infants undergoing patent ductus arteriosus ligation, a fentanyl anesthetic resulted in improved protein metabolism.[11,12]

The assessment of intravascular volume status can be quantified using weight, fluid balance records, and occasional invasive monitoring with central venous pressure. Assessment of metabolic demands is not as straightforward. Unless nitrogen balance studies are readily accessible, the best estimates for caloric provision are based on the infant's gestational age and formulas for resting energy expenditure in the acute and recovery phases, which are best modified with estimated stress factors.

Anthropometric parameters remain the mainstay of neonatal nutritional assessment, so feedback on nutrition interventions is not immediate. It

would be ideal to assess parameters in real time and make the necessary adjustments to ensure a positive nitrogen balance along with anticipated weight gain. In the absence of this technology, however, the focus remains on maintaining euglycemia and avoiding hyperlipidemia and azotemia/uremia, while providing an escalating number of balanced macronutrients in the form of carbohydrates, lipids, and protein.

Laboratory parameters may be used to assess nutrition status; however, in infants, they must be used as trends rather than absolute measures because there are often no gestationally appropriate controls.[13] Principal laboratory markers include total protein, albumin, prealbumin (evaluated in the context of a normal C-reactive protein [CRP]), and retinol-binding protein. These function as measures of protein anabolism after the acute phase of injury and are difficult to interpret early in the postoperative state, but they are valuable as preoperative assessment tools. This caution is emphasized in a recent ASPEN position paper.[14] Often, nonprotein calories of 60 to 80 kcal/kg/d, perhaps even less, are sufficient to meet initial neonate goals.[15]

Documented studies indicate that preterm neonates often require a generous protein supply, perhaps as high as 4 g/kg/d, which primarily provides a substrate for tissue repair but does not independently prevent catabolism of the existing muscle mass. Counting this protein delivery as energy-yielding caloric intake may result in inadequate caloric provision; this is the basis for calculating and targeting nonprotein calories in the acute perioperative setting. To provide an optimal substrate for nutrient assimilation, a nonprotein calorie-to-nitrogen ratio of 130:1 to 210:1 is generally recommended as the target PN solution.

Many of these recommendations came from studies in the early years of PN development.[16–18] In practice, we aim for a target of 180:1. However, while the calculation of caloric targets of nonprotein calories may be important in the early perioperative phase, targets should revert to total caloric intake once the acute wound-healing demands return toward baseline. The time for this transition is perhaps best estimated by normalization of CRP and should correspond to clinical indicators such as wound status, return of intestinal function, and lack of infectious complications.

PN-Associated Cholestasis and Other Origins

Cholestasis is a significant problem in pediatric surgical patients, who frequently require prolonged PN support and are at further risk for hepatic injury because of their underlying diagnosis, nonenteral feeding status, and susceptibility to sepsis. Newborn infants may have transient indirect hyperbilirubinemia; the marker of significant cholestasis is a direct bilirubin exceeding 2 mg/dL. This is often accompanied by elevation of the serum transaminases; gamma-glutamyl transpeptidase is the most sensitive to ongoing inflammation. The alkaline phosphatase level must be interpreted cautiously, as much of this enzyme may be derived from bone rather than liver and fractionated evaluation may be necessary. With the onset of jaundice, some key interventions must occur before ascribing the finding to PN–associated liver disease (PNALD). An ultrasound evaluation of the liver and gallbladder is necessary to document the absence of gallstones, sludge, and ductal dilation. Cholelithiasis is a known consequence of massive enteral resection. Ultrasound also serves to document the direction of portal venous blood flow, which should be toward the liver parenchyma. Hemolysis should also be excluded before a PNALD diagnosis.

For patients who are anticipated to have a prolonged dependence on PN (>1 mo), several hepatoprotective strategies are generally instituted. The initiation of enteral feeds is the single most important intervention in limiting cholestasis.[19] “Cycling” refers to delivery of the PN solution over a limited number of hours per day. Although the hepatoprotective benefit of delivering PN on this schedule is difficult to separate from the myriad other hepatoprotective strategies for modern PN management, it is based on trying to establish normal physiologic glucose homeostasis, when this is disrupted by exogenous provision of glucose by PN. The primary limiting factor in establishing this therapy is the infant’s ability to tolerate extended periods without access to glucose, given limited glycogen stores.

Seizures from hypoglycemia carry the most profound risk for neurological devastation. The initiation of this strategy in term infants usually corresponds to the onset of a baseline enteral feeding regimen to support euglycemia. The procedure for cycling involves reducing the rate of the PN infusion to 50% for 1 hour before discontinuing the infusion and reinitiating the next PN solution at 50% of the goal rate for 1 hour before

increasing to the goal rate. Determining the target number of hours off PN also involves calculating the consequent glucose infusion rate (GIR) in the limited period of infusion and not blindly exceeding standards. While infants are hospitalized, they continue to receive lipid infusions over 24 hours to help minimize the use of additional carrier fluids for medication administration and avoid repeated entry into saline-locked or heparin-locked lines. Once on home PN, lipids are infused over the same time interval as the dextrose and amino acid solution, allowing the line to be heparin-locked once daily.

Another hepatoprotective strategy involves maintaining specific relative ratios between macronutrients. Examples of this include targeting a nonprotein calorie-to-nitrogen ratio of approximately 180:1 and ensuring that lipid calories do not exceed 30% of total nonprotein calories. The specific role of lipids in preventing and potentially reversing cholestasis has been the subject of much investigation. Lipids are a dense source of calories and have been particularly useful in fluid-restricted preterm infants. The commercially available formulation of lipids is an omega 6-rich soy-based substrate with intrinsically proinflammatory properties. The use of fish oil-based omega 3-rich emulsion has been associated with the reversal of cholestasis and even avoidance of cholestasis when used preemptively,[20,21] although the same effect has been achieved by restricting the infusion of commercially available agents to 1 g/kg/day.[21,22] The future promises to provide us with more complex balanced lipid emulsions that may be used with less impact on the GIR (as high as 15 mg/kg/min)—a necessary consequence of lipid restriction.[23]

Recurrent infections are another source of strain on the liver and may contribute to progressive dysfunction. While the care and maintenance of central venous access is not generally considered a specifically hepatoprotective strategy, the avoidance of central line-associated bloodstream infections is an important goal. Any infection further compounds the potential for progressive cholestasis. Many bloodstream infections originate from enteric organisms that breach the mucosal barrier and enter first the portal and then the systemic circulation. Management of the intestinal microflora may require the use of antibiotics and probiotics when recurrent Gram-negative and fungal infections occur. When stenosis

or stricture results in segmental regions of dilation and stasis, resection or stricturoplasty may be required, followed by tapering enteroplasty for autologous reconstruction. These issues are also discussed in Chapter 25, "Intestinal Failure."

As the infant enters the recovery phase without any infectious or wound-healing complications, the focus changes toward the more typical pediatric goals of nutrition support covering both acute needs and those for growth and development. At this point, documentation of weight gain, normalization of acute-phase reactants (eg, CRP), and establishment of increasing prealbumin values become the primary outcome measures. As mentioned previously, the focus on providing protein purely for wound-related anabolism is reduced at this point, and caloric provision should include protein-derived calories to avoid the complications of overfeeding.

Initiation and Choice of Enteral Alimentation

EN is incrementally introduced when there is evidence of GI tract motility (onset of stooling or stoma output) and assurance that newly created anastomoses have achieved satisfactory healing. General principles in managing postoperative patients include a conceptual understanding of normal postoperative events such as paralytic ileus, delayed gastric emptying, the effect of narcotic analgesics, and the peri-anastomotic edema that may impede transit during the first 48 hours after surgery. Guidelines for determining the ability to initiate feeding include (a) an assessment of gastric output in terms of volume and nature (bilious/nonbilious); (b) a physical examination for abdominal distention and the presence of bowel sounds; and (c) an assessment of output, whether by stoma or per rectum. It is important to remember that motility recovers first in the distal intestine, so an isolated stool does not indicate recovery of overall GI motility. The recognition of potential intestinal complications such as an anastomotic leak, intra-abdominal sepsis, wound failure at the level of the abdominal wall closure, and even stoma-related problems (eg, stomal stenosis or prolapse), is critical.[24]

The timing of feeding initiation therefore depends on an assessment of the risks and benefits of providing enteral nutrients. Choice and mode of feeding are often determined by the infant's gestational maturity, the history

of mucosal injury/disruption, the effectiveness of motility, the urgency to transition off PN, and the presence of gastroesophageal reflux (GER). In general, human milk should remain the first choice because of its qualities related to optimizing gut mucosal function and immunity. Although donor human milk lacks some of the immune benefits, it remains a desirable nutrient source.

When commercial formulas are necessary, infants who have no history of a compromised intestinal wall (eg, mucosal damage, transmural edema/fibrosis) can be started on standard hydrolyzed whey-based formulas for gestational age; infants with a positive history should be started on a more elemental substrate to optimize absorption in the presence of a compromised mucosal barrier. Casein hydrolysates (such as Pregestimil and Alimentum) are common options for infant surgical patients; the choice of a specific formula is often based on fat composition and osmotic load. However, these specialized formulas provide only a fraction of the calcium and phosphorus needed for a preterm infant, and this must be considered with supplementation when possible.

Elemental formulas that consist of amino acids and were designed to obviate protein allergies (eg, Neocate, EleCare) may in some instances be better tolerated in those with compromised motility as well. Theoretically, they reduce the luminal content of nutrients that reach the distal intestine. In addition, hydrolyzed formulas limit bacterial overgrowth and carbohydrate fermentation, both of which result in excess reducing substances being excreted along with luminal fluids in the form of diarrhea or frequent loose stools. As the patient's intestinal tract recovers, transitioning to a more complex and age-appropriate formula can be accomplished gradually. Infants with congenital disorders that do not affect the intestine itself, such as omphalocele, congenital diaphragmatic hernia (CDH), malrotation without volvulus, pyloric stenosis, and thoracic conditions, should be able to tolerate standard formulas.

Guidelines for caloric estimates in critically ill surgical infants requiring respiratory support are difficult to establish but are best assessed using a metabolic cart.[7] The acutely ventilated patient probably does not require a major revision in energy provision, but infants who are chemically relaxed, actively ventilated, and not participating in the work of breathing may

benefit from an objective assessment. Most recent publications have focused on a subset of neonatal cardiac surgery patients[2,3] who can be analyzed as a reasonably cohesive group. Outside this group are infants with CDH who are intubated but variably assisted with ventilation and require attention to avoid an inappropriate respiratory quotient, which might adversely impact their ability to eliminate CO2. Each of these patients is unique, and generic formulas cannot be used.

The goal is to have a patient who is in optimal nutritional shape. This is a multifactorial evaluation: the surgeon hopes to see that the infant has an appropriate weight gain of 1% to 2% of body weight per day and is demonstrating appropriate somatic growth in length, head circumference, and triceps skinfold measurement. For patients who will require another surgical intervention, the progressive increase of serum albumin toward the normal range is also a reassuring parameter. To achieve these goals, one can ideally provide a balanced enteral and parenteral regimen. Sufficient EN (trophic or greater) should be provided to stimulate the mucosa, maintain mucosal health, and promote motility. The limits of "tolerance" are probably best defined by evaluating the volume and nature of the output. Stool output per rectum is difficult to quantify other than by frequency; more than 8 stools per day would be indicative of feeding intolerance. Stoma output, on the other hand, is easier to quantify, as outputs are evaluated in the context of total enteral intake and should not exceed 30% by volume.

Other formulas for assessment of normal stoma output are based on weight, with expected output estimated at 1 mL/kg/h and tolerable amounts to allow progression of enteral feeds set at either 30 mL/kg/d or 2 mL/kg/h. Excess output serves as an indicator of inadequate absorptive capacity and osmotic fluid loss and should be further evaluated by assay or measurement of stool-reducing substances, stool pH, and fecal fat. Reducing substances will shed light on carbohydrate malabsorption: contents of 1% or greater in the presence of loose stools constitute an indication for intervention, depending on the type of enteral intake. Stool pH reflects whether there are organic acids generated by unabsorbed sugars, which can occur independently from the presence of reducing substances. The percentage of

unabsorbed dietary fat can be estimated by quantifying the amount of fat in the stool sample.

Ideally, a target caloric goal is established for each patient, and EN is pushed to the limit of tolerance, with PN providing the balance of calories necessary to achieve weight gain and laboratory goals. Aggressive advancement of EN needs to be balanced with concerns about surpassing tolerance and induction of intestinal diseases such as necrotizing enterocolitis (NEC). The use of distal refeeding provides a valuable adjunct in situations where ostomies and mucous fistulas have been created, at least contributing to the restoration of a complete enterohepatic pathway for bile if the distal ileum has been retained.[25] However, the benefits of distal refeeding are counterbalanced by the often complex contraptions that are needed to collect and reinfuse stoma output. There is also a risk of perforating the distal intestine with repeated catheterization. The decisions involved in these complicated cases require that all care providers reach a consensus on short-term and long-term plans for the patient. Only then can the ideal nutrition support plan be instituted.

All surgical patients must be monitored carefully for the onset of jaundice. Often the default reason for the onset of direct hyperbilirubinemia is the use of PN; however, surgical patients can develop intestinal obstruction at the level of an anastomosis, at the level of a proximal stoma, or a random site due to peritoneal adhesions or previous ischemia resulting in stricture formation. These conditions must remain in the foreground as correctable causes of obstructive jaundice. Other conditions include drug-related cholestasis (seen with cephalosporins), low-grade sepsis, and even secondary disorders such as biliary tract disease (gallstones and sludge).

Surgical Considerations for Nutrition Support in Infants With Specific Congenital Disorders

Proximal Intestinal Obstruction

A congenital proximal intestinal obstruction is usually recognized antenatally or in the immediate postnatal period and typically prompts

urgent operative intervention. While surgery can be temporized with effective nasogastric suction, operative delay is reserved for infants with suspected congenital heart disease who will require further evaluation (ie, patients with esophageal atresia and duodenal atresia) or who would benefit from stabilization of their transitional circulation changes before undergoing anesthesia and operative stress. Although unusual, concerns about the presence of an underlying nonsurvivable metabolic disorder or lethal chromosomal disorder constitute another justification for delaying surgical intervention.

Esophageal Atresia

The most complex cases involve infants who have esophageal atresia and are significantly preterm and/or have low birth weight. Surgery may safely be delayed 1 to 2 days while postnatal circulation stabilizes and the infant undergoes screening for disorders in the VACTERL association (vertebral, anorectal, cardiac, tracheo-esophageal, renal, and limb anomalies). During this time, most neonates will be started on at least peripheral PN, with a plan to escalate to central PN once appropriate venous access has been established via a temporary umbilical venous catheter, a peripherally inserted central catheter (PICC) line, or a surgically placed central venous line inserted at the time of operative repair. The expectation is that the infant will not be able to use the intestinal tract until approximately 7 days after surgery when the esophageal anastomosis is evaluated for patency and the absence of leaks.

The placement of a transanastomotic feeding tube at the time of the operation is controversial and is surgeon-dependent. The association with anastomotic complications remains speculative but unsubstantiated in the literature.[26] When a leak occurs, the nonenteral alimentation period may extend for another 5 to 7 days, since there is no safe esophageal access to the stomach or beyond. Even in the presence of a transanastomotic tube, feeding is not initiated because of concerns about GER with gastric feeding. The use of gastrostomy tubes (G-tubes) has generally been limited to infants with long-gap atresia who will undergo esophageal reconstruction/repair later, or infants who are expected to have poor oral-motor skills or other feeding dysfunction based on concomitant disorders

(eg, trisomy, retrognathia). Given the reliance on PN for 7 days or more, most neonatal centers will place central venous access preoperatively (PICC line) or at the time of reconstruction. Because these considerations for alimentation are not based on technique, there is no difference in the postoperative management of thoracoscopic or open repair.

After the esophageal anastomosis is verified to be free of leaks using a contrast esophagram, the contrast is often followed through the duodenum, primarily to establish the absence of malrotation. Duodenal stenosis due to annular pancreas and duodenal atresia can coexist with esophageal atresia. This will not be apparent during surgery because the abdominal cavity is not entered. Enteral feeds can be commenced, preferably by mouth, to avoid repeated instrumentation of the esophagus. Esophageal dysmotility is common and has been manometrically documented as an interruption of the progression of the peristaltic wave at the level of anastomosis.

The more capacious proximal pouch initially requires time to empty into the narrower distal segment. As the infant grows, the two segments will become more consistent in caliber in the absence of stricture formation at the anastomosis. Delayed emptying of the proximal pouch will result in oral regurgitation and tracheal compression, which becomes clinically evident as desaturation with feeds. These behaviors are anticipated in the early course, and any exacerbation should be considered a symptom of a progressive anastomotic stricture. Infants must have the head of their bed elevated and should be fed upright.

The goal of oral feeding is to allow the infant to practice frequently with low-volume amounts (5−10 mL every 3 h). Once small amounts are tolerated, gradual progression may occur. Because GER will likely be the next hurdle for feeding progression, it is more effective to provide frequent lower-volume feeds every 3 hours. When breastfeeding is initiated, it should be limited similarly in time and the feeding interval should be progressed as the infant tolerates it. Although it is difficult to measure breastfeeding intake, reports indicate that weighing the infant pre-feed and post-feed may be a useful method. Alternatively, if the typical volume of human milk generated on a given schedule is known, a measured quantity of milk can be expressed before feeding the infant.

These infants are prone to acid reflux, which is detrimental to anastomosis and can promote stricture formation. Acid reduction therapy

should be started in the immediate postoperative period and maintained for 6 to 12 months. Metoclopramide may be helpful when feeds are first initiated to promote gastric emptying, although this medication comes with a risk for dystonia, and parents must be aware of the risk/benefit relationship. Optimally, the infant will progress to full feedings over 5 to 7 days. Infants with symptomatic tracheomalacia may have delayed progression, requiring repeated intubation for mechanical ventilatory support, or they may require support with high-flow nasal cannula oxygen, which compromises their ability to tolerate gastric feeds. In these instances, it may be advisable to place a transpyloric feeding tube to enable the infant to take EN and be weaned off PN while the airway disability is being addressed. Severe cases may require placement of a G-tube, however, there is reluctance to do so because of the potential for further affecting the abnormal Angle of His (at the gastroesophageal junction) and potentiating reflux.

Surgical therapy for GER, while necessary in a subset of infants, is avoided whenever possible because of the inherent dysmotility of the esophagus, which may not be able to overcome any degree of distal obstruction, and the shortened length of the esophagus. While these concerns may be considered surgically with a performance of a “floppy” or looser fundoplication and/or esophageal lengthening procedures such as the Collis gastroplasty, these are best avoided unless a recalcitrant esophageal stricture forms.[27]

During infancy, the choice of formula should be based on gestational age. There are no specific intestinal absorptive defects to prompt the use of more elemental formulas. The caloric concentration of infant formulas is often necessary and advisable to accomplish nutrition goals, given the propensity for GER. Long-term nutrition problems in esophageal atresia relate to ongoing issues with GER and proximal strictures. Surveillance esophagrams are sometimes indicated, and mechanical or hydrostatic fluoroscopic dilatation is usually effective in treating strictures. With progression to solid foods, these children must be coached to chew well and consume liquids with their meals to overcome any potential residual esophageal dysmotility. It is not unusual for overly large pieces of food to become lodged at the level of the anastomosis and result in esophageal

obstruction. This problem tends to resolve itself with age, maturity, and increasing esophageal caliber.

Duodenal Atresia

Duodenal atresia can be identified antenatally, providing an opportunity for prenatal counseling. This section focuses on the concern for potential associated anomalies (cardiac and chromosomal) and the timing and strategy for operative repair. While most infants can undergo this reconstructive operation within 48 hours of birth, surgery may be delayed for infants who are preterm or have congenital heart disease, prolonging the need for PN. Based on the specific functional cardiac defect, a decision can be made to proceed early with abdominal surgery before pulmonary pressures rise significantly and impact perioperative fluid and cardiac management. This can reduce the cholestatic consequences of the anatomic obstruction and prolonged PN, a combination that may become detrimental with time.

For anatomic reasons, the repair of duodenal atresia involves no resection; instead, it involves creating an anastomosis that joins the dilated proximal segment to a segment of the much smaller distal duodenum. During surgery, an assessment of the distal bowel is made to ensure that there are no further sites of atresia. The proximal duodenum is assessed in terms of its caliber for possible tapering duodenoplasty. Furthermore, the overall situation is assessed to determine the potential need for prolonged gastric decompression via gastrostomy. With a satisfactory anastomosis, the stomach remains decompressed for an average of 5 days. The pylorus remains incompetent in the immediate perioperative period, so the resolution of bilious output is not a reliable indicator of improved gastric emptying. Because a duodenal leak can be a catastrophic complication, a contrast study for anatomic and functional evaluation is obtained in infants before commencing feeds. In the absence of a contrast study, a progressive decrease in output indicates forward peristalsis through the anastomosis and is the best indication that it is safe to start enteral feeds.

When human milk is not available, the choice of infant formula is based on gestational age. There are no predictable associated absorption disorders to require specialized formulas. The mode of feeding depends on the child’s

anatomic and functional considerations. While intermittent oral feeds may be a successful strategy, often a more rapid transition from PN to EN is achieved with continuous gastric feeds that are then transitioned to bolus and oral feeds.

Certainly, oral feeds can be added on top of continuous feeds to allow the infant to acquire oral motor skills. The more complicated infants have greater duodenal dysmotility and may have required a tapering enteroplasty; they often have a G-tube inserted to facilitate gastric decompression, thereby protecting the anastomosis, and allowing the infant greater success in extubating from mechanical ventilation without a nasogastric tube in place. Given the potentially complex and prolonged postoperative course in this disorder, PN is started routinely and converted to central formulation once central venous access has been established.

Jejunoileal Atresia

As the anatomic site of obstruction extends further distally, the immediate postoperative problems related to the provision of EN are generally less frequent and less severe. These proximal obstructions can occur in isolation or in various constellations of increasing complexity.

In the simple mucosal web or single transmural atresia, operative considerations are relatively simple if the infant has normal overall intestinal length. A resection of the abnormally dilated jejunal segment and primary anastomosis to the distal unused bowel results in the least size discrepancy between adjacent limbs of the intestine and has the highest success rate for recovery of bowel function. These infants would be anticipated to tolerate the onset of enteral feedings after bilious nasogastric output has resolved and volumes have decreased in concert with the passage of bile-pigmented stool output. This can occur 5 to 10 days after surgery and mandates the use of PN in the interim.

Infants with multiple intestinal atresia have reduced overall bowel length. Operative methods to salvage length must be considered with the infant's gestational age and how it relates to the ongoing longitudinal growth of the intestine. Infants delivered at term and diagnosed with multiple intestinal atresia have less opportunity to compensate for lost intestinal length. The most proximal segment of the intestine will be the

only segment dilated, and length can be preserved by performing a standard longitudinal tapering enteroplasty. Only in the event of severe congenital short bowel should more novel techniques such as the serial transverse enteroplasty procedure[28] or Bianchi be considered to optimize salvage of mucosal surface area and promote intestinal contractility. As many as possible of the subsequent atretic portions of the intestine should be salvaged using a "shish kebab" technique, in which continuity is created over a silastic catheter.[29] Surgical clinical judgment will dictate which segments are reasonable to salvage, as leaking or obstructed anastomoses will only compromise recovery.[30]

In the most complex variant of jejunoileal atresia, the "apple peel deformity," there is a complicated malformation of the proximal intestine along with preservation of the distal ileum on a vascular pedicle that provides retrograde perfusion for a variable length of intestine. It is important to recognize the anatomic appearance of the twisted intestine "maypoled" around the single vascular trunk originating from the distal ileal arcade, so that further inadvertent vascular compromise is avoided by torque from a poorly aligned enteric anastomosis. Furthermore, careful perioperative fluid management is essential to preserve adequate perfusion to the distal-most intestine. Hypotension will result in splanchnic vasoconstriction, compromising mucosal flow to this vulnerable section of the bowel.

Nutrition considerations in these infants focus on the provision of adequate PN calories via central access, with early contemplation of techniques to limit cholestatic disorders. This is necessary because the process of completing the conversion to enteral feeds may be prolonged by dysmotility and complications such as NEC. With the intent to gradually stimulate the bowel for adaptation, continuous feeds are most often initiated, and the infants (who often have G-tubes to facilitate this) are allowed to sham-feed by mouth and are eventually converted later to full bolus feeds by mouth or G-tube.

Distal Intestinal Obstruction

Distal intestinal obstruction usually involves the distal ileum and beyond. These infants will present with abdominal distention that is not relieved

with nasogastric decompression. Distal ileal atresia or obstruction from inspissated meconium can result in volvulus of the distended, fluid-filled segment and cause ischemic necrosis of more extensive regions of the intestine. In the absence of significant intestinal loss, these conditions are unlikely to require more than conventional perioperative nutrition support. Resection of the right colon, including the ileocecal valve, is usually well tolerated. The need for replacement of vitamin B12 must be considered later (age 2 years) if a significant portion of the terminal ileum accompanies the resection. More extensive colon resections, such as those encountered in patients with Hirschsprung's disease, have more significant effects on the resorption of water and electrolytes. Patients with Hirschsprung's disease and anorectal malformations require long-term dietary management focused on achieving optimal evacuation of stool.

Colon Atresia

Colon atresia is a rare condition, accounting for only 10% of all intestinal atresia. A vascular defect at the level of the middle colic artery is most common, resulting in an interruption of continuity at the mid-transverse colon. The right colon becomes massively distended since a competent ileocecal valve may not allow for the distribution of the enteric contents into the terminal ileum.

Operatively, there are several solutions for this condition. An extended right hemicolectomy with anastomosis of the ileum to the transverse colon results in permanent loss of a significant surface area for nutrient and water absorption. Fortunately, the left colon can compensate for water absorption with adaptation, and the patient should not have persistent watery stools. More complicated solutions focus on preserving the right colon with a proximal diverting stoma in the hopes that it will decompress and regain its normal caliber and motility. Nutrition considerations for these patients are generally simple and are impacted by whether a second reconstructive operation is necessary.

Meconium Ileus and Variants

This is the earliest clinical presentation of cystic fibrosis, and early recognition may be protective of pulmonary disease because therapy can be

undertaken pre-emptively. Clinically, it presents as distal ileal obstruction due to inspissated luminal contents. Meconium ileus may be complicated further by either (a) perforation of the obstructed bowel, resulting in meconium peritonitis; or (b) volvulus of the distended bowel, resulting in ischemia and stricture formation that may appear identical to an atresia. Simple meconium ileus in which there is only luminal inspissation can often be decompressed with sequential retrograde gastrograffin enemas, but surgery is sometimes necessary. In the process of decompressing the obstructed segment with saline or N-acetylcysteine irrigation, it is possible to perforate or excessively traumatize the intestine. Often the safest choice is placement of a T-tube that provides access for continued postoperative irrigation and gradual resolution of the obstruction.

In the event of complicated meconium ileus due to luminal discontinuity, resection and primary anastomosis may be possible, but because of the risk of recurrent distal obstruction, creating a "vented" anastomosis (Bishop Koop or Santulli stoma) provides the greatest assurance of success. This allows the enteric contents to evacuate via stoma should distal obstruction reoccur and provides direct access to the distal bowel to treat with 3% N-acetylcysteine solution.

The most difficult variant to deal with operatively is meconium peritonitis because it may not be possible to identify the perforation site or mobilize it to create a stoma. If possible, a proximal diverting stoma becomes necessary, with staged exploration and restoration of continuity later. It is helpful if the distal end of the bowel can be identified to prepare it for the subsequent operation and consideration of distal refeeding of proximal stoma output. In rare cases, the entire bowel may be extensively entrapped by the leaked meconium, with no bowel visible. Wide drainage of the meconium-covered peritoneal surfaces for a few weeks while maintaining the infant on PN is an option allowing for slow separation of the inflamed intestines from the meconium surface and may avoid injury to the initially hidden intestinal mass.

Nutrition management of these infants requires consideration of a likely underlying diagnosis of cystic fibrosis, which must be verified by testing. In the past, EN with a protein hydrolysate formula or human milk did not require the provision of pancreatic enzymes, however, it is now common practice to provide these enzymes to optimize whatever enteral intake is

available for absorption. This practice must be balanced with past concerns about mucosal damage from specific formulations of enzyme dosing.

An infant with a diverting stoma who will require a second complicated operation 6 weeks or more in the future is a classic example that involves nutrition decision-making. Cholestatic jaundice is based on PN exposure as well as possible underlying liver disease associated with cystic fibrosis. Once intestinal continuity to a stoma or the rectum is established postoperatively, the goal is to wean PN support expeditiously while recognizing that these infants tend to have higher-than-usual caloric requirements.

Hirschsprung's Disease

Hirschsprung's disease is a consequence of the absence of the ganglion cells from the rectum and distal-most colon, typically involving the rectosigmoid. The enteric ganglion cells are essential for relaxation of the intestine, and their absence results in a functional obstruction of the colon where the ganglion cells are missing (aganglionosis). With this obstruction, there is dilation of the normal colon proximal to the transition zone beyond which the infant's neural crest cells failed to migrate during the embryonic period.

Hirschsprung's disease most often affects term or near-term infants; it is unusual in preterm infants. The newborn who is diagnosed and promptly undergoes reconstructive surgery—whether open, laparoscopic-assisted, or transanal—is likely to be able to start normal EN within 5 days of the operation. Therefore, after the child has been diagnosed, the provision of peripheral PN during the first few days of life is probably sufficient. This scenario, however, changes with a late diagnosis of Hirschsprung's disease, which is often associated with significant malnutrition, enterocolitis, and long-segment disease. These situations are independent predictors of a difficult postoperative course; surgeons will often choose not to operate immediately and instead manage these patients medically (with irrigations if the transition zone is distal) or perform a stoma at the point where ganglion cells are present. Failure of the initial reconstruction potentially leads to a lifetime of anorectal disability.

Once diverted or established on an effective irrigation program, the alimentary tract can again be challenged with nutrients and should be able to function appropriately, allowing the infant to receive nutrition. The infant with total colon aganglionosis is essentially diverted at the level of the terminal ileum and may require PN support transiently until adaptation has occurred. The rare infant with aganglionosis extending into the small intestine will often have severe short bowel syndrome (SBS) and must be managed accordingly. These are some of the most challenging patients to manage in terms of their fluid needs.

Anorectal Malformations

Children with isolated anorectal malformations generally have no specific nutrition requirements. Their anorectal defect will either respond to progressive dilation, allowing for a delayed operative intervention, or will require a diverting colostomy. These children grow and develop normally in the absence of associated disorders.

After reconstruction, children with Hirschsprung's disease and low variants of imperforate anus will have issues related to stooling, with some developing severe functional constipation that may progress to overflow incontinence. Children with high imperforate anus tend to have problems with fecal incontinence, either due to absence of the sphincter complex or deficient innervation. Appropriate dietary management, along with a supervised bowel management program, is essential to the well-being of children with this spectrum of disease. Dietary considerations include the provision of sufficient nonabsorbable fiber intake, along with sufficient liquid intake to ensure daily evacuation.

Abdominal Wall and Diaphragm

Omphalocele

Omphalocele and gastroschisis are two very distinct congenital disorders with completely different considerations in terms of their postnatal GI function. While both conditions involve the presence of an abdominal wall defect, the intestine is protected within a membrane in patients with omphalocele and is not subject to the fascial constriction and amniotic exposure encountered in gastroschisis. Omphalocele can be associated with

genetic disorders as well as renal and cardiac defects, and these conditions typically determine outcomes in these patients. Beckwith-Wiedemann syndrome is diagnosed when the omphalocele is associated with macroglossia, hypoglycemia, and hemihypertrophy.

Hypoglycemia is a transient metabolic condition with no long-term implications for glycemic control, but the syndrome places the patient at risk for solid organ tumors. Associated congenital heart disease may involve various intracardiac defects or a constellation of defects involving the heart, pericardium diaphragm, and sternum, which are referred to as the pentalogy of Cantrell. Depending on the size of the abdominal wall defect, the liver and intestine are typically extra-abdominal, and reconstruction can be accomplished in one stage rather than multiple.

A small omphalocele can be closed within days after birth once associated anomalies have been excluded. The child is typically kept *nil per os* (NPO) preoperatively; this may not be strictly necessary, but it is convenient for preoperative evaluations. Once a small omphalocele is closed, enteral alimentation can be commenced as soon as there is evidence of GI motility/function. While there are no predictable GI problems, extrinsic gastric compression from the oversized liver and GER are not uncommon and may require transient postpyloric feeding.

In the more complicated giant omphaloceles, PN is commonly started to bridge the child's nutrition needs while multiple operative procedures interfere with consistent EN. Ethical considerations arise when an infant with omphalocele is diagnosed with a lethal chromosomal disorder such as trisomy 18. Often the surgical condition can be managed in a nonoperative manner and EN can be delivered in a relatively noninvasive manner via a nasogastric feeding tube if the child will not feed by mouth. The outcomes of omphalocele should be excellent except for the most complex disorders.

Gastroschisis

Gastroschisis is frequently the more complex abdominal wall defect from the standpoint of operative interventions and nutrition support. This abdominal wall defect is typically a relatively small, full-thickness aperture to the right of the umbilical cord insertion. Much of the GI tract is extruded through this defect and is bathed in amniotic fluid throughout pregnancy.

The exposed intestine is at risk for torsion and lymphovascular impairment from a tight fascial aperture, which creates a relatively fixed defect as the intestine and its mesentery continue to grow. The intestinal wall can become engorged and thick from limited lymphovascular outflow and become necrotic once arterial inflow is compromised.

Postnatal management of the exposed intestine is accomplished by several techniques based on the physical findings. If the bowel is not excessively thick and matted, bedside reduction of the intestine and coverage of the defect with the residual umbilical tissue is an elegant option. If this is not feasible, then the creation of a temporary "silo" is accomplished with the use of a sterile, transparent plastic bag that is oblong and has a flexible ring at the open end. It is placed over the intestines, accommodating them vertically, and the ring is placed through the fascial opening and rests on the undersurface of the abdominal wall. Gravity and gradual compression of the silo, from the top down, forces the intestine into the accommodating abdominal space, ultimately allowing for abdominal wall closure.

Surgical closure at birth, which was the mainstay in the past, is usually reserved for those instances when operative exploration is felt to be mandatory based on findings such as a remnant necrotic segment of bowel at the defect and therefore a likely complete obstruction proximal to this, with a need to understand how much residual bowel remains for management of the consequent short bowel syndrome. Of note is that stomal diversion is typically not possible due to the much-reduced abdominal surface area. The edematous/thickened bowel is not very forgiving to surgical interventions. For those infants without SBS because of gastroschisis, there do not appear to be any remarkable differences in outcomes concerning time to full feeds and hospital discharge, regardless of the type of closure.[31]

The most important predictor of outcomes appears to be the original condition of the intestine.[32] The intestinal surface in gastroschisis has a variable appearance and ranges from nonedematous, pliable, and virtually normal intestine without surface adhesions to stiff, edematous bowel whose contour and continuity cannot be assessed visually or even by palpation. Further complicating the presenting features is the tendency for these

children to have a shorter-than-normal length of intestine. Fortunately, some of these changes resolve with time; however, the time to normal intestinal peristalsis can be quite variable. After an extended period of observation of 4to 6 weeks without evidence of bowel continuity, contrast studies are indicated to evaluate whether an intestinal atresia is present. Evaluation much earlier is without benefit, as the abdomen will be quite hostile to exploration secondary to adhesions.

An interesting situation arises when an atretic segment is recognized at birth. Although the intuitive response would be to divert at that level to allow for some enteral stimulation, this is not generally advisable. There is limited abdominal wall surface area for a stoma, and the edema of the intestine rarely allows it to reach the abdominal wall in an orientation that is feasible for creation of a stoma. It is currently considered best practice to close the abdomen and correct the atresia in a second operation.[33]

Given the primary dysfunction of the intestine on multiple levels, these infants may require an extended period of PN support. During the initial few weeks, the infant remains decompressed with a nasogastric tube. Again, in contrast to other children who may require prolonged decompression, there is a reluctance to perform any visceral procedure, even a gastrostomy, due to abdominal wall constraints and the altered surface characteristics of the GI tract. Unless these children are substantially preterm, they usually have an uneventful perioperative course with a short duration of mechanical ventilation.

There are no known interventions that lead to a more rapid resolution of intestinal edema. In general, these infants require up to 180 to 200 cc/kg/d of intravenous fluid support in the first few days, as they are projected to be relatively volume-depleted on presentation and continue to require good vascular perfusion of the intestine. The peripheral edema that may appear occurs on a different basis than that of the intestine, which likely happens because of vascular and lymphatic congestion at the fascial ring defect. In contrast to the peripheral edema, it is unlikely that diuresis would affect this visceral edema in the early phases.

The onset of intestinal feeding must coincide with evidence of effective full intestinal peristaltic activity as indicated by decreasing nasogastric output and onset of stooling. Early feeding into a dysmotile and

transmurally altered intestine likely accounts for the higher incidence of NEC in gastroschisis than in any other gestational age-matched infant population. The mode of feeding has been long debated. Bolus feeds offer the theoretic advantage of optimally stimulating pancreatobiliary secretions, while continuous feedings are likely to advance more rapidly to full volumes, obviating the need for prolonged PN support. Continuous feedings can certainly be augmented by interval bolus feeds, allowing the child to develop the necessary oral feeding skills, and possibly stimulating GI hormones.

Vigilance is essential as the enteral component is advanced. Guidelines for the advancement of feeds should consider the frequency of stools as well as the pH and reducing substances, as these may indicate poor absorption or an excessive osmotic load. Because of the perceived fragility of the intestine, this author's practice is generally to use a more elemental formula and limit the osmolality, trying not to increase the caloric density of feeds until the child is almost fully established on EN.

Setbacks relate to septic events concerning the central line, which are usually Gram-negative in etiology and reflect the ongoing reduced mucosal barrier defense in the intestine. Given the combination of cholestasis and poor motility, these patients are excellent candidates for cycled enteral antibiotics to obviate bacterial overgrowth and its complications. Gastroschisis is one of the more common causes of neonatal SBS. The etiologies involve congenital torsion or ischemic necrosis of entire segments of the intestine, simple atresias, and postnatal loss of the intestine because of poor perfusion, NEC, or surgical catastrophes. Caloric estimates for the needs of these infants depend on their phase of recovery. In the initial postnatal period, there appears to be an intense inflammatory state as evidenced by elevated CRP, which resolves as the bowel recovers. The incidence of cholestatic jaundice is likely multifactorial in this population.[34]

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) involves a heterotopic location for the viscera within either chest cavity, as well as associated defects in lung and pulmonary vascular development and maturation. While the former is a surgically correctable defect, the second component determines the child's

clinical course and ultimate prognosis. Infants with CDH, therefore, fall into several categories. There are those with a diaphragmatic defect, usually first detected postnatally, in whom there is little hemodynamic and pulmonary compromise; they tolerate surgery well and can be transitioned relatively quickly to enteral feedings. Infants in whom the defect was identified early in gestation tend to have a greater degree of pulmonary hypoplasia and more difficulty with pulmonary hypertension; they may require cardiac and pulmonary support via ECMO. As a result, nutrition support for this disorder spans the entire spectrum and must be individualized.

The GI tract, although displaced initially, is fundamentally normal in terms of its motility and absorption capacity. As such, there are no specific recommendations for the type of enteral alimentation. The fact that total fluid provision will likely be restricted in postoperative patients as they are weaned off ventilatory support must be considered. While it is enticing to provide highly concentrated formulas, it must be balanced with the potential for mucosal damage leading to enteric-derived sepsis in vulnerable infants who likely have multiple vascular access points. Provision of adequate calories is likely best accomplished with highly concentrated formula once the infant has tolerated enteral feedings and becomes limited in the amount of volume that can be delivered for reasons of gastric capacity and emptying.

All children with CDH have some degree of foregut dysmotility, which renders them at risk for GER. The risk of reflux with aspiration is particularly pronounced in these patients, who already have a compromised pulmonary system, given the nature of the congenital defect. This risk forms the basis for providing continuous feeds initially to fulfill enteral needs and then transitioning them to bolus feeds. Again, the provision of continuous enteral feedings should not be a disincentive for oral feeds. Feeding can be structured to deliver the targeted volume of feeds over 1 hour or even more as the child tolerates.

Infants with CDH and severe cardiopulmonary compromise who require maximal medical support for control of pulmonary hypertension are often severely fluid-restricted, which further limits the ability to provide adequate nutrition support. The assessment of caloric needs is especially difficult because there are so many confounding factors, such as level of sedation,

possible chemical muscular relaxation, degree of mechanical respiratory support, and level of temperature support. During this phase, the goal of nutrition support is to provide the essential components to allow for basic metabolic needs and tissue repair.

Calories earmarked for growth and development become priorities as the infant's clinical condition improves. When these patients required cardiopulmonary support on ECMO, it was assumed that as the lungs were being "rested," the metabolic demands would decrease. This assumption, however, is incorrect and these patients continue to exhibit a hypermetabolic response that persists after decannulation.[35,36]

In the past, there has been debate about the safety of administering lipids to an infant on ECMO. The consensus now is that lipids can safely be administered via a central line separate from the ECMO circuit. In contrast, the dextrose and amino acid solution is typically administered via the cannulae, which allows for safe delivery of dextrose concentrations greater than 20% because there are sufficiently high flow rates directly into the atrium. The provision of high glucose loads along with insulin therapy is beneficial in this population to limit protein catabolism.[37–39]

Hepatobiliary Disorders

Biliary Atresia

Infants presenting with direct hyperbilirubinemia are promptly evaluated for surgically correctable biliary tract disorders such as biliary atresia and choledochal cyst. While other conditions such as neonatal hepatitis also lead to similar laboratory presentations, they (as well as a host of infectious disorders and enzymatic defects) require medical support only. Biliary atresia most often becomes evident at 1 month of age, and the infant may have experienced malnutrition of unknown etiology. Hallmarks of clinical diagnosis include jaundice, acholic stools, and dark urine. Ultrasound, HIDA (hepatobiliary iminodiacetic acid) scan, and percutaneous liver biopsy should confirm the diagnosis. Once established, preoperative administration of vitamin K is one of the standard recommendations to optimize coagulation parameters. The diagnosis is further confirmed intraoperatively by demonstrating a lack of an extrahepatic ductular system.

Reconstruction involves the creation of a jejunal limb that is anastomosed to the portal plate, the region of the liver where the hepatic ducts would be presumed to originate from the liver parenchyma. In fortunate situations, there is early evidence of bile flow with resolution of the hyperbilirubinemia. Postoperative steroids are frequently used as a choleretic and to reduce parenchymal inflammation in the liver. This postoperative course is typically 5 days of non-enteral alimentation to allow for healing of the intestinal anastomosis, with subsequent initiation of enteral feedings. Unfortunately, with a frequent delay in diagnosis to 2 months of age, some infants will be in very poor nutritional condition. On preoperative assessment, some surgeons will opt to place central venous access at the time of operation to provide the debilitated child with some interim nutrition to optimize healing and prevent further weight loss.

There is no indication for preoperative nutrition repletion because decompression of the obstructed biliary tract is the most important goal. Postoperative feedings are generally breast milk if available or a protein hydrolysate formula with approximately 50% medium-chain triglyceride oil, because medium-chain triglycerides are more easily absorbed by infants with liver disease. These children have an impaired ability to digest fats and require supplementation with fat-soluble vitamins A, D, E, and K. There are reports of these infants requiring a disproportionately larger caloric intake than others their size.

More on nutrition support of children with surgically non-correctable liver disease is discussed in Chapter 24, "Hepatic Disease."[40,41]

Choledochal Cyst

Infants with choledochal cyst may present during the neonatal period or later, but generally before 5 years of age. The acute presentation may include pancreatitis in addition to hyperbilirubinemia. These children rarely have chronic malnutrition despite complaints of abdominal pain. After resection of the choledochal cyst, which involves variable portions of the extrahepatic ductal system and reconstruction of biliary outflow with a standard Roux-en-Y hepaticojejunostomy, these patients will be able to consume a normal diet and in the absence of significant underlying liver disease do not need special nutritional formulations.

Other (Non-GI) Malformations

Thoracic Disorders

Children who require thoracic operations for congenital lung lesions or even foregut duplications can be treated by routine postoperative guidelines and have no special nutritional considerations other than those imposed by virtue of prolonged ventilatory support and concern for reflux with aspiration. Many of these operations can now safely be achieved with minimally invasive techniques, further reducing surgical stress and postoperative pain response, and minimizing wounds to heal. Infants born with chylothorax, or those who develop it because of perioperative complications, can be managed depending on the amount of daily chylous output with gut rest and PN support, and the subsequent introduction of enteral feeds with high concentration of medium-chain triglyceride oil.

Urologic, Neurosurgical, and Orthopedic Disorders

Infants born with complex urological defects such as bladder exstrophy and cloacal exstrophy will require several staged surgical interventions by various specialists. The intestinal tract is intact and generally normal in bladder exstrophy, but there is imperforate anus with exteriorization of the hindgut between the 2 bladder halves in cloacal exstrophy. This portion of the hindgut will need to be tubularized to create a distal stoma or require proximal diversion. Hydronephrosis, prune belly syndrome, and other congenital renal anomalies may have evidence of renal insufficiency or failure that will require adjustments to the infant's nutrient intake as discussed in other chapters. Congenital neurosurgical and orthopedic interventions generally do not involve the peritoneal cavity or even the retroperitoneum and, therefore, do not impact enteral feeding status. Depending on the extent of operation and metabolic stress, adjustments primarily affect caloric goals and will need to be individualized.

Neonatal Airway Disorders

Infants who require interventions to their airway frequently have associated aerodigestive disorders that may extend to foregut dysmotility syndromes. Reconstructive interventions for laryngomalacia, subglottic stenosis, and tracheomalacia require protection of the airway from GER. Often

tracheostomy can be averted by appropriate management of enteral feedings, along with pharmacologic interventions to limit exposure of the glottic structures to acid gastric contents. This may require insertion of a postpyloric feeding tube to ensure continued nutrition support without the risk of reflux. If the reflux is chronic in nature, early consideration for a Nissen fundoplication is appropriate.

Infants with airway compromise have an increased work of breathing and may exhibit malnutrition despite mechanical feeding. Once supported with a tracheostomy, the infant will often show rapid catch-up growth and can sustain a reduction in caloric goals. It is important to remember that despite the presence of a tracheostomy, the airway is not completely protected from either GER or aspiration of salivary secretions, because the pediatric airway often does not require a cuffed tracheostomy, and every conscious effort is made to preserve some airflow past the cords to prevent progressive subglottic stenosis.

Nutrition Support in Infants With Acute GI-Related Disorders

Necrotizing Enterocolitis

NEC remains one of the most frequent indications for emergency surgery on preterm neonates. Although mortality has decreased over time and management of intestinal dysfunction has improved, NEC remains a diagnosis with significant morbidity and mortality. Although this is not intended to be an exhaustive summary of the pathophysiology of NEC, it is important to understand some of the mechanisms thought to be responsible for its development, as they influence the way surgeons treat infants who have experienced mucosal injury and may be at further risk.

NEC is best considered as the result of the exposure of an immature and naïve intestinal tract with potentially compromised perfusion to pathogenic organisms that traverse the intestinal barrier and initiate gut-derived sepsis syndrome. The gut mucosal barrier in preterm infants is compromised on several levels.[42] The normally acidic environment of the stomach serves as an initial barrier to microbes, but acid production is often immature and is altered iatrogenically with acid-suppressing medications in the hopes of

avoiding gastritis and ulceration. Other factors include the limited supply of luminal protective factors such as the lectins and immunoglobulin A provided by human milk.

Structurally, the mucosal surface provides opportunities for the attachment of bacteria via a decreased mucus barrier, tight junctions that may not be as tight in older, full-term infants, and active translocation mechanisms that are suited for sampling a safer environment than that provided in a neonatal intensive care unit. Mucosal integrity may become further compromised with decreased visceral perfusion. The mucosa are at greatest risk with hypoperfusion, and mucosal sloughing, as evidenced by bloody stools, is an early indication of potential NEC (Bell stage 1 NEC). Altered perfusion may be the consequence of primary cardiac events (eg, congenital heart disease, patent ductus arteriosus), pulmonary compromise with consequent hypoxia and resultant shunting away from the viscera, and other events, such as hemorrhage (eg, pulmonary, intraventricular). Beyond the mucosal border, the immaturity of the host immune system is overcome due to the limited phagocytic and bactericidal activity of neutrophils and other components of the gut-associated lymphoid tissue. These speculated factors may all contribute to facilitating an enteric source of sepsis.

The etiology of NEC is manifold and complex.[43,44] The radiographic hallmarks are pneumatosis intestinalis and portal venous gas, both of which portend that there has been transgression of the mucosa by gas-producing organisms. If the sepsis can be controlled and the intestine can maintain its integrity, no operative intervention is necessary (Bell stage 2 NEC). However, if evidence of perforation occurs or the abdominal sepsis fails to come under control, operative intervention becomes necessary (Bell stage 3 NEC). The options are often dictated by the infant's size and degree of clinical instability. In the smallest and most unstable infant, placement of a peritoneal drain may be all that can be safely offered, while in larger or more stable infants, a limited laparotomy at the bedside or in the operating room may allow for more definitive therapy. A multi-institutional Neonatal Network trial has shown that there is no statistical difference in treatment-based outcomes; however, there is a trend to improved outcomes with laparotomy for those with presumed NEC.[45]

At surgery, the extent of intestinal involvement becomes apparent. In the least severe circumstances, a limited segment of intestine has transmural gangrene or has perforated. A choice between resection and diversion with stoma versus primary anastomosis is made based on the patient's overall condition and the condition of the intestine. In infants with more extensive and even skip involvement, proximal diversion and excision of only those areas of definite gangrene become the guiding principles to preserve as much intestinal length as possible. Despite optimal management, these affected areas may progress to full-thickness gangrene or heal as fibrotic strictures, further compromising residual length and potentially resulting in SBS. Survival is only possible if the sepsis is controlled.[46]

Acute management focuses on providing adequate perfusion to the residual intestine to allow it to recover from the initial insult. This results in the generous provision of intravenous fluids early on and the restriction of fluids upon resolution of the sepsis to optimize pulmonary function. However, this approach compromises the ability to provide optimal nutrition consistently. Enteral feeding would be considered no earlier than 7 days after surgery. As in other complex GI disorders, a coherent plan must be generated by the managing teams to best use a combination of EN and PN. Recurrent sepsis and progressive cholestatic jaundice are the predictors of mortality. All techniques available should be used to limit these complications in these patients. Reconstitution of the full GI tract is accomplished after 6 weeks to limit operative complications and to give sufficient time for strictures to form and be identified so that they can be treated in the same operation.[47]

Even in infants managed without operative intervention, clinicians must maintain suspicion for developing strictures, particularly if the colon was involved, which can be difficult to tell nonoperatively. Fluoroscopic studies can be used in antegrade or retrograde fashion before reconnection or in early difficulties with the reinstitution of feeds to identify or rule out stricture formation. Aggressive feeding of an infant with a distal bowel obstruction will only lead to a recurrence of NEC.[48] While the specific amino acid composition of neonatal PN is addressed in other sections, much attention has been focused on the utility of providing glutamine to this

population with a compromised gut mucosal barrier; however, this does not appear to be an effective strategy.[49,50]

Infants who survive the early postoperative course associated with NEC are among those at the highest risk for intestinal dysfunction, SBS, and cholestasis. All nutrition techniques described earlier in relation to the initiation of trophic feedings, enteral antibiotics, and cycling of PN should be applied in this context. The optimal timing of refeeding and stoma closure remains a topic of controversy and is often determined individually or according to institutional preferences rather than by evidence-based protocols.

Isolated Intestinal Perforation

Isolated intestinal perforation closely mimics NEC in that it presents with evidence of visceral perforation (usually pneumoperitoneum in the absence of pneumatosis) or portal venous gas and thus requires some surgical intervention. Infants with this disorder usually have extremely low birth weight (<750 g), are in their first week of life, and may not have been fed. The diagnosis is often speculative since many patients are treated with peritoneal drainage only, and isolated involvement of a small intestinal segment cannot be verified without surgery. These infants generally have a better prognosis because of limited colonization of the GI tract during the first week of life, better source control of sepsis once the abdomen has been drained, a self-sealing perforation site, and consequently a less profound sepsis syndrome. The initiating events remain elusive but may be related to focal perfusion defects or focal luminal injury by medications such as indomethacin.

The same concerns about indications for laparotomy, length of NPO status, and length of antibiotic therapy apply as for infants with NEC. From a nutrition standpoint, one assumption is that the remainder of the GI tract will not have experienced the same generalized mucosal insult as encountered in NEC, and that enteral feedings and rehabilitation should be achievable with greater success rates.

Intestinal Malrotation and Midgut Volvulus

Midgut volvulus resulting from intestinal malrotation can occur at any age, as described in both prenatal and adult patients, however, the first month of life is the most common time of presentation. An infant born with intestinal malrotation who experiences a midgut volvulus can be severely compromised. With timely diagnosis and intervention, the midgut (proximal jejunum to mid-transverse colon) should be salvageable. In surgery, the abdomen may be filled with chylous ascites from obstruction and rupture of the mesenteric lymphatics. Untwisting of the mesenteric pedicle will restore venous drainage and allow for improved arterial inflow. Resection is considered only if there are regions of complete necrosis. Any intestinal segment with borderline perfusion is retained and reassessed at 24 hours with a second-look laparotomy to avoid unnecessary resection leading to SBS.

Depending on the extent of the intestinal injury, these infants must initially be fed cautiously to avoid a "second hit" to a compromised bowel. The perioperative nutrition support team must target metabolic needs as well as protein substrate for tissue repair. In the absence of any significant intestinal resection, there should be no ongoing considerations. The management of children who suffer massive intestinal loss is covered in Chapter 25, "Intestinal Failure." As with NEC, infants with midgut volvulus and necrosis are most likely to have lost the terminal ileum and will likely require vitamin B12 supplementation in the future.

Pyloric Stenosis

Infants with pyloric stenosis primarily require rehydration and correction of electrolytes preoperatively but then can resume a normal infant diet. Initiation varies by institution, but generally, no postoperative feeding tubes are placed, as they put the exposed pyloric channel mucosa at risk of perforation. These infants are typically hungry and have good feeding skills. The feeding protocol in our institution was developed to provide a consistent algorithm that allows the vast majority of infants to be discharged home within 24 hours of surgery. We hold oral feeds for 6 hours and then test the stomach with 2 small-volume (15 mL) Pedialyte feeds 2 hours apart. If the child experiences no vomiting, then formula or human

milk is offered at 30 mL volumes every 3 hours and advanced by 15 mL every second feed to a maximum of 60 mL, providing the necessary volumes for the average 3-3.5-kg infant with pyloric stenosis. At this point, the infant can be discharged home and feedings advanced by the parents as tolerated, with the provision that individual volumes should not be excessive to minimize reflux.

Recurrent vomiting will always raise the specter of recurrent stenosis or an incomplete operation, both of which are rare events in experienced hands. The infant's stomach is capacious given the preoperative obstruction, but more frequent limited volume feeds will assure retention of feeds and optimal absorption. All parents are amazed by the infant's persistent need to feed within the first month postsurgery. This resolves spontaneously as the child achieves "catch-up" growth. Persistent vomiting should prompt consideration of GER, which can be ameliorated with antacid therapy, including a dose of sodium bicarbonate, which may also help disintegrate a mucus plug in the pyloric channel. More serious considerations should include the potential for an intraoperative bowel injury or wound/fascial dehiscence, but typically these infants will have other symptoms in addition to persistent vomiting. If acid suppression was provided perioperatively, it can usually be discontinued at the follow-up visit 3 to 4 weeks later. Most of these infants have undergone multiple formula changes prior to their diagnosis, and we reassure parents that the formula is now less important and to use what they have at home or is most accessible.[51]

The technique (laparoscopic or open) of pyloromyotomy does not have an impact on feeding tolerance or discharge time.

Nutrition Support in Children and Adolescents Requiring Surgery

General Principles

The guiding principles of surgery are to minimize the risk for perioperative complications, minimize pain and discomfort, support nutritional needs to avoid a prolonged catabolic state, and restore the patient to their optimal state of health as expeditiously as possible. Generally, risk stratification in

surgery is linked to wound class (clean-contaminated), underlying comorbidities, and context of operation (emergent vs elective).

The concept of Enhanced Recovery After Surgery (ERAS) protocols was first applied in adult colorectal operations, which are considered high risk based on wound classification and comorbidities. Similar multidisciplinary protocols were extended to patients with oncologic pathology who were particularly at risk for complications related to their baseline poor nutritional and proinflammatory status. Interventions such as preoperative smoking cessation, management of body temperature, and assessment of preoperative glucose levels were demonstrated to be effective measures.[52]

The application of ERAS protocols has been variably instituted in pediatric and neonatal surgery and evidence-based support is not yet extensive.[53,54] Translation of these protocols to the pediatric population would require identifying and studying patient subgroups that have the potential for a measurable reduction of complications, decreased hospital length of stay, and more rapid return to normal activities, to scientifically analyze the outcomes. The existing pediatric studies therefore focus on patients with standardized operations such as cholecystectomy and those with inflammatory bowel disease (IBD) undergoing colorectal operations.[55,56]

Concepts that have been adopted without much challenge include the notion that clear liquids can be tolerated until 2 hours before undergoing anesthesia and that this practice improves gastric emptying. The concepts of restricting solid foods 6 hours before anesthesia and longer periods of NPO are now considered detrimental to the patient's preoperative condition. The development of these pediatric and neonatal[57] protocols is still in evolution, and even specialty organizations, such as the American Pediatric Surgical Association Quality and Safety Committee, who have existing protocols, have not endorsed extensive guidelines, as many such protocols are not evidence-based (see https://www.pedsurglibrary.com/apsa/view/PedSurg%20Resource/1884016/all/Enhanced_Recovery_After_Surgery__ERAS_?q=ERAS).[52,55]

In older children and adolescents, many of the surgical interventions for GI problems are of an acute nature (ie, appendicitis, Meckel's diverticulum, duplications of the GI tract, intestinal obstruction due to hernia) where there

are typically no premorbid nutrition impairment concerns. Children presenting with more chronic disorders, such as IBD, polyposis syndromes, and chronic GER require a closer evaluation of their nutrition status before elective surgery is contemplated. Despite these logical considerations, there is a paucity of data to correlate preoperative nutritional assessment with postoperative outcomes.[58]

Some of these chronic conditions result from neonatal interventions with adapted SBS, late stenosis, and dysmotility in atresia (duodenal and jejunoileal) patients. Malignancies affecting the GI tract are rare and most frequently involve lymphomas, although carcinoid tumors, desmoid tumors, and other solid visceral tumors will impact the GI tract. Abdominal visceral transplantation is yet another surgical intervention requiring specialized focus on nutrition management,[59] but these more complex topics including inflammatory bowel disease, malignancy, and transplantation are addressed in the respective chapters.

Nutrition management of acutely ill surgical patients is generally focused on resumption of enteral intake but when this becomes delayed beyond 5 to 7 days, PN support is considered. It is evident from the critical care literature that many of these acutely ill patients are significantly undernourished while in the intensive care unit (ICU). There is also evidence that simple calculation of resting energy expenditure without accounting for physical activity underestimates caloric requirements.[60,61] While an attempt is made to provide early enteral feedings to medical and trauma patients in the ICU setting, these principles cannot be applied to surgical patients who are likely at higher risk for anastomotic breakdown; abdominal sepsis; and the development of complications such as surgical site infections, fascial dehiscence, and enterocutaneous fistulae, which then further complicate clinical and nutrition management. Despite these surgical concerns, the initiation of enteral feedings should be a clinical goal to allow transition from PN support at the earliest feasible time. The ability to handle complex wound failure has been markedly improved with advances in enterostomal care and the use of negative pressure wound devices that contribute to more rapid closure of open wounds and even enterocutaneous fistulae. The earlier control of fluid and protein losses from these wounds should favorably impact overall protein balance.

The subset of children who present the highest risk for emergency operation are those with chronic malnutrition. Examples include children with malnutrition who have congenital heart disease or developmental delay resulting in inadequate oral intake, and children with spine deformities (severe kyphosis, scoliosis) who are at risk for superior mesenteric artery syndrome, in which there is duodenal obstruction from extrinsic compression of the third portion of the duodenum between the superior mesenteric artery and the vertebral column. Children with spastic quadriplegia and seizure disorders may have limited gastric capacity and poor gastric emptying with a tendency to reflux, limiting their enteral intake. Children with malignancies are often nutritionally depleted because of the disease process, but also from the therapies applied. At children's hospitals, we are now much more attuned to the preoperative nutrition evaluation of these patients to optimize outcomes from often extensive surgical interventions. Much of the focus, therefore, is on the provision of feeding access for nutrition support.

Feeding Access in Pediatrics

Many children are referred for placement of enteral feeding devices. If access is required for more than a temporary situation, the options include the various techniques of gastrostomy placement (eg, percutaneous endoscopic gastrostomy, laparoscopic G-tube, open G-tube), insertion of a gastrojejunal device, and direct jejunal feeding tubes. Despite their seemingly simple and innocuous nature, these interventions have the potential for complications and morbidity.[62,63]

When placing a gastrostomy, it is important to consider the potential for increased reflux because of anatomic alterations. Children who have typically consumed only small amounts of food may not have evidence of reflux until larger volumes are directly administered into the gastric lumen. A preoperative evaluation should be conducted to assess the risks, particularly when these children are developmentally delayed and at risk for aspiration. Anatomic evaluation with an upper GI fluoroscopy study will determine whether there are impediments to proper gastric emptying that may be amenable to correction in the same operation. Malrotation with partial duodenal obstruction by Ladd's bands should be considered.

Typically, a pH study or impedance study is conducted to address whether GER is present, and to what extent. If an anti-reflux operation is being considered, a nuclear medicine gastric emptying scan may be useful, and can also provide information about reflux, although it is less quantifiable than the tests noted previously. Gastric outlet procedures (eg, pyloromyotomy, pyloroplasty) are occasionally considered for patients at increased concern for early failure of a fundoplication.

Insertion of Gastrostomy Tube

When a G-tube is inserted for the sole purpose of providing enteral access, enteral feedings can be commenced within 24 hours of operation. With open and laparoscopic techniques, there may be some initial postoperative ileus; however, the main reason for decompressing the stomach (or at least avoiding exogenous input) is to allow a seal to form between the gastrostomy and the abdominal wall so that when retching and vomiting occur, there is no extravasation between these structures into the peritoneal cavity.

The administration method for enteral feedings depends on the child's underlying situation. If the feedings are for oral supplementation, then oral intake can be started and G-tube feeds given as small bolus volumes, increased according to tolerance. In children with neurological deficits or developmental delay, initiation of G-tube feeds may be best assessed by open-vented feeds.

Rapid egress of formula from the feeding bag into the stomach with no regurgitation into the tube suggests a large-capacity stomach that will accommodate additional volumes, whereas slow evacuation into the stomach suggests a smaller stomach capacity or increased resistance because of abdominal wall contraction, possibly from pain or spasticity. In this latter situation, it may be more efficient to provide initial feeds as slow continuous drips rather than as bolus volumes. Closed infusion of feeds is the least cumbersome method, but risks GER with the potential for aspiration or requires communication from the patient that the stomach is full. This may be exhibited as retching or visceral pain initiated by overdistention.

In some children with significant reflux, there may be concerns about proceeding with a fundoplication. The child may be so nutritionally depleted that the risks are not in favor of proceeding with a major operation. In this situation, a gastrostomy tract can become the conduit for a gastrojejunostomy tube, which allows for gastric decompression and jejunal feedings. The disadvantage to the commercially available button gastrojejunostomy tubes is that they have a minimum size of 16 French and are excessively large and stiff for infants, but they become usable at a patient size of about 10 kg. In smaller patients, other devices can be manipulated to achieve the same tasks. However, these tubes are meant as transient feeding support devices, and repeated insertion by required fluoroscopy is not ideal for pediatric patients. Our institution uses them as a bridge to help patients achieve an improved nutrition state and become better candidates for fundoplication.

Children with neurodevelopmental impairment, spasticity, and seizures often have a higher risk for disruption of their fundoplication, and avoiding this operation with the use of jejunal tubes is enticing. Discussions with the child's family and caretakers should evaluate the operative risk but also whether continuous feeding via a gastrojejunostomy tube or jejunostomy tube will interfere with daily activities. These tubes do not allow for bolus feedings other than through the gastrostomy limb. Often the ability to provide intermittent bolus feeds provides significant improvement in quality of life for both the child and the family.[64] With the advent of laparoscopic fundoplication, there is less surgical impact in terms of abdominal wall wound healing and pain, although early studies showed that surgical stress regarding hormone release was not altered. With excellent short-term results, this operation has gained favor; however, its long-term efficacy, especially in higher-risk populations, is still under evaluation.[65]

Primary jejunostomy tubes are avoided except in the most chronic and perhaps institutionalized patients since they represent a long-term commitment to continuous enteral feedings. Operatively, a tract is developed through the abdominal wall and an imbricated jejunal limb before the tube enters the jejunal lumen. This establishes a relatively long tract for reliable replacement of the tube in the correct orientation and

minimizes leakage risk. These tubes have a role in the management of complex surgical patients.

When preoperative nutrition repletion is not feasible before an urgent surgical intervention, provide early nutrition support, which may require central venous access or reliable enteral access for this purpose at the time of operation.

Test Your Knowledge Questions

1. Which of the following strategies is considered beneficial in reducing cholestasis?
   A. Provision of >40% of calories as lipid emulsion
   B. Maintaining GIR >15 mg/kg/min
   C. Continuous provision of PN
   D. Initiation of enteral feedings
2. Which of the following is a contraindication to commencing enteral feedings?
   A. Bilious nasogastric output in jejunoileal atresia
   B. Contrast extravasation on postoperative day 7 after esophageal atresia repair
   C. Abdominal distention with lack of stoma output
   D. All of the above
3. On a 3-kg infant status post-stoma closure after resection for NEC, when should enteral feedings be limited?
   A. Number of bowel movements exceeds 8 over a 24-hour period
   B. Reducing substances <−1/2%
   C. Fecal pH >−7
   D. Mucoid stools
4. Which clinical diagnosis causes impairment of intestinal motility and may require prolonged PN support?
   A. Gastroschisis
   B. Omphalocele
   C. Hirschsprung’s disease
   D. Malrotation without midgut volvulus

References

1. Alverdy JC. Hypermetabolism and nutritional support in sepsis. *Surg Infect (larchmt).* 2018;19(2):163–167. https://doi.org/10.1089/sur.2017.313
2. van Niekerk G, Meaker C, Engelbrecht AM. Nutritional support in sepsis: when less may be more. *Crit Care*. 2020;24(1):53. https://doi.org/10.1186/s13054-020-2771-4
3. Barlow B, Santulli T, Heird W, Pitt J, Blanc W, Schullinger J. An experimental study of acute necrotizing enterocolitis—the importance of breast milk. *J Pediatr Surg*. 1974;9(5):587–595. https://doi.org/10.1016/0022-3468(74)90093-1
4. Nydegger A, Bines JE. Energy metabolism in infants with congenital heart disease. *Nutrition*. 2006;22(7–8):697–704. https://doi.org/10.1016/j.nut.2006.03.010
5. Owens J, Musa N. Nutrition support after neonatal cardiac surgery. *Nutr Clin Pract*. 2009;24(2):242–249. https://doi.org/10.1177/0884533609332086
6. Vaidyanathan B, Radhakrishnan R, Sarala D, et al. What determines nutritional recovery in malnourished children after correction of congenital heart defects? *Pediatrics*. 2009;124(2):e294–e299. https://doi.org/10.1542/peds.2009-0141
7. Chawla BK, Teitelbaum DH. Profound systemic inflammatory response syndrome following non-emergent intestinal surgery in children. *J Pediatr Surg.* 2013;48:1936–1940. https://doi.org/10.1016/j.jpedsurg.2013.05.065
8. Jaksic T, Shew SB, Keshen TH, Dzakovic A, Jahoor F. Do critically ill surgical neonates have increased energy expenditure? *J Pediatr Surg*. 2001;36(1):63–67. https://doi.org/10.1053/jpsu.2001.20007
9. Garza JJ, Shew SB, Keshen TH, Dzakovic A, Jahoor F, Jaksic T. Energy expenditure in ill premature neonates. *J Pediatr Surg*. 2002;37(3):289–293. https://doi.org/10.1053/jpsu.2002.30821
10. Pierro A, Eaton S. Metabolism and nutrition in the surgical neonate. *Semin Pediatr Surg*. 2008;17(4):276–284. https://doi.org/10.1053/j.sempedsurg.2008.07.006

11. Gruber EM, Laussen PC, Casta A et al. Stress response in infants undergoing cardiac surgery: a randomized study of fentanyl bolus, fentanyl infusion, and fentanyl-midazolam infusion. *Anesth Analg*. 2001;92(4):882–890. https://doi.org/10.1097/00000539-200104000-00016
12. Shew SB, Keshen TH, Glass NL, Jahoor F, Jaksic T. Ligation of a patent ductus arteriosus under fentanyl anesthesia improves protein metabolism in premature neonates. *J Pediatr Surg*. 2000;35(9):1277–1281. https://doi.org/10.1053/jpsu.2000.0350001
13. Hulst JM, van Goudoever JB, Zimmermann LJI, Tibboel D, Joosten KFM. The role of initial monitoring of routine biochemical nutritional markers in critically ill children. *J Nutr Biochem*. 2006;17(1):57–62. https://doi.org/10.1016/j.jnutbio.2005.05.006
14. Evans DC, Corkins MR, Malone A, Miller S, Mogensen KM, Guenter P, Jensen GL; American Society for Parenteral and Enteral Nutrition (ASPEN) Malnutrition committee. The use of visceral proteins as nutrition markers: an ASPEN Position Paper. *Nutr Clin Pract*. 2021;36(1):22–28. https://doi.org/10.1002/ncp.10588
15. Reynolds RM, Bass KD, Thureen PJ. Achieving positive protein balance in the immediate postoperative period in neonates undergoing abdominal surgery. *J Pediatr*. 2008;152(1):63–67. https://doi.org/10.1016/j.jpeds.2007.05.042
16. Peters C, Fischer JE. Studies on calorie to nitrogen ratio for total parenteral nutrition. *Surg Gynecol Obstet*. 1980;151(1):1–8.
17. Dempsey DT, Mullen JL, Crosby LO, Hurwitz S. Calorie-nitrogen interactions in the parenterally fed primate. *Surgery*. 1988;103(1):94–98.
18. Waitzberg DL, Plopper C, Terra RM. Postoperative total parenteral nutrition. *World J Surg*. 1999;23(6):560–564. https://doi.org/10.1007/pl00012347
19. Javid PJ, Collier S, Richardson D, et al. The role of enteral nutrition in the reversal of parenteral nutrition-associated liver dysfunction in infants. *J Pediatr Surg*. 2005;40(6):10151018. https://doi.org/10.1016/j.jpedsurg.2005.03.019
20. Gura K, Duggan C, Puder M, et al. Reversal of parenteral nutrition-associated liver disease in two infants with short bowel syndrome using

parenteral fish oil: implications for future management. *Pediatrics*. 2006;118:e197–201. https://doi.org/10.1542/peds.2005-2662
21. de Meijer VE, Gura KM, Le HD, Meisel JA, Puder M. Fish oil–based lipid emulsions prevent and reverse parenteral nutrition–associated liver disease: the Boston experience. *JPEN J Parenter Enteral Nutr*. 2009;33(5):541–547. https://doi.org/10.1177/0148607109332773
22. Lee SI, Valim C, Johnston P, et al. The impact of fish oil–based lipid emulsion on serum triglyceride, bilirubin, and albumin levels in children with parenteral nutrition–associated liver disease. *Pediatr Res*. 2009;66(6):698–703. https://doi.org/10.1203/pdr.0b013e3181bbdf2b
23. Blackmer A, Warschausky S, Siddiqui S, et al. Preliminary findings of long-term neurodevelopmental outcomes of infants treated with intravenous fat emulsion reduction for the management of parenteral nutrition associated cholestasis. *JPEN J Parenter Enteral Nutr.* 2015;39(1):34–46. https://doi.org/10.1177/0148607114551965
24. Boarini JH. Principles of stoma care for infants. *J Enterostomal Ther*. 1989;16(1):21–25. https://pubmed.ncbi.nlm.nih.gov/2745850/
25. Al-Harbi K, Walton JM, Gardner V, Chessell L, Fitzgerald Pg. Mucous fistula refeeding in neonates with short bowel syndrome. *J Pediatr Surg*. 1999;34(7):1100–1103. https://doi.org/10.1016/s0022-3468(99)90575-4
26. Alabbad SI, Ryckman J, Puligandla PS, Shaw K, Nguyen LT, Laberge J. Use of transanastomotic feeding tubes during esophageal atresia repair. *J Pediatr Surg*. 2009;44(5):902905. https://doi.org/10.1016/j.jpedsurg.2009.01.027
27. Goyal A, Jones MO, Couriel JM, Losty PD. Oesophageal atresia and tracheo-oesophageal fistula. *Arch Dis Child Fetal Neonatal Ed*. 2006;91(5):F381–F384. https://doi.org/10.1136/adc.2005.086157
28. Ching YA, Fitzgibbons S, Valim C, et al. Long-term nutritional and clinical outcomes after serial transverse enteroplasty at a single institution. *J Pediatr Surg*. 2009;44(5):939–943. https://doi.org/10.1016/j.jpedsurg.2009.01.070
29. Yardley I, Khalil B, Minford J, Morabito A. Multiple jejunoileal atresia and colonic atresia managed by multiple primary anastomosis with a single gastroperineal transanastomotic tube without stomas. *J Pediatr*

Surg. 2008;43(11):e45–e46. https://doi.org/10.1016/j.jpedsurg.2008.07.021
30. Piper HG, Alesbury J, Waterford SD, Zurakowski D, Jaksic T. Intestinal atresias: factors affecting clinical outcomes. *J Pediatr Surg*. 2008;43(7):1244–1248. https://doi.org/10.1016/j.jpedsurg.2007.09.053
31. Pastor AC, Phillips JD, Fenton SJ, et al. Routine use of a SILASTIC spring-loaded silo for infants with gastroschisis: a multicenter randomized controlled trial. *J Pediatr Surg*. 2008;43(10):1807–1812. https://doi.org/10.1016/j.jpedsurg.2008.04.003
32. Bergholz R, Boettcher M, Reinshagen K, Wenke K. Complex gastroschisis is a different entity to simple gastroschisis affecting morbidity and mortality—a systematic review and meta analysis. *J Pediatr Surg*. 2014;49:1527–1532. https://doi.org/10.1016/j.jpedsurg.2014.08.001
33. Phillips JD, Raval MV, Redden C, Weiner TM. Gastroschisis, atresia, dysmotility: surgical treatment strategies for a distinct clinical entity. *J Pediatr Surg*. 2008;43(12):2208–2212. https://doi.org/10.1016/j.jpedsurg.2008.08.065
34. Walter-Nicolet E, Rousseau V, Kieffer F, et al. Neonatal outcome of gastroschisis is mainly influenced by nutritional management. *J Pediatr Gastroenterol Nutr*. 2009;48(5):612–617. https://doi.org/10.1097/mpg.0b013e31818c5281
35. Muratore CS, Utter S, Jaksic T, Lund DP, Wilson JM. Nutritional morbidity in survivors of congenital diaphragmatic hernia. *J Pediatr Surg*. 2001;36(8):1171–1176. https://doi.org/10.1053/jpsu.2001.25746
36. Keshen TH, Miller RG, Jahoor F, Jaksic T. Stable isotopic quantitation of protein metabolism and energy expenditure in neonates on- and post-extracorporeal life support. *J Pediatr Surg*. 1997;32(7):958–962. https://doi.org/10.1016/s0022-3468(97)90377-8
37. Shew SB, Keshen TH, Jahoor F, Jaksic T. The determinants of protein catabolism in neonates on extracorporeal membrane oxygenation. *J Pediatr Surg*. 1999;34(7):1086–1090. https://doi.org/10.1016/s0022-3468(99)90572-9
38. Agus MSD, Javid PJ, Ryan DP, Jaksic T. Intravenous insulin decreases protein breakdown in infants on extracorporeal membrane oxygenation.

J Pediatr Surg. 2004;39(6):839–844. https://doi.org/10.1016/j.jpedsurg.2004.02.013
39. Hulst JM, van Goudoever JB, Zimmermann LJ, et al. Adequate feeding and the usefulness of the respiratory quotient in critically ill children. *Nutrition*. 2005;21(2):192–198. https://doi.org/10.1016/j.nut.2004.05.020
40. Willot S, Uhlen S, Michaud L, et al. Effect of ursodeoxycholic acid on liver function in children after successful surgery for biliary atresia. *Pediatrics*. 2008;122(6):e1236–1241. https://doi.org/10.1542/peds.2008-0986
41. DeRusso P, Ye W, Shepherd R, et al. Growth failure and outcomes in infants with biliary atresia: a report from the biliary atresia research consortium. *Hepatology*. 2007;46(5):1632–1638. https://doi.org/10.1002/hep.21923
42. Petrosyan M, Guner Y, Williams M, Grishin A, Ford H. Current concepts regarding the pathogenesis of necrotizing enterocolitis. *Pediatr Surg Int*. 2009;25(4):309–318. https://doi.org/10.1007/s00383-009-2344-8
43. Neu J. Necrotizing enterocolitis: The future. *Neonatology*. 2020;117(2):240–244. https://doi.org/ 10.1159/000506866
44. Meister AL, Doheny KK, Travagli RA. Necrotizing enterocolitis: it's not all in the gut. *Exp Biol Med (Maywood)*. 2020;245(2):85–95. https://doi.org/10.1177/1535370219891971
45. Blakely ML, Tyson JE, Lally KP, et al. Initial laparotomy versus peritoneal drainage in extremely low birthweight infants with surgical necrotizing enterocolitis or isolated intestinal perforation: a multicenter randomized clinical trial. *Ann Surg*. 2021;274(4):e370–e380. https://doi.org/10.1097/sla.0000000000005099
46. Hall NJ, Peters M, Eaton S, Pierro A. Hyperglycemia is associated with increased morbidity and mortality rates in neonates with necrotizing enterocolitis. *J Pediatr Surg*. 2004;39(6):898–901. https://doi.org/10.1016/j.jpedsurg.2004.02.005
47. Al-Hudhaif J, Phillips S, Gholum S, Puligandla PP, Flageole H. The timing of enterostomy reversal after necrotizing enterocolitis. *J Pediatr Surg*. 2009;44(5):924–927. https://doi.org/10.1016/j.jpedsurg.2009.01.028

48. Bohnhorst B, Müller S, Dördelmann M, Peter CS, Petersen C, Poets Cf. Early feeding after necrotizing enterocolitis in preterm infants. *J Pediatr*. 2003;143(4):484–487. https://doi.org/10.1067/s0022-3476(03)00443-8
49. Albers MJIJ, Steyerberg E, Hazebroek FWJ, et al. Glutamine supplementation of parenteral nutrition does not improve intestinal permeability, nitrogen balance, or outcome in newborns and infants undergoing digestive-tract surgery: results from a double-blind, randomized, controlled trial. *Ann Surg*. 2005;241(4):599–606. https://doi.org/10.1097/01.sla.0000157270.24991.71
50. Calder P. Immunonutrition in surgical and critically ill patients. *Br J Nutr*. 2007;98(suppl 1):S133–S139. https://doi.org/10.1017/s0007114507832909
51. St. Peter SD, Tsao K, Sharp SW, Holcomb III GW, Ostlie DJ. Predictors of emesis and time to goal intake after pyloromyotomy: analysis from a prospective trial. *J Pediatr Surg*. 2008;43(11):2038–2041. https://doi.org/10.1016/j.jpedsurg.2008.04.008
52. Iqbal U, Green JB, Patel S, et al. Preoperative patient preparation in enhanced recovery pathways. *J Anaesthesiol Clin Pharmacol*. 2019;35(suppl 1):S14–S23. https://doi.org/10.4103/joacp.joacp_54_18
53. Brindle ME, Heiss K, Scott MJ, et al. Embracing change: the era for pediatric ERAS is here. *Pediatr Surg Int.* 2019;35:631–634. https://doi.org/10.1007/s00383-019-04476-3
54. Loganathan AK, Joselyn AS, Babu M, Jehangir S. Implementation and outcomes of enhanced recovery protocols in pediatric surgery: a systematic review and meta-analysis. *Pediatr Surg Int.* 2022;38:157–168. https://doi.org/10.1007/s00383-021-05008-8
55. Phillips MR, Adamson WT, McLean SE, et al. Implementation of a pediatric enhanced recovery pathway decreases opioid utilization and shortens time to full feeding. *J Pediatr Surg.* 2020;55(1):101–105. https://doi.org/10.1016/j.jpedsurg.2019.09.065
56. Purcell LN, Marulanda K, Egberg M, et al. An enhanced recovery after surgery pathway in pediatric colorectal surgery improves patient outcomes. *J Pediatr Surg.* 2021;56(1):115–120. https://doi.org/10.1016/j.jpedsurg.2020.09.028

57. Brindle ME, McDiarmid C, Short K, et al. Consensus guidelines for perioperative care in neonatal intestinal surgery: Enhanced Recovery After Surgery (ERAS) society recommendations. *World J Surg*. 2020;44(8):2482–2492. https://doi.org/10.1007/s00268-020-05530-1
58. Wessner S, Burjonrappa S. Review of nutritional assessment and clinical outcomes in pediatric surgical patients: does preoperative nutritional assessment impact clinical outcomes? *J Pediatr Surg*. 2014;49:823–830. https://doi.org/10.1016/j.jpedsurg.2014.01.006
59. Asfaw M, Mingle J, Hendricks J, Pharis M, Nucci A. Nutrition management after pediatric solid organ transplantation. *Nutr Clin Pract*. 2014;29:192–200. https://doi.org/10.1177/0884533614521242
60. van der Kuip M, de Meer K, Westerterp KR, Gemke RJ. Physical activity as a determinant of total energy expenditure in critically ill children. *Clin Nutr*. 2007;26(6):744–751. https://doi.org/10.1016/j.clnu.2007.08.005
61. Singer P, Berger MM, Van den Berghe G, et al. European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on parenteral nutrition: intensive care. *Clin Nutr*. 2009;28(4):387–400. https://doi.org/10.1016/j.clnu.2009.04.024
62. Vervloessem D, van Leersum F, Boer D, et al. Percutaneous endoscopic gastrostomy (PEG) in children is not a minor procedure: risk factors for major complications. *Semin Pediatr Surg*. 2009;18(2):93–97. https://doi.org/10.1053/j.sempedsurg.2009.02.006
63. Beres A, Bratu I, Laberge J. Attention to small details: big deal for gastrostomies. *Semin Pediatr Surg*. 2009;18(2):87–92. https://doi.org/10.1053/j.sempedsurg.2009.02.005
64. Veenker E. Enteral feeding in neurologically impaired children with gastroesophageal reflux: Nissen fundoplication and gastrostomy tube placement versus percutaneous gastrojejunostomy. *J Pediatr Nurs*. 2008;23(5):400–404. https://doi.org/10.1016/j.pedn.2007.08.012
65. Kane TD. Laparoscopic Nissen fundoplication. *Minerva Chir*. 2009;64(2):147–157.

Test Your Knowledge Answers

1. The correct answer is **D**. The initiation of enteral feedings is the most effective intervention to stimulate hepatobiliary secretions and leads to the resolution of cholestasis. Excessive calories from lipid and carbohydrate are provocateurs of cholestasis. Cycling of PN has been touted to reduce cholestasis.
2. The correct answer is **D**. Persistent bilious drainage from the stomach implies distal obstruction. The exception is congenital duodenal atresia resulting from congenital dilation and incompetence of the pyloric channel. Despite evacuation of duodenal content in a prograde manner, there may be some retrograde flow into the stomach. Contrast extravasation in esophageal atresia should initially be managed with continued NPO to allow the leak to seal without exogenous contamination of the mediastinum. Passage of a transpyloric feeding tube would require excessive manipulation. Abdominal distention with lack of stoma output is indicative of ileus or intestinal obstruction.
3. The correct answer is **A**. Advancement of enteral feedings is safe when there is no evidence of diarrhea or malabsorption. Reducing substances <1/2% and fecal pH >7 are indicative of appropriate absorption. Mucoid stools are a nonspecific finding that are concerning only if they contain gross blood. Increased frequency of bowel movements is a generic indicator for feeding intolerance; however, consideration must also be given to the quantity and nature of the stool. Small smears are not considered bowel movements, whereas large-volume watery output is of concern.
4. The correct answer is **A**. The hallmark of gastroschisis is that most patients have intestinal wall edema and serositis, resulting in the inability to determine whether there is continuity or an atresia present. This is further compounded by the fact that the intestine returns to normal morphology over a variable period ranging from 4 to 10 weeks. The intestine in omphalocele is normal other than its covered extra-abdominal location. In the absence of other disorders, these infants tolerate enteral feedings promptly. Patients with Hirschsprung's disease have impaired motility, but once they are diagnosed, they undergo a primary reconstruction or diverting colostomy and should have no

extended dependence on PN. The intestine in congenital malrotation is functionally normal, although there may be some delayed gastric emptying associated with Ladd's bands. If midgut volvulus occurs, the patient is at risk of losing the entire midgut intestine.

PART IV

Nutrition Care

30. Assessment of Nutrition Status by Age and Determining Nutrient Needs

Ellen Wagner, MD
Timothy Sentongo, MD

31. Nutrition Access

Katina Rahe, RN, BSN, CPN

32. Enteral Nutrition Support

Jessica Monczka, RD, CNSC
Sarah Simental, MS, RD, CSNC, CSPCC

33. Parenteral Nutrition Support

Kathleen M. Gura, PharmD, FASHP, FPPA, FASPEN, FMSHP, BCNSP
Catherine M. Crill, PharmD, FCCP, BCPS, BCNSP

34. Evaluation and Monitoring of Pediatric Patients Receiving Specialized Nutrition Support

Elaina Szeszycki, PharmD, CNSC
Wendy Cruse, MMSc, RDN, CSPCC
Clare McLaughlin, RDN, CSPCC

35. Ethical Issues in Providing Nutrition

Kelly Cronin Komatz, MD, MPH, FAAP, FAAHPM

30

Assessment of Nutrition Status by Age and Determining Nutrient Needs

Ellen Wagner, MD and Timothy Sentongo, MD

Learning Objectives

1. Identify the domains and documentation of pediatric nutrition assessment.
2. Apply the definition and documentation of pediatric malnutrition.
3. Know the potential nutrition deficiencies and excesses commonly found among the pediatric population.
4. Explain how to estimate the nutrient requirements for a pediatric nutrition support patient and adjust based on appropriate monitoring.

Introduction

Practical pediatric nutrition support involves an accurate assessment of protein and calorie needs followed by delivery of adequate nutrients to optimize growth and functional development. The nutrition intervention should mitigate any negative nutrition effects on organ and cellular function. Lack of appropriate nutrition results in malnutrition, which encompasses excess weight gain and inadequate growth. Deviation from expected growth is one of the major clinical manifestations of malnutrition.

Malnutrition (both over- and under-nutrition) is associated with increased morbidity, impaired functional capacity, and decreased survival. The growth rates and nutrition-related morbidity risks vary by childhood growth phase (eg, infancy, mid-childhood, and adolescence). Early infancy is a period of rapid gains in weight and length; however, persistence of increased growth beyond infancy into mid-childhood predicts an increased risk of becoming overweight or obese.[1] Furthermore, severe malnourishment during infancy and early childhood is associated with a greater than 9-fold risk of death from intercurrent illness compared with lesser degrees of malnutrition.[2,3] In addition to the macronutrient requirements, a wide variety of other nutrients have important health implications. For instance, adequate dietary calcium intake during childhood, adolescence, and early adulthood is essential for achieving a peak bone mass that is protective against earlier onset of osteoporosis during later adulthood.[4] Therefore, continual nutritional assessment is necessary for enabling practitioners to identify infants, children, and adolescents at risk for weight loss, poor growth, obesity, and specific macro- or micronutrition deficits or excesses.

The domains of pediatric nutritional assessment are 1) Anthropometry, 2) Assessing the dynamism of growth (rate of change in growth z-scores), 3) Establishing the duration of growth abnormalities, 4) Determining the etiology of abnormal growth, and 5) Assessing the impact of the growth abnormalities on functional capacity (see Table 30-1).[5] The recommended protein, energy, and micronutrient requirements for healthy children and adolescents established by the Institute of Medicine are outlined in the dietary reference intakes (DRIs) according to age.[6] However, during illness and in patients with severe malnutrition, abnormal body composition, or obesity, the individual energy requirements may need to be directly measured or estimated using age- and gender-appropriate energy prediction equations.[7]

TABLE 30-1. Key Domains to be Encompassed During Pediatric Nutrition Assessment[5]

Domain A	Anthropometric variables • Weight (kg), length (cm), height (cm), head circumference (cm) • Weight-for-length, BMI (kg/m^2) • Mid-arm circumference (cm) • Triceps skin fold thickness (mm) • Percentile growth charts: Fenton, WHO growth standard, CDC growth reference • Use of z-scores • WHO skinfold data for children age 3–59 mo: https://www.who.int/tools/child-growth-standards/standards/arm-circumference-for-age
Domain B	Dynamism of growth • Change in growth z-score
Domain C	Duration of nutritional abnormalities • Acute (less than 3-month duration) vs. chronic (greater than 3-month duration)
Domain D	Etiology/pathogenesis of nutritional abnormalities • Dietary intakes and mechanism of nutritional imbalance
Domain E	Impact of nutritional abnormalities on the patient's function and development

Abbreviations: BMI, body mass index; CDC, Centers for Disease Control and Prevention; WHO, World Health Organization.

Growth Standards, References, Percentiles, and Z-Scores

Percentiles and z-scores are used to compare growth measurements with a growth standard from reference populations. Repeated longitudinal measurements provide the most informative assessment of growth status and interpretation of percentiles and z-scores. The clinical needs, rate of growth of the particular parameter, associated measurement error, and availability of growth velocity data for the measured growth parameter

direct the frequency for obtaining the growth measurements. Length and height have an associated measurement error of 0.6 cm[8]; therefore, the suggested interval is every 2 to 6 months for children ages birth to 24 months and every 6 to 12 months for ages 2 to 20 years. Weight changes more rapidly regardless of age and is associated with a lower measurement error. Weight gain velocity charts in increments of 1, 2, 3, 4, and 6 months are available for children aged birth to 12 months[9]; therefore, weight gain velocity may be monitored every 1 to 4 months from birth to 12 months. After 1 year of age, weight gain can be observed every 6 to 12 months in stable children and more frequently when clinically indicated. Single data points of growth measurements are helpful for screening but unreliable for the correct interpretation of growth. Soft tissue circumferences and skinfold anthropometry are also practical single-data growth screening tools.

Percentiles are only adequate for assessing growth when anthropometric measurements fall within the 3rd to 97th percentile (under 2 SDs from the mean and median value). In situations where growth measurements fall outside the normal range (eg, <3rd or >97th percentile), percentiles are inadequate for quantifying the degree of malnutrition. Standard deviation scores, also referred to as z-scores, are the recommended approach for quantifying growth status, especially when measurements fall outside the normal range. A growth z-score value quantifies the number of standard deviations a growth measurement differs from the mean value (z-score of 0). Z-score values of −2.0, 0, and +2.0 correspond to the 3rd, 50th, and 97th percentiles respectively. Z-scores are very helpful in quantifying the severity of deviant growth, including risk for mortality. For example, children with weight-for-length/height z-score <−3.0 (severe malnutrition) were found to have >9-fold increased risk of death from intercurrent illness compared to children with lesser degrees of malnutrition.[2,3] Therefore, the z-score can be used to identify children at risk for malnutrition-related complications (eg, refeeding syndrome) who thus need close monitoring during the initial phases of nutritional rehabilitation.[10,11]

Preterm Infants

The 2013 revised Fenton[12] gender-specific weight, length, and head circumference growth charts for newborns between 22 and 50 weeks post-conception age are the most widely used growth references for preterm infants. They assume that the ideal weight gain, linear growth, and head circumference velocity should be equivalent to fetal development. The revised Fenton charts' growth percentiles section for infants between 40 and 50 weeks post conception age transitions smoothly into the birth to 10 weeks section of the World Health Organization (WHO) growth standards for children ages birth to 24 months (see Appendix 30-1 and 30-2). An equally reliable alternative for assessing the growth of newborns and preterm infants is the Olsen[13] growth charts. These gender-specific charts provided a reference for growth parameters (ie, weight, length, and head circumference) and body mass index (BMI) for infants between 22 and 42 weeks postconception age.[14] The Olsen growth curves are derived from an extensive database containing a racially diverse group of infants. As such, they reflect current advances in prenatal care.[13,14]

Newborn term and preterm infants are classified by birth weight (see Table 30-2) and gestational age (GA). The latter is calculated using the Ballard newborn maturational exam or by referencing the prenatal ultrasound or the date of the birthing parent's last menstrual period.[15] Thereafter, serial longitudinal measurement of weight, length, and head circumference is the primary method for monitoring and assessing nutrition status and adequacy of growth. Low birth weight (LBW) characterizes infants with a birth weight <2500 g, regardless of gestational age; small for gestational age (SGA) or intrauterine growth restriction (IUGR) refers to newborns with birth weight <10th percentile for GA. LBW and SGA may result from preterm birth, restricted intrauterine growth, genetics, or a combination of multiple factors.[16,17] Infants who are SGA at birth but have proportional reductions in weight, length, and head circumference are categorized as "symmetrical," "proportional," or "stunted" IUGR. "Asymmetrical," "disproportional," or "wasted" IUGR refers to infants born underweight (ie, <10th percentile) but with normal length and head circumference. Asymmetrical SGA accounts for 70% to 80% of children

with IUGR. The most frequent cause is uteroplacental insufficiency or related events.[17] Infants with asymmetrical IUGR have greater potential postnatal catch-up growth and less severe cognitive deficits than those with symmetrical IUGR.[16] Large for gestational age (LGA) refers to newborns with a birth weight >90th percentile for GA. The major causes of LGA include maternal diabetes, Beckwith-Wiedemann syndrome, and other genetic disorders.

TABLE 30-2. Classification of Preterm and Newborn Infants by Birth Weight and Growth Percentile

Category	**Birth Weight**
Term, LGA	>4500 g
Term, normal for gestation age	2500–4499 g
LBW	<2500 g
VLBW	<1500 g
ELBW	<1000 g
Micro preemie	<750 g
Classification	**Birth Weight for Gestation Age Percentile**
LGA	Birth weight >90th percentile
SGA; IUGR	Birth weight <10th percentile

Abbreviations: ELBW, extremely low birth weight; IUGR, intrauterine growth restriction; LBW, low birth weight; LGA, large for gestation age; SGA, small for gestation age; VLBW, very low birth weight.

Term Infants Birth–24 Months and Ages 2–20 Years

In children born at term, growth from birth to 4 months should be analyzed using the WHO international growth standards[18], which were created based on the growth of healthy breastfed infants born to healthy mothers[19] (see Appendix???, 30-2). Healthy, full-term, breastfed infants typically gain weight faster than their formula-fed age counterparts during the first 3 to 4

months of life, then slow down during the remainder of infancy.[18] Therefore, after the age of 4 months, underweight or low weight gain identified on the WHO growth standards indicates a significant growth problem. Growth in children from ages 2 to 20 years should be analyzed using the Centers for Disease Control and Prevention (CDC) growth reference charts published in 2000.[19]

Sexual Maturity Staging

Assessment of pubertal status is essential for correctly interpreting linear growth during adolescence (ie, ages 10–19 y). The presence of malnutrition or a chronic disease before or during pubertal growth may slow linear growth and lead to achievement of a final height below genetic potential.[20] Both forms of malnutrition (ie, obesity and underweight) may affect the onset and amount of pubertal linear growth spurt. Childhood obesity is associated with an earlier start of pubertal growth, while undernutrition and wasting may delay the onset of puberty. The pubertal stage can be determined by physical exam or patient report based on self-assessment pictographs[21,22] (see Appendices 30-3a and 30-3b). The beginning of peak velocity in height gain and the onset of secondary sexual characteristics occurs during Tanner stage 3. In males, the first secondary sexual characteristic to reach peak growth velocity is penile growth (around age 13 y), closely followed by testis volume, pubic hair stage, and, finally, height. In girls, the sequence is initially peak growth in height (at mean age 11.9 y) followed by progression in breast development (around age 12 y), pubic hair, and then menarche (at mean age 13.1 y). Peak height velocity approaches 10 cm/y for boys and 8 cm/y for girls.[23,24]

Disease-Specific Growth References

Cerebral Palsy

Growth and nutrition assessment is improved by categorizing children according to motor disability level and the presence or absence of a feeding tube.[25,26] Age and gender-based growth references for children and

adolescents with cerebral palsy categorized according to motor and feeding ability (with or without feeding tube) are available online (https://www.LifeExpectancy.org/articles/GrowthCharts.shtml). The classification system for motor disability in children with cerebral palsy is the 5-level Gross Motor Function Classification System (GMF-CS) presented in Table 30-3. The severity of disability influences the growth goals and expectations in children with cerebral palsy. Children with GMF-CS levels I and II, which correspond with less severe motor disabilities related to cerebral palsy, are expected to grow better and weigh more than those with GMF-CS levels III through V.[27] Growth curves are also available for upper arm length and lower limb lengths of children with quadriplegic cerebral palsy.[28] However, basic assessment using a reliably measured weight and appropriate growth reference offers more practical benefits compared to a detailed evaluation that is based on potentially inaccurate limb length measurements.[26]

TABLE 30-3. Gross Motor Function Classification System[27]

GMF-CS	Function
I	Walks without limitation
II	Walks with limitations
III	Walks using a hand-held mobility device
IV	Self-mobility with limitations; may use powered mobility
V	Transported in a manual wheelchair

Abbreviation: GMF-CS, Gross Motor Function Classification System.

Genetic Disorders

Disease-specific growth reference charts for several genetic disorders including trisomy 21 (Down syndrome), achondroplasia, Marfan's syndrome, William's syndrome, and Fragile X are available online and freely accessible in a virtual issue of the *American Journal of Medical Genetics*.[29]

Domain A: Anthropometry

The anthropometric variables routinely used for growth assessment and monitoring are

- weight (kg)
- length (cm) (in children <24 mo)
- height (cm) (in children >2 y)
- head circumference (cm) (in children <36 mo)
- mid-upper arm circumference (cm)
- triceps skinfold (mm)

Weight and linear growth (length/height) may be combined to derive weight-for-length status or compute BMI (kg/m^2), which are helpful indicators of leanness and fatness. The anthropometric measurements must be compared with the appropriate growth standard or reference data to enable proper interpretation.

Weight

Weight in infants (<12 mo) is measured with minimal clothing and without diapers to the nearest 0.01 kg. Older children should be measured to the nearest 0.1 kg while wearing little or no outer clothing and no shoes.[8] Weight is a composite measure; therefore, it does not differentiate the specific contributions of muscle, fat tissue, bone mass, or excess fluid (eg, edema or ascites). Tall, thin children may weigh the same as similarly aged children who are short and overweight. Therefore, weight measurements alone are inadequate for interpreting growth and nutritional status.

Linear Growth Length and Height

Linear growth in children ages <24 months and older but unable to stand erect unsupported is measured with the child lying supine on a length board. Linear growth in children ages >2 years is determined based on standing height measured using a wall-mounted stadiometer. The child's heels, buttocks, and back should be against the stadiometer. The head should be parallel to the floor with the Frankfurt plane (an imaginary line extending from the lower margin of the orbit to the upper margin of the auditory meatus).[8] Interpretation of linear growth in young children should factor

that whereas hereditary factors influence 80% to 90% of final height[30], birth length is more significantly influenced by maternal size and prenatal factors.[31] After that, catch-up or catch-down growth occurs, resulting in acceleration or deceleration of linear growth to the child's genetic potential by ages 11 to 12 months.[31] After age 2 years, hereditary factors greatly influence linear growth; therefore, comparison of measured height with the mid-parental height (m-PH) aids interpretation. The m-PH is determined using the Tanner-Goldstein-Whitehouse equation.[24] For girls, subtract 13 cm from the father's height, add the result to the mother's height, and calculate the average. For boys, add 13 cm to the mother's height, then add the result to the father's height and calculate the average. The value of m-PH is then plotted as the height corresponding to age 20 years on the 2–20 years growth percentile chart.

When extrapolated, the child's current height percentiles should fall within the percentiles corresponding to 8.5 cm above (corresponding to the 97th percentile for m-PH) and 8.5 cm below (corresponding to the 3rd centile for m-PH). Children with height percentiles that fall outside this 17-cm range can be interpreted as growing outside their genetic potential for linear growth. Extremely tall/long or short statures may be associated with genetic conditions like Marfan syndrome, achondroplasia, osteogenesis imperfecta, trisomy 21 (Down syndrome), and Turner syndrome. Furthermore, unexpected short stature in children may also result from chromosomal nondisjunction, translocation, or mosaicism. Therefore, the interpretation of linear growth must screen for genetic determinants and be based on comparisons with the appropriate growth reference.

Weight-for-Length and BMI

Weight-for-length and BMI are used to assess the appropriateness of weight for stature (eg, underweight and wasting, healthy weight, risk for overweight, obesity, and severe obesity). The numeric ranges of normal BMI vary with age and growth phase (eg, infancy vs early childhood, mid-childhood, and adolescence). Therefore, percentiles or z-scores but not the actual BMI value should be the basis for interpreting BMI status. See Table 30-4 for the interpretation of weight-for-length and BMI percentiles and z-scores. Acute malnutrition results from an abrupt reduction in the daily

energy and protein intake necessary for supporting normal growth and physical activity. This may arise from factors external to the child (environmental) or from clinical illnesses negatively affecting food intake, absorption, and nutrient utilization. The result is weight loss or lack of weight gain without a noticeable effect on stature. Therefore, the clinical manifestation of acute malnutrition specifically entails underweight status or wasting. Children with acute malnutrition have great potential to regain weight and resume their pre-illness growth after the malnutrition-inciting event is corrected.[32]

TABLE 30-4. Primary Indicators for Pediatric Malnutrition When Only Single Data Point is Available

	Mild Malnutrition	Moderate Malnutrition	Severe Malnutrition
WFL-z	−1.0 to −1.9	−2.0 to −2.9	≤ −3.0
BMI-z	−1.0 to −1.9	−2.0 to −2.9	≤ −3.0
LA-z/HA-z	−1.0 to −1.9	−1.0 to −1.9	≤ −3.0
MUAC	−1.0 to −1.9	−1.0 to −1.9	≤ −3.0

Abbreviations: WFL-z: Weight-for-length z score; BMI-z, body mass index for age z-score; LA-z/HA-z, length-for-age or height-for-age z-score; MUAC-z, mid arm circumference for age z-score.

MUAC-z can be obtained from: https://www.who.int/tools/child-growth-standards/standards/arm-circumference-for-age

Adapted from Becker et al.[47]

Chronic (>3 mo) inadequate protein and calorie intake results in slow/delayed linear growth, and severe and prolonged inadequacy may lead to stunting/linear growth failure, which is defined by a length/height z-score below −2.0.[33] Stunting during the first 2 years of life is a marker of severe nutrient deficiency associated with increased risk for reduced neurodevelopmental and cognitive function,[34] and elevated risk of chronic disease during adulthood. Furthermore, extended rapid weight gain following recovery from childhood severe malnutrition appears to be a risk factor for overweight, obesity, and cardiovascular disease in adulthood.[35]

Head Circumference

Head circumference (cm) is measured using a non-stretchable measuring tape[8] and plotted using the WHO international growth charts. Growth in brain mass, synaptic function, and neurodevelopment occur most rapidly during the first 3 years of life. Therefore, an increase in head circumference is a surrogate measure of brain growth. Decreased head circumference is among the sequelae of severe chronic malnutrition and predicts delays in learning and psychomotor development.[36]

Soft Tissue Anthropometry

Mid-Upper Arm Circumference and Triceps Skinfold

Mid-upper arm circumference (MUAC) and triceps skinfold thickness (TSF) measurements help assess body composition (eg, fat mass, fat-free mass), especially in children with growth measurements (eg, weight, length/height, BMI) that plot at the lower end on the standard growth charts. Soft tissue anthropometry requires a well-trained anthropometrist for reliable and reproducible measurements.[8] Detailed instructions concerning technique and appropriate tools for measuring circumferences, skinfolds, and extremity lengths are presented in the *Anthropometric Standardization Reference Manual* by Lohman et al.[37]

Mid-Upper Arm Circumference

MUAC is a composite measure of mid-upper arm muscle, fat, and bone.[8] It is relatively stable in children from 6 to 59 months. An absolute MUAC value of <115 mm (regardless of age) is designated by the WHO as a screening tool for severe malnutrition in need of immediate medical intervention.[38] MUAC is measured with the individual's upper arm parallel to the body and bent to a 90-degree angle at the elbow. The distance between the acromion (the bony protrusion on the posterior of the upper shoulder) and the olecranon (the tip of the elbow) is measured, and the midpoint between them is marked. After that, the individual's arm should be relaxed and hang loosely by the side of the body. A non-stretchable measuring tape positioned snugly (but not pinching the skin) at the marked mid-point but not pinching the skin is then used to measure the

circumference in mm. See Appendix 30-4 for the reference data and percentiles for MUAC by Frisancho.[39] MUAC *z* scores for children ages 3 to 59 months are available from WHO reference data.[40]

Triceps Skinfold

TSF thickness is a measurement of mid-arm subcutaneous fat. Fat mass is an indicator of the body's energy reserves. TSF, while not a malnutrition indicator, is the best single anthropometric indicator of body fat percentage in children ages 6 to 12 years.[41] Fat stores at the mid-arm are depleted during nutrition restriction but are rapidly replenished with nutrition intervention.[42] Therefore, TSF thickness is a valuable measurement for both the initial assessment and subsequent monitoring of response to nutrition intervention. TSF loses its correlation with body fat percentage after 12 years of age due to pubertal changes and gender-related differences in body fat deposition and lean tissue gain.[43,44]

TSF thickness is measured using a skinfold caliper at the exact location of the MUAC (refer to MUAC measurement in the previous section). The child's arm should hang loosely at the side, and the examiner should grasp a vertical pinch of skin and subcutaneous fat between the thumb and forefinger, about 1 cm above the previously marked mid-point. A skinfold is pulled away from the muscle, the caliper is applied to the marked mid-section, and a reading is taken when the caliper dial stabilizes.[37] Three separate caliper measurements should be obtained in quick succession, and the average of the three should be recorded in millimeters. See Appendix 30-5 for TSF reference data by Frisancho.[39]

Domain B: Dynamism of Growth

Growth in healthy children is sustained at stable rates, thus remaining within the same percentile and z-score range throughout childhood and into adolescence. Accelerated versus decelerated growth is an increase or decline in *z*-score of ≥1.0 compared to a previous anthropometric measurement. A change in *z* score of ≥1.0 is equivalent to crossing over one

major percentile channel (3rd, 15th, 50th, 85th, or 97th) on the WHO or CDC growth monitoring charts.[45]

A z-score difference of ≥0.67 between two longitudinally obtained growth measurements is considered as significant change.[1,46] The Academy of Nutrition and Dietetics (AND) and the American Society for Parenteral and Enteral Nutrition (ASPEN) consensus document on definition, documentation, reporting, and monitoring of pediatric malnutrition in clinical and research settings utilizes a z-score difference of 1.0 as representing significant change.[47] This higher cut-off value increases the specificity of a malnutrition diagnosis based on the new consensus criteria.

Domain C: Medical History and Physical Exam

Medical history is essential to determine the cause of growth and nutritional disturbances and differentiate acute from chronic malnutrition. The CDC's definition of *acute* is a medical condition, illness, or injury that ordinarily lasts less than three months, or was first noticed within three months of the date when evaluated. On the contrary, *chronic* is defined as medical conditions that have been present for longer than three months.[5,48] Acute malnutrition disproportionately impacts weight while minimally affecting or preserving length/height, resulting in underweight/wasting (decreased weight for length/height), and decreased BMI. Chronic malnutrition significantly negatively impacts both weight gain and linear growth, leading to short stature compared to the predicated genetic potential. A z-score for length/height below −2.0 is referred to as linear growth failure. If the nutritional insult continues, delays in brain growth may also occur and anthropometrically manifest as slowed gains in head circumference.[49] Acute malnutrition is generally rapidly responsive to nutritional intervention after correction of the inciting trigger. Chronic malnutrition is associated with high risk of long-term negative health neurodevelopmental sequelae especially if it occurs during the first two years of life.[50] Table 30-5 lists the physical and laboratory findings corresponding with acute versus chronic malnutrition and nutrient deficiencies.

TABLE 30-5. Nutrition Concerns Based on Physical Examination[96,100–102]

Site	Physical Examination	Potential Nutritional/Metabolic Status
Skin	Pallor	Iron, folate, vitamin B12, riboflavin deficiency
	Dry scaly skin	Essential fatty acid and biotin deficiency; vitamin A excess or deficiency
	Necklace distribution dermatitis, rough skin	B3 (Niacin) deficiency
	Acral distribution dermatitis	Zinc deficiency
	Peri orifice (oral, vulval/perianal) distribution dermatitis	Biotin deficiency
	Acanthosis	Obesity/Metabolic syndrome
	Edema: swollen feet, ankles, indentation of skin with application of pressure	Hypoproteinemia, edematous malnutrition
Nails	Koilonychia (spoon shaped nails)	Iron deficiency. Also deficiency of riboflavin, vitamin C and B3 (pellagra)
	Transverse leukonychia (opaque white band affecting multiple nails)	PEM, zinc deficiency, pellagra (B3) and inadequate dietary calcium
	Hapalonychia (soft nails)	Deficiency of vitamin A, B6 (pyridoxine), C, D and inadequate dietary calcium
	Beau's lines (Transverse grooves or depression)	Period of severe illness: PEM, pellagra
Neck	Enlarged thyroid	Iodine deficiency
Face	Moon face	Edematous PEM (kwashiorkor)
	Bilateral temporal wasting	Severe *PEM
	Apathy	Chronic *PEM
Mouth	Oral mucocutaneous rash, angular stomatitis, cheilosis	Deficiency of vitamin B vitamins (riboflavin, B3, B6, Biotin), iron deficiency

Site	Physical Examination	Potential Nutritional/Metabolic Status
	Bleeding gums	Vitamin C deficiency
Tongue	Atrophic glossitis (burning tongue)	Deficiency of iron, riboflavin, B6, B3, vitamin B12
	Diminished taste	Zinc deficiency
Eyes	Night blindness, Bitot's spots, corneal keratosis, keratomalacia	Vitamin A deficiency
Hair	Dull, easily pluckable, hypopigmented	*PEM (kwashiorkor)
	Increased lanugo body hair	History of significant weight loss
	Hypopigmented hair	*PEM, copper deficiency
	Brittle easily breakable hair	Zinc deficiency
	Hair loss, alopecia	Biotin deficiency, low ferritin; vitamin A toxicity
Dentition	Excessive dental carries	Inadequate fluoride, nighttime bottle, increased consumption of sweet liquids
Abdomen	Distension: hepatomegaly	Fatty liver from severe malnutrition
	Distension: Ascites	Hypoproteinemia, edematous malnutrition
Bones	Tibial bowing/genu varum	Rickets, vitamin D deficiency
Musculoskeletal	Muscle twitching: face = Chvostek sign; carpal muscles = Trousseau sign	Vitamin D deficiency with hypocalcemia
Temperature	Hypothermia	Severe *PEM, global malnutrition
Heart rate	Low heart rate/bradycardia	Severe *PEM, global malnutrition
	Tachycardia, lactic acidosis	Beri Beri (thiamin deficiency)

Abbreviation: PEM: protein-energy malnutrition.

Domain D: Determining Etiology and

Pathogenesis of Abnormal Growth

Screening for Underlying Disease

The strongest predictor of malnutrition is the presence of an underlying disease.[5] Inflammatory conditions may induce decreased appetite and poor food intake while increasing calorie requirements and promoting catabolism and nutrient-wasting (eg, cytokine-driven anorexia and skeletal muscle breakdown).[51] Malnutrition in patients with inflammatory disorders is often refractory to merely providing nutrients[52] without adequately treating the underlying clinical illness. Therefore, nutrition assessment should include an inference of the mechanisms leading to nutrient imbalance. Serum concentrations of several nutrition biomarkers may transiently decrease during the first 3–5 days of a systemic inflammatory response. These include: transthyretin (prealbumin), retinol-binding protein, zinc, selenium, and vitamins A, D, B6, and C.[53,54] Therefore, measuring serum C-reaction protein (CRP) is helpful to screening for potential effects of systemic inflammation on nutritional biomarkers.[54]

Domain E: Assessment of Nutrition-Related Functional Status and Developmental Outcomes

Functional capacity and neurocognitive development are both negatively impacted by malnutrition. Muscle function is dependent on lean body mass and strength. Severe malnutrition leads to depletion of skeletal muscle mass resulting in less strength, slowed achievement of age-appropriate motor skills, and delayed opportunities for actions independent of a caregiver.[36,55] Stunted children have delayed progression in learning and development of motor skills compared to their healthy counterparts.[36,55] Nutrition therapy and participation in early intervention therapies with motor and psychosocial stimulation yields significantly better long-term improvements in growth, motor, and cognitive development compared to only administering nutrients.[56,57]

EXAMPLE You are asked to evaluate a 5-month-old previously healthy former full-term normal birth weight (3100 g) female infant admitted to the hospital because of poor growth. She initially presented at age 3 months with feeding problems that were diagnosed as pharyngeal dysphagia with an increased risk for aspiration. She was prescribed nasogastric feeds; however, it frequently gets dislodged, and the caregivers are inconsistent with immediately replacing it. The infant's newborn screen was normal, and the history is negative for vomiting or diarrhea. On physical assessment, she's not dysmorphic. She has poor head control and can only roll from supine to partially prone. Her current growth measurements are weight: 4910 g (below the3rd percentile; z-score −2.79); length 60.8 cm (7th percentile; z-score −1.46); weight-for-length: below the 3rd percentile; z-score −2.28; and head circumference 40.3 cm (18th percentile; z-score −0.90). The current labs show prealbumin of 19 mg/dL (nl greater than 21).

NUTRITION ASSESSMENT Growth assessment (Domains A, B, and C): 5-month-old female infant with moderate acute malnutrition.

Pathogenesis (Domain D): i) Feeding dysfunction with inadequate calorie intake, and ii) suspected inconsistent administration of supplemental feeds by caregivers, resulting in poor weight gain.

Functional impact (Domain E): Delays in motor Development (eg, not yet rolling over).

Definition and Documentation of Pediatric Malnutrition

The World Health Organization (WHO) criteria for diagnosing severe acute malnutrition in children aged 6–60 months and determining need for urgent action are: weight-for-height z score <−3.0, absolute MUAC <115 mm, or the presence of bilateral pedal edema.[38] In their consensus-driven, evidence-informed approach, AND and ASPEN recommend standardizing the definition, documentation, reporting, and monitoring of pediatric malnutrition in clinical and research settings. The recommended indicators that should be documented include anthropometry, z-scores, weight gain velocity (<2 years), weight loss (2–20 years), deceleration in weight for

length/height z-score, and inadequate nutrient intake.[47] The overall nutrition status score is based on the worst of all the indicators. Table 30-4 shows malnutrition indicators based on single data growth measurements. See Table 30-6 for the malnutrition diagnosis indicators based on data from multiple growth measurements.

TABLE 30-6. Primary Indicators for Pediatric Malnutrition When 2 or More Data Points are Available

	Mild Malnutrition	Moderate Malnutrition	Severe Malnutrition
Age < 24 m: weight gain velocity z score	−1.0 to −1.9	−2.0 to −2.9	≤ −3.0
Age 2–20 y: weight loss	5% of usual weight	7.5% of usual weight	≥10% of usual weight
Deceleration in WFL-z or BMI-z	Decline of 1 z-score	Decline of 2 z-scores	Decline of 3 z-scores
Inadequate nutrient intake	51–75% estimated energy/protein needs	26–50% estimated energy/protein need	≤25% of estimated energy/protein need

Abbreviations: BMI, body mass index; WFL-z, weight-for-length z-score.

Weight gain velocity z-score for a children age birth to 24 mo can be obtained from: https://www.who.int/tools/child-growth-standards/standards/weight-velocity

The 2015 ASPEN-AND consensus criteria only referred to WFL-z; however, available Centers for Disease Control and Prevention data confirms BMI as indicative of underweight: https://www.cdc.gov/obesity/basics/childhood-defining.html

Weight gain velocities of healthy infants and children under age 2 years can be highly variable, with fluctuations occurring during consecutive growth intervals even in the absence of illness or other morbidities.[9] It is not unusual for a child's weight gain velocity to appear at the 95th percentile (z-score +2.0) for one month but then briefly decline to the 16th percentile (z-score −1.0) in the subsequent month, yet on average track consistently near the same growth percentile. Therefore, the WHO has

published gender-specific weight gain velocity standards in 1-, 2-, 3-, 4- and 6-month intervals for children under age 2 years that enable providers to quickly identify abnormal deviations in growth velocity. Therefore, determining the status of weight gain velocity now only requires two comparison weight measurements that closely fit into the assigned intervals.[9]

EXAMPLE A Department of Children and Family Services worker refers a very active 23-month-old male with feeding problems and dependence on gastrostomy-tube feeds because of concerns about his growth. At age 21 months the enteral nutrition (EN) was changed from a 1.5 kcal/mL, 120 mL + water 80 mL (total of 200 mL) × 5 bolus to a blenderized EN 1.3 kcal/mL, 120 mL + water 80 mL (total of 200 mL) × 5 boluses. His weight at 21 months was 9.68 kg.

- On admission, age 23 months: weight is 8.90 kg (z-score −2.65); length is 83.2 cm (z-score −1.36); weight-for-length z score is −2.77
- Growth at 21 months: weight is 9.6 kg (z-score −1.85); length is 83.0 cm (z-score −0.98); weight-for length z-score is −1.74
- 2-month interval weight difference: −700 g
- 2-month growth velocity z-score: −3.0 (based on reference WHO growth velocity charts).[9]
- Dietary intake prior to EN change: 900 kcal/d
- Dietary intake after EN change: 780 kcal/d
- Difference in nutrient intake: 120 kcal/d
- Estimated caloric needs: 950 kcal (calculated using WHO resting energy expenditure (REE) x 1.8 for catch-up growth)

What is his nutrition diagnosis based on ASPEN-AND consensus criteria?

- Weight gain velocity z score: −3.0 indicates severely delayed
- Weight-for-length z-score: −2.77 indicates moderate malnutrition
- Weight-for-length z score deceleration: within 1 to 1.9 indicates mild deceleration (see Table 30-6)
- Inadequacy of intake: 82% or estimated
- Overall degree of malnutrition: Severe*

*The overall nutrition score is based on the worst score of all the indicators.

Pediatric Obesity

Obesity specifically denotes excess body fat or adiposity. The morbidity from obesity is primarily linked to excess body fat.[58] The morbidities associated with obesity include mental health and psychological issues, asthma, obstructive sleep apnea, orthopedic problems, cardiovascular disease, and metabolic syndrome.[59] BMI-for-age is the recommended screening tool for overweight, obesity, and severe obesity in children aged 2 to 20 years (see Table 30-7).[60,61] BMI is inadequate for differentiating between increased weight from excess body fat (adiposity) versus increased lean tissue (muscle and bone); however, BMI values over the 95th percentile are highly correlated with increased body fat and the co-morbidities of cardiovascular disease.[62,63]

TABLE 30-7. CDC and WHO Classification of Pediatric and Adult Obesity[68,103]

Weight Status Category	BMI Range Percentile Range	Obesity Classification
Underweight	<5th percentile	
Healthy weight	5th percentile to ≤85th percentile	
Overweight	85th percentile to <95th percentile	
Obesity	>95th percentile to 120% of the 95th percentile BMI for age	Class I
Severe obesity	>120% of the 95th percentile BMI for age, or absolute BMI ≥ 35 kg/m^2	Class II
Morbid obesity	Absolute BMI 40 to 49.9 kg/m^2	Class III
Severe morbid obesity	Absolute BMI >50 kg/m^2	Class III

Abbreviations: BMI, body mass index; CDC, Centers for Disease Control and Prevention; WHO, World Health Organization.

The American Heart Association (AHA) and the 2023 American Academy of Pediatrics (AAP) clinical practice guidelines for the evaluation and treatment of children and adolescents with obesity have defined severe obesity in children aged 2 years or older and adolescents as a BMI greater than or equal to120 percent of the 95th percentile for age or a numeric BMI greater than or equal to 35 kg/m^2.[61,64] The AHA also recommends the consistent use of these cut-offs to standardize the definition of severe obesity in clinical and research settings.[61] Including an absolute BMI threshold (ie, 35 kg/m^2) aligns the pediatric definition of severe obesity with class II/III obesity in adults that is significantly linked to adverse health and all-cause mortality.[65] Reliance on actual percentiles or z-scores for monitoring obesity was discovered to be problematic because at extremely high BMIs, large changes in weight are associated with very small changes in BMI percentiles and z-scores.[66] Therefore, the new measurable criterion is more practical because it standardizes diagnosis, risk assignment, and outcome monitoring in pediatric obesity,[61] The AHA also recommends against skinfold thickness and waist circumference measurements to define severe obesity. This is for two reasons: user variability and the likelihood that body tissue will exceed the capacity of standard calipers.[61] Gulati et al.[66] led the creation of new obesity-centered BMI charts for children ages 2–20 years. The charts add several higher percentile curves (expressed as percentages of the standard 95th percentile) ranked in 10-percent intervals (ie, 110th to 190th). These charts allow practitioners to quickly classify obesity severity status and visually track even with comparatively small weight-change trends. In December 2022, the CDC published new extended BMI growth charts for high BMIs in children aged 2–20 years.[67]

The new charts add percentile lines above the standard 97th percentile, including a channel corresponding with 120 percent of the 95th percentile BMI for age(ie, the cut-off for childhood obesity).The highest channel corresponds with an adulthood BMI of 60 kg/m^2. The ranges between the percentile channels correspond with the WHO-based classes: I (30–35 kg/m^2), II (35 to 40 kg/m^2), and III (greater than 40 kg/m^2) obesity in adults.[68]

Overweight and obesity evaluations should be individualized to the child's clinical presentation and family history. Practitioners should use people-first language (e.g. "a child with high weight" or "a child with obesity" rather than "an overweight child" or "an obese child").[64] The record should screen for factors and symptoms associated with obesity (eg, snoring caused by obstructive sleep apnea, physical activity, exercise tolerance, mental health concerns, endocrine disorders, family history of overweight/obesity, lipid disorders, diabetes, and heart disease). The physical exam includes the calculation of BMI, classification of obesity, and assessment for hypertension, as well as acanthosis nigricans. The laboratory evaluation should screen for glucose intolerance, dyslipidemia, and increased hepatic transaminases which are suggestive of the fatty liver (see Table 30-8).[69]

TABLE 30-8. Clinical Features Encountered During Evaluation of Pediatric Obesity

Findings	Potential Conditions
History	
Developmental delay	Genetic disorders
Poor linear growth	Hypothyroidism, Cushing's syndrome, Prader-Willi syndrome
Headaches	Pseudotumor cerebri
Nighttime breathing difficulty or daytime somnolence	Sleep apnea, obesity hypoventilation syndrome
Abdominal pain	Gall bladder disease, GERD
Hip or knee pain	Slipped capital femoral epiphysis
Oligomenorrhea or amenorrhea	Polycystic ovary syndrome
Physical Examination	
Dysmorphic features	Genetic disorders including Prader-Willi syndrome
Moon facies	Cushing's syndrome, primary versus secondary (corticosteroid medication induced)
Blurred optic discs	Pseudotumor cerebri
Hirsutism	Polycystic ovary syndrome, Cushing's syndrome (primary or secondary)
Acanthosis nigricans	Insulin resistance, non-insulin-dependent diabetes mellitus
Truncal obesity	Risk of cardiovascular disease, Cushing's syndrome; steroids
Abdominal skin striae	Cushing syndrome—primary or secondary
Undescended testicle	Prader-Willi syndrome
Limited hip range of motion	Prader-Willi syndrome
Lower leg bowing	Blount's disease
Laboratory Findings	
Elevation in lipid and/or triglyceride values	Hyperlipidemia, metabolic syndrome
Increased hepatic transaminases	Fatty liver
Increase serum glucose, Hemoglobin A1C	Insulin resistance, NIDDM Type 2 DM

Abbreviations: DM, diabetes mellitus; GERD, gastroesophageal reflux disease; NIDDM, non-insulin dependent diabetes mellitus.

Percentage of Body Fat

Body fat percentage percentile charts based on dual-energy X-ray absorptiometry (DEXA) measurements of fat mass and lean tissue in children and adolescents aged 8–9 years have been published by the CDC.[70] A body fat percentage above the 75th percentile corresponds with a BMI at or above the 95th percentile and is also significantly associated with increased risk for dyslipidemia.[63,71] However, percentile charts for body fat percentage may underestimate obesity in children with both fat-mass and lean body mass. Similarly, body fat percentage may be higher in patients with medical conditions that disproportionately deplete lean tissue (eg, cachectic obesity, sarcopenic obesity, juvenile rheumatoid arthritis, Crohn's disease and end-stage renal disease).[72] Therefore, additionally measuring fat mass index (FMI, kg/m^2) and lean body mass index (LBMI, kg/m^2) is recommended to overcome the inadequacies of BMI and body fat percentage. FMI and LBMI can be calculated using DEXA-derived fat mass (kg) and lean body mass (kg) divided by the child's height in meters squared (m^2). Percentile growth charts for FMI and LBMI in children aged 8–20 years are available.[44] The importance of assessing and monitoring body composition due to loss of lean tissue is associated with decreased survival and higher risk for medication toxicity in patients with cancer.[72] Therefore, the future of nutrition assessment is to regularly measure and utilize information about a patient's fat mass and lean body mass during medical management.[73]

Determination of Nutrient Needs

The nutritional requirements for infants, children, and adolescents are the levels of energy, protein, and micronutrient intake from food that balance expenditure and losses and are associated with growth and deposition of tissue at rates consistent with good health.[74] In preterm infants, it is the level of protein, energy, fluid, and micronutrient intake that will support

growth in weight and composition at rates similar to a normal fetus of same postconceptional age.[69]

Protein and Energy Requirements of the Premature Infant

Preterm birth interrupts the rich supply of nutrients that support normal growth and development of the fetus. Inadequate postnatal nutrition and acute neonatal illnesses (eg, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis) are major causes of restricted growth in preterm and LBW infants. The nutritional goals for preterm infants encompass supporting growth similar to intra-uterine rates and stimulating the gastrointestinal tract to gradually assume full responsibility for digestion and absorption of nutrients.[75] The average amounts of daily parenteral and enteral protein and energy intake needed to achieve growth in preterm infants at rates similar to fetal growth at similar corrected gestation age are presented in Table 30-9.[75] Parenteral nutrition should be promptly initiated within 24 hours of birth if goal enteral feeds cannot be safely administered. When the administration of EN is approved, enteral feeds can be introduced at trophic rates (ie, 12–24 mL/kg/d). These feeds can then be gradually advanced in increments of 18–30 mL/kg/day, based on clinical and gastrointestinal tolerance or in accordance with the unit's feeding protocol. The goal is to reach enteral volumes of 150–180 mL/kg/d, as tolerated.[76] The PN is correspondingly reduced and eventually discontinued at enteral intake volumes of 80–100 mL/kg/d.[76] Human milk is the preferred EN because of its multiple benefits. These include trophic effects on the immature gastrointestinal tract, enhanced gastric emptying, immunological benefits, reduced risk of developing necrotizing enterocolitis, and earlier achievement of full enteral feedings.[69] Human milk alone has inadequate protein and calories to optimally meet all the preterm infant's nutrition needs. Therefore, fortification to 22–24 kcal/oz is recommended when the level of enteral intake reaches 40–100 mL/kg/d, depending on the patient's clinical status.[76] Daily growth is assessed by plotting weekly measurements of weight, length, and head circumference

on the Fenton gender-specific growth charts. The goal daily average weight gain varies according to corrected gestational age (CGA). The average fetal rates of weight gain are 20–23 g/kg/d at CGA 23–25 weeks; 17–20 g/kg/d at CGA 26–29 weeks; 13–17 g/kg/d at CGA 30–34 weeks, and 10–13 g/kg/d at CGA 35–37 weeks.[76] Extreme changes in weight and length may be due to fluid shifts, medical conditions, or measurement error. Likewise, rapid gains in head circumference may be an early indication of hydrocephalus, signaling the need for immediate evaluation. Therefore, these factors should all be considered before modifying an infant's nutrition support regimen. Because poor early postnatal growth is associated with impaired long-term neurocognitive development,[75] it is important to monitor preterm infant growth closely beyond hospital discharge. Formula-fed preterm infants should continue to receive special post-discharge formula appropriately fortified with macro- and micronutrients until they attain post-natal catch-up growth, which typically does not occur until at least 40 weeks CGA.[77]

TABLE 30-9. Protein and Energy Intakes Needed to Achieve Fetal Rates of Weight Gain for Preterm Infants75

Body weight, g	500–700	700–900	900–1200	1200–1500	1500–1800	1800–2200
Fetal weight gain, g/d	13	16	20	24	26	29
Fetal weight gain, g/kg/d	21	20	19	18	16	14
Protein (g/kg/d)						
Inevitable loss	1.0	1.0	1.0	1.0	1.0	1.0
Growth	2.5	2.5	2.5	2.4	2.2	2.0
Required protein intake						
Parenteral	3.5	3.5	3.5	3.4	3.2	3.0
Enteral	4.0	4.0	4.0	3.9	3.6	3.4
Energy (kcal/kg/d)						
Loss (expenditure)	60	60	65	70	70	70
Resting expenditure	45	45	50	50	50	50
Other expenditure	15	15	15	20	20	20
Growth (accretion)	29	32	36	38	39	41
Required intake						
Parenteral	89	92	101	108	109	111
Enteral	105	118	119	127	128	131
Protein/energy, g/100 kcal						
Parenteral	3.9	3.8	3.5	3.1	2.9	2.7
Enteral	3.8	3.7	3.4	3.1	2.8	2.6

Calcium and Phosphorous Requirements

The last trimester of pregnancy is the period of most significant bone mineral accretion. Therefore, infants born prematurely before 28 weeks GA have a high risk for low bone mass and metabolic bone disease (ie, osteopenia of prematurity). Furthermore, during the first few weeks of life, adequate intake of calcium and phosphorous is limited by the inability to

tolerate full EN and incompatibility-related restrictions in PN admixtures. Metabolic bone disease is often diagnosed by the appearance of demineralized bone and fractures on plain x-ray; however, these are both late findings.[78] Serum alkaline phosphatase concentrations increase with deficiency of mineral substrate (eg, calcium, phosphorous, vitamin D) or high bone turnover. High serum alkaline phosphatase inversely correlates with low serum phosphorous. A combination of serum alkaline phosphatase greater than 900 units/L and serum inorganic phosphate below 1.8 mmol/L has high sensitivity and specificity for reduced bone mineral content measured by DEXA.[79] Providing adequate calcium and phosphorous to maintain normal serum phosphorous concentrations optimizes bone mineralization. Commercial preterm infant formulas with increased protein, calories, calcium, and phosphorous are available.[69]

Protein and Energy Requirements of Full-Term Infants and Children

The components of energy expenditure are basal metabolism, thermic effect of food, the energy cost of growth, energy expended for physical activity, and energy utilized for temperature regulation.[6] Protein is essential to maintain cellular integrity, function, healing, health, and reproduction. During nutrition support, sufficient nonprotein calories (eg, carbohydrates and fats) must be provided so that the body does not revert to the metabolism of amino acids to meet energy needs.[80]

Nutrition Requirements by Age

Energy and Protein Requirements for Infants Aged Birth to 6 Months

Infants double their birth weight by the age of 6 months and triple it by the age of 12 months.[81] From birth to 6 months, the recommended protein, energy, and micronutrient intakes are based on an adequate intake (AI) level derived from the average daily protein, calorie, and micronutrient intake of healthy full-term infants born to healthy mothers and who are exclusively

breastfed and well-nourished. For infants aged 7–12 months, the AI is based on nutrients provided by 0.6 L/d of human milk, the average volume consumed in this age category, and the usual intake of complementary weaning foods infants consume.[6]

Protein and Energy Requirements after Age 6 Months

Protein Requirements

The recommended protein intake for children aged 7–12 months and 14–18 years is based on an estimated average requirement (EAR) value. The EAR for protein is the average daily protein intake level estimated to meet the requirement of half the healthy individuals in a particular life stage and gender group. The recommended protein intake for children aged 1–13 years is based on a Recommended Dietary Allowance (RDA) value. The RDA is the average daily dietary intake level sufficient to meet the nutrient requirement of nearly all (ie, 97–98 percent) of healthy individuals in a particular life stage or gender group.[6]

Energy Requirements

Estimation of energy requirements in healthy children aged birth–18 years with normal growth, body composition, and physical activity levels are calculated using the 2005 Dietary Reference Intake/Institute of Medicine (IOM) age, weight, and physical activity level-based equations included in Appendix 30-6.[6]

Estimating Energy Requirements During Illness

Indirect Calorimetry

During nutrition support, reliance on population-based Dietary Reference Intakes to guide individual energy intake during clinical illness is inappropriate because several factors that impact energy expenditure may be present. They include fever, sepsis, inflammation, sedation, decreased physical activity, mechanical ventilation, surgery, and medications.[82] The complications of overfeeding (eg, hyperglycemia, hypercapnia, lipogenesis,

hepatic steatosis), are equally as important as iatrogenic malnutrition. Therefore, the appropriate protein and energy needs must be correctly estimated and reliably delivered. Measuring resting energy expenditure using indirect calorimetry is the most accurate method for determining caloric needs to avoid hypo- or hyper-feeding.[82] Sufficient nonprotein calories (eg, carbohydrates and fats) must be provided so that the carbon skeletons of amino acids are not used to meet energy needs.[80] Energy expenditure measurements obtained using an indirect calorimeter while the patient is resting are called resting energy expenditure, kcal/d (REE). The inspired and expired air are sampled for 30 to 60 minutes, then at least 15 to 45 minutes of steady state oxygen consumption and carbon dioxide production are used to calculate energy expenditure using the Weir equation. The result is then extrapolated to 24 hours to determine the REE, kcal/d. The measured REE (mREE) is approximately equivalent to the basal metabolic rate (BMR). Total energy expenditure (TEE, kcal/d), which is the clinically required information, is determined by multiplying mREE with a coefficient based on the patient's physical activity level (PAL), illness severity, or both.

Resting Energy Expenditure Prediction Equations

When indirect calorimetry is unavailable, REE can be estimated using REE prediction equations (pREE). The two validated and most frequently used equations in pediatrics are the WHO age-, sex- and weight-based energy prediction equation[74] and Schofield age-, sex-, weight- and height-based[83] energy prediction equation. See Appendix 30-1 for the prediction equations. The Schofield REE equations, which include height, appear to have better accuracy in patients with altered body composition (eg, overweight/obesity or malnutrition).[84,85]

Normal Metabolism versus Hypo- and Hypermetabolic States

Determination of normal, hypo-, and hypermetabolic status is made by comparing the difference between mREE and pREE. The value of mREE

should be within 10 percent of the pREE. Patients with mREE within 90–110 percent of the predicted value are considered eumetabolic.[86] Therefore, mREE values below 90% and above 110 percent of pREE indicate hypometabolism versus hypermetabolism, respectively.

REE is primarily dependent on the amount of fat-free mass, which in turn is composed of muscles, organs, and tissues with various levels of metabolic activity. Conditions that cause depletion of muscle mass (eg, anorexia, malnutrition, and sarcopenia) result in decreased metabolism. Clinical states like burn injury are associated with hypermetabolism.[87] Other important factors that may upregulate metabolism include systemic inflammation through cytokine expression, thyroid hormones and catecholamine release, and central nervous system sympathetic nervous input.[88] Some medications also directly affect REE (eg, nifedipine may directly increase metabolism while chemical paralysis may reduce REE by 24 to 33 percent).[87,88]

EXAMPLE A 6-year-old boy, recently internationally adopted, only weighs 16 kg (0.3rd percentile, z-score −2.76). His height is 110 cm (3.6th percentile, z-score −1.8), and his BMI is 13.2 kg/m^2 (1.1th percentile, z-score −2.3). He's a picky eater but normally active and does not have malabsorption symptoms. The parents are seeking nutritional advice to help him gain weight. Therefore, his REE was measured to determine the metabolic rate and serve as a basis to calculate his energy needs, including a goal to gain 1 kg weight in the next 30 days.

- The estimated energy cost of 1 kg of body weight is 7700 kcal (approximately 5–8 kcal/g[89,90]).
- The mREE by indirect calorimetry was 900 kcal/d.
- The pREE based on Schofield's prediction equation, used because of his underweight status, is 871 kcal/d.
- The child has normal metabolism since mREE is within 10 percent of pREE.
- His physical activity coefficient is 1.5 (normally active).
- Therefore, the child's daily TEE, (kcal/d) at the current level of physical activity and growth rate is 900 × 1.5 = 1350 kcal/d.

- The energy cost growth for the goal 1 kg weight gain in 30 days is 7700 kcal/kg ÷ 30 days = 256 kcal/d.
- For an additional 256 kcal/d × 30 days, he will meet the goal of 7700 kcal.
- Therefore, the projected daily energy intake required to achieve a 1 kg weight gain at the current level of physical activity is 1350 + 256 = approximately 1606 kcal/day.

Vitamin and Mineral Needs

Calcium

Calcium is essential for its roles in intermediary metabolism and biochemical reactions at the cellular level. Calcium also has a significant structural role in the body—calcium and inorganic phosphorous combine to form crystalline hydroxyapatite, which makes up 60 percent of bone tissue.[91] Maintaining adequate calcium intake during childhood and adolescence is necessary to optimize the achievement of peak bone mass and decrease the risk of early-onset osteoporosis during adulthood.[69] Wyshak and Frisch[92] report a strong association between high consumption of cola beverages and increased risk for bone fractures in girls. Whether the risk results from excess consumption of phosphorus in the form of colas or diminished intake of calcium intake from declined consumption of dairy products (ie, milk) is undetermined. Dual-energy x-ray absorptiometry (ie, DEXA scan) is the method used to measure bone mass and mineral density. Notably, it confers only negligible levels of radiation exposure.[69]

Human milk is the optimal primary nutritional source of calcium and phosphorus during the first year of life. Preterm infant formulas are fortified with calcium and phosphorous in a 2:1 ratio to optimize absorption and bone mineralization. The bioavailability of calcium in human milk is more significant than that found in infant formulas and cow's milk. Therefore, standard infant formulas contain increased calcium concentrations to be more comparable to that found in human milk.

Calcium retention is relatively low in toddlers and increases as puberty approaches. Data from balance studies suggest that maximal net calcium balance is achieved with intakes of 1200 to 1500 mg daily in most healthy

adolescents.[69] Calcium intakes on food labels are indicated as a percentage of the Daily Value in each serving. The value for calcium is currently set at 1000 mg daily. Calcium supplementation should be considered for children on dairy-restricted diets or prolonged therapy with medications that inhibit calcium absorption or enhance excretion (eg, glucocorticoids).[69] Of note, excess calcium consumption does come with an increased risk for adverse events including hypercalciuria, hypercalcemia, and risk for kidney stones. The AI levels for calcium are presented in Table 30-10.

TABLE 30-10. Recommendations for Adequate Dietary Calcium (elemental) Intake in the United States69

Age	ADI Calcium, mg/d (mmol/d)
0–6 mo	210 (5.3)
7–12 mo	270 (6.8)
1–3 y	500 (12.5)
4–8 y	800 (20.0)
9–18 y	1300 (32.5)
19–50 y	1000 (25)
50 to >70 y	1200 (30)

Abbreviation: ADI, adequate dietary intake.

Iron

Iron deficiency anemia is the single most common nutrient deficiency in the world.[69] The adverse effects of iron deficiency include anemia complications and increased risks for cognitive and neurodevelopmental delays. Clinical signs of iron deficiency include pallor, hair loss, koilonychia, and glossitis (see Table 30-5). The recommended screening tests for iron deficiency include obtaining a complete blood count, iron level, saturation, total iron binding capacity (TIBC), and ferritin. See Table 30-11 for the laboratory indicators of declining iron status. Ferritin is also an acute-phase protein; therefore, it should not be relied on during acute inflammation. Other potential causes for low mean corpuscular volume

(MCV) include anemia of chronic disease, sideroblastic anemia, and thalassemia traits.[93]

TABLE 30-11. Progression of Biochemical Indicators or Iron Status

Biochemical Marker	Early Phase Iron Deficiency	Mid Phase with Compensation	Late Phase: Established Iron Deficiency
Serum iron	↓	↓↓	↓↓↓
Percent saturation	↓	↓↓	↓↓↓
Ferritin	↓	↓↓	↓↓↓
Total iron binding capacity	Normal	↑	↑↑
Mean corpuscular volume	Normal	↓	↓↓
Red blood cell distribution width	Normal	Normal	↓
Hemoglobin	Normal	Normal	↓

Children with a history of premature birth are at risk for developing iron deficiency because more than 80 percent of a newborn infant's iron stores are accrued during the third trimester of pregnancy. Other settings associated with increased iron deficiency include toddlers transitioning from iron-fortified formula to cow's milk consumption, children with caregivers of low socio-economic status, overweight children, adolescent females with increased menstrual losses, athletes, patients with malabsorption disorders, occult gastrointestinal bleeding, and illnesses associated with chronic inflammation. During active inflammation, there is cytokine-induced malabsorption of dietary iron.[93] This is mediated through the upregulation of hepatic synthesis of hepcidin which, in the presence of TNF-alpha, causes degradation of ferroportin, the enteric iron exporter.[93,94] Also, adequate intake of riboflavin (Vitamin B2) is essential for optimized absorption and utilization of iron.[94]

Dietary iron may be ingested as heme iron (Fe^{2}+ or ferrous) or nonheme iron (Fe^{3}+ or ferric). Ferrous iron is abundant in animal meats, whereas ferric iron is mainly found in fortified grains, beans, lentils, nuts and seeds, and certain vegetables. Ferrous iron and heme remain in solution in the stomach, and alkaline pH is encountered in the intestine; however, ferric iron is insoluble above pH 5. Therefore, ferric iron must be reduced to ferrous before absorption in the duodenum. Absorption of ferric iron may also be enhanced by chelation to ascorbic acid, amino acids, or other dietary agents that remain soluble in the alkaline duodenum.[95] Thus, achlorhydria, gastric acid suppression, and gastric bypass are major risk factors for pernicious anemia. Iron supplementation can be administered by either the enteral or parenteral route. The recommended enteral iron dose for treating iron deficiency anemia is 3–6 mg/kg/day of elemental iron administered in three divided doses for at least four weeks with concomitant vitamin C supplementation to enhance intestinal absorption.[69] Dosing of parenteral iron infusions depends on the iron deficit and is reserved for those with poor tolerance or response to enteral supplementation.

Prophylactic iron supplementation is recommended for those with an increased risk of iron-deficiency anemia.[69] Iron intake requirements for premature infants range from 2 mg/kg/d for infants with birth weights between 1500 and 2500 g to 4 mg/kg/d for infants weighing less than 1500 g at birth.[69] Adequate iron stores are needed for optimal growth and development. According to the AAP, all formula-fed infants should receive an iron-fortified formula (iron content 10–12 mg/dL) from birth to 12 months. Infants who are exclusively breastfed should be started on an iron supplement of 1 mg/kg/d beginning at the age 4 months.[69]

Vitamin D

Vitamin D deficiency is attributed to exclusively breastfed infants due to breast milk's low vitamin D content, patients with fat malabsorption secondary to exocrine pancreatic insufficiency, and cholestatic liver disease. Vitamin D deficiency may also occur in populations living at latitudes with prolonged seasons of decreased sun exposure. Cases of nutritional rickets caused by significant vitamin D deficiency continue to be reported in the United States and other Western countries. The AAP guidelines recommend

a daily intake of 400 international units of vitamin D for all infants, children, and adolescents starting from the first few days of life.[69]

Fluoride

Fluoride is an essential nutrient for preventing and controlling dental caries. Fluoride prevents caries by reducing tooth enamel solubility, reducing the effects of plaque-forming pathogens, and promoting the remineralization of demineralized areas.[96] Recommendations to prevent dental caries include establishing and maintaining good oral hygiene, optimizing exposure to topical fluoride, limiting consumption of sweets and frequent snacking, and eliminating bedtime consumption of sweet liquids.[96] Many foods contain natural fluoride, and many kinds of toothpaste and oral gels come fluoridated. However, community water fluoridation at 0.7 ppm is considered the most beneficial and inexpensive method of ensuring exposure to fluoride and reducing the incidence of dental caries. Therefore, when fluoridated community drinking water is unavailable, the AAP encourages local pediatricians to advocate for fluoridation and determine individual children who may require topical or systemic supplementation with fluoride.[69,96,97]

Refeeding Syndrome

Refeeding syndrome is a feeding-induced spectrum of electrolyte, fluid, and metabolic abnormalities occurring in previously starved or severely malnourished patients because of the rapid metabolic shift from nd itstarvation-related fat and protein catabolism to increased carbohydrate metabolism and insulin secretion as anabolic effects. Refeeding syndrome must always be considered when initiating nutrition support (see Chapter 17, “Eating Disorders,” for more detail on this topic).

Conclusion

A systematic approach to nutrition assessment in children provides important insights into a patient’s health status and risk of morbidity and mortality from intercurrent illness. Anthropometric measurements should be

interpreted using the appropriate age, gender, and disease-specific growth standard or reference data. The use of z scores is helpful in estimating growth velocity and quantifying the severity of abnormal growth when anthropometric measurements fall outside the normal percentile ranges. Nutrition assessment is incomplete without identifying and documenting the cause or source of growth abnormalities and their impact on function. Finally, nutrition assessment is a continuous activity.

Test Your Knowledge Questions

1. A 21-month-old male with biliary atresia status post Kasai portoenterostomy currently on supplemental nasogastric tube feeds presents for pre-liver transplant follow-up. He weighs 8.3 kg and is 81 cm long. At age 13 months, he weighed 7.3 kg and was 73 cm long. What is your assessment of his nutrition status?
   A. Normal growth on current feeding regimen
   B. Underweight but growing steadily on his curve
   C. Stunted growth on the current feeding regimen
   D. Wasting and increased risk for mortality
2. Review the following statements and indicate whether they are **True** or **False**:
   A. Obesity may be defined as weight-for-length or BMI greater than the 85th percentile.
   B. The risk of mortality in children with moderate malnutrition is very similar to that of children with mild malnutrition.
   C. A mid-upper arm circumference measurement of <115 mm corresponds with severe malnutrition regardless of age.
   D. A height z-score of 1.0 (85th %) corresponds with tall stature.
3. Link the following nutrients with deficiency or toxicity symptoms. Select each nutrient only once. 1. Niacin; 2. Iron; 3. Copper; 4. Zinc; 5. Biotin; 6. Calcium; 7. Pyridoxine; 8. Riboflavin
   A. Peri-orifice distributed dermatitis, glossitis, alopecia
   B. Glossitis, cheilosis, pallor, koilonychia
   C. Dysphagia, microcytosis, vegan diet, menorrhagia
   D. Transverse leukonychia, alopecia, dermatitis, dysgeusia

E. Anemia, hypopigmented hair, osteopenia
F. Diarrhea, dermatitis, dementia, death

4. You are asked to evaluate the growth status of a 5-year-old girl with cerebral palsy, history of dysphagia, and feeding tube who wears ankle braces and ambulates independently. What is the appropriate reference to use?
   A. WHO growth charts for children age birth to 60 months
   B. CDC growth charts for children aged 2–20 years
   C. Cerebral palsy GMF-CS I chart for tube fed children
   D. Cerebral palsy GMF-CS II chart for tube fed children
   E. Cerebral palsy GMF-CS III chart for tube fed children
   F. None of the above
5. Which of the following methods is the most reliable for estimating body fat and lean tissue?
   A. Skinfold anthropometry
   B. Bioelectrical impedance analysis (BIA)
   C. Body Mass Index (BMI)
   D. Dual x-ray absorptiometry (DEXA)
6. Answer **True** or **False** to the following:
   A. Reference data is available for body fat percentage
   B. Malnourished patients may have an increased body fat percentage
   C. BMI is strongly correlated with body fat percentage.

References

1. Cameron N, Demerath EW. Critical periods in human growth and their relationship to diseases of aging. *Am J Phys Anthropol*. 2002; (Suppl 35):159–184. https://doi.org/10.1002/ajpa.10183
2. Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet*. 2010;375(9730):1969–1987. https://doi.org/10.1016/s0140-6736(10)60549-1
3. Olofin I, McDonald CM, Ezzati M, Flaxman S, Black RE, et al; Nutrition Impact Model Study (anthropometry cohort pooling). Associations of suboptimal growth with all-cause and cause-specific

mortality in children under five years: a pooled analysis of ten prospective studies. *PLoS One*. 2013;8(5):e64636. https://doi.org/10.1371/journal.pone.0064636
4. Pan K, Zhang C, Yao X, Zhu Z. Association between dietary calcium intake and BMD in children and adolescents. *Endocr Connect*. 2020;9(3):194–200. https://doi.org/10.1530/EC-19-0534
5. Mehta NM, Corkins MR, Lyman B, Malone A, Goday PS, et al. Defining pediatric malnutrition: a paradigm shift toward etiology-related definitions. *J Parenter Enteral Nutr*. 2013;37(4):460–481. https://doi.org/10.1177/0148607113479972
6. Food and Nutrition Board, I.o.M., Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids (Macronutrients). A report of the panel on macronutrients, subcommittees on upper reference levels of nutrients and interpretation and uses of dietary references, and the standing committee on the scientific evaluation of dietary reference intakes. ed. I.o.M. Food and Nutrition Board., Washington DC: National Academy of Press, Washington DC; 2005.
7. Mehta NM, Skillman HE, Irving SY, Coss-Bu JA, Vermilyea S, et al. Guidelines for the provision and assessment of nutrition support therapy in the pediatric critically ill patient: Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition. *J Parenter Enteral Nutr*. 2017;41(5):706–742. https://doi.org/10.1177/0148607117711387
8. Zemel BS, Riley EM, Stallings VA. Evaluation of methodology for nutritional assessment in children: anthropometry, body composition, and energy expenditure. *Annual Review of Nutrition*. 1997;17:211–235. https://doi.org/10.1146/annurev.nutr.17.1.211
9. World Health Organization (WHO). WHO: Weight increments by birth-weight groups. Child-growth-standards;2006 [updated 2022 Dec 31; cited 2023 May 19]; Available from: https://www.who.int/tools/child-growth-standards/standards/weight-velocity
10. WHO. WHO Guideline: updates on the management of severe acute malnutrition in infants and children [Internet]. Geneva: World Health

Organization; 2013. p1–123 Available from: https://www.who.int/publications/i/item/9789241506328
11. Fuentebella J, Kerner JA. Refeeding syndrome. *Pediatr Clin North Am*. 2009;56(5): 1201–10. https://doi.org/10.1016/j.pcl.2009.06.006
12. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr*. 2013;13: 59. https://doi.org/10.1186/1471-2431-13-59
13. Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. New intrauterine growth curves based on United States data. *Pediatrics*. 2010 Feb;125(2):E214–224. https://doi.org/10.1542/peds.2009-0913
14. Olsen IE, Douglas Lawson M, Ferguson AN, Wilson CG. BMI curves for preterm infants. *Pediatrics*. 2015 Mar;135(3):E572–581. https://doi.org/10.1542/peds.2014-2777
15. Lee AC, Panchal P, Folger L, Whelan H, Whelan R, et al. Diagnostic accuracy of neonatal assessment for gestational age determination: a systematic review. *Pediatrics*. 2017 Dec;140(6). https://doi.org/10.1542/peds.2017-1423
16. Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. *Bull World Health Organ*. 1987;65(5):663–737.
17. Sharma D, Shastri S, Sharma P. Intrauterine growth restriction - part 2. J *Matern Fetal Neonatal Med*. 2016 Dec;29(24):4037–4048. https://doi.org/10.3109/14767058.2016.1154525
18. Grummer-Strawn LM, Reinold C, Krebs NF. Use of World Health Organization and CDC growth charts for children aged 0–59 months in the United States. *MMWR Recomm Rep*. 2010 Oct 8;59(RR-9):1–15.
19. Kuczmarski RJ, Ogden CL, Guo SS, et al. CDC growth charts: United States. Adv Data. 2000 Apr 27;(314):1–27. Available from: https://www.cdc.gov/nchs/data/ad/ad314.pdf
20. Sentongo TA, Korff S, Ament ME, Stallings VA, Zemel BS. Growth, body composition, and nutritional status in children and adolescents with Crohn's disease. *J Pediatr Gastroenterol Nutr*. 2000 Jul;31(1):33–40. https://doi.org/10.1097/00005176-200007000-00009
21. Morris NM, Udry JR. Validation of a self-administered instrument to assess stage of adolescent development. *J Youth Adolesc*. 1980

Jun;9(3):271–280. https://doi.org/10.1007/bf02088471
22. Schall JI, Zemel BS, Kawchak DA, Ohene-Frempong K, Stallings VA. Self-assessment of sexual maturity status in children with Crohn's disease. *J Pediatr*. 2002 Aug;141(2):223–229. https://doi.org/10.1067/mpd.2002.125907
23. Cole TJ, Pan H, Butler GE. A mixed effects model to estimate timing and intensity of pubertal growth from height and secondary sexual characteristics. *Ann Hum Biol*. 2014 Jan;41(1):76–83. https://doi.org/10.3109/03014460.2013.856472
24. Tanner JM, Goldstein H, Whitehouse RH. Standards for children's height at ages 2–9 years allowing for heights of parents. *Arch Dis Child*. 1970 Oct;45(244):755–762. https://doi.org/10.1136/adc.45.244.755
25. Day SM, Strauss DJ, Shavelle RM, Reynolds RJ. Mortality and severity in cerebral palsy patients aged 6 to 25 years. *Dev Med Child Neurol*. 2007 Mar;49(3):167–171. https://doi.org/10.1111/j.1469-8749.2007.00167.x
26. Brooks J, Day S, Shavelle R, Strauss D. Low weight, morbidity, and mortality in children with cerebral palsy: new clinical growth charts. *Pediatrics*. 2011 Aug;128(2):E299–307. https://doi.org/10.1542/peds.2010-2801
27. Bax M, Goldstein M, Rosenbaum P, Leviton A, Paneth N, et al. Proposed definition and classification of cerebral palsy, April 2005. *Dev Med Child Neurol*. 2005 Aug;47(8):571–576. https://doi.org/10.1017/s001216220500112x.
28. Spender QW, Ransford A, Dunnett SB, et al. Assessment of linear growth of children with cerebral palsy: use of alternative measures to height or length. *Dev Med Child Neurol*. 1989 Feb;31(2):206–214. https://doi.org/10.1111/j.1469-8749.1989.tb03980.x
29. Hall JG, Allanson JE, Gripp KW, Slavotinek AM. Special Section. Syndrome-specific growth charts. *Am J Med Genet A*. 2012 Nov;158A(11):2645–2646. https://doi.org/10.1002/ajmg.a.35704.
30. Silventoinen K, Magnusson PK, Tynelius P, Kaprio J, Rasmussen F. Genetic regulation of growth from birth to 18 years of age: the Swedish young male twins study. *Am J Hum Biol*. 2008 May–Jun;20(3):292–298. https://doi.org/10.1002/ajhb.20717

31. Smith DW, Truog W, Rogers JE, Greitzer LJ, Skinner AL, McCann JJ. Shifting linear growth during infancy: illustration of genetic factors in growth from fetal life through infancy. *J Pediatr*. 1976 Aug;89(2):225–230. https://doi.org/10.1016/s0022-3476(76)80453-2
32. Gorstein J, Sullivan KM, Parvanta I, Begin F. Issues in the assessment of nutritional status using anthropometry. *Bull World Health Organ*. 1994;72(2):273–283.
33. de Onis M, Branca F. Childhood stunting: a global perspective. *Matern Child Nutr.* 2016;12(Suppl 1):12–26. https://doi.org/10.1111/mcn.12231
34. Hoddinott J, Behrman JR, Maluccio JA, et al. The economic rationale for investing in stunting reduction. *Matern Child Nutr*. 2013 Oct;9(Suppl 2):69–82 https://doi.org/10.1111/mcn.12080
35. Stettler N. Nature and strength of epidemiological evidence for origins of childhood and adulthood obesity in the first year of life. *Int J Obes (Lond)*. 2007 Jul;31(7):1035–1043. https://doi.org/10.1038/sj.ijo.0803659
36. Park H, Bothe D, Bolt D, Davenport M. The impact of nutritional status and longitudinal recovery of motor and cognitive milestones in internationally adopted children. *Int J Environ Res Public Health*. 2011 Jan;8(1):105–116. https://doi.org/10.3390/ijerph8010105
37. Lohman TG, Roche AF, Martorell R. Anthropometric Standardization Reference Manual. Champaign, IL: Human Kinetics; 1988.
38. WHO. WHO child growth standards and the identification of severe acute malnutrition in infants and children: a joint statement by the World Health Organization and the United Nations Children's Fund. Geneva: World Health Organization; 2009.
39. Frisancho AR. New norms of upper limb fat and muscle areas for assessment of nutritional status. *Am J Clin Nutr*. 1981 Nov;34(11):2540–2545. https://doi.org/10.1093/ajcn/34.11.2540
40. de Onis M, Yip R, Mei Z. The development of MUAC-for-age reference data recommended by a WHO Expert Committee. *Bull World Health Organ*. 1997;75(1):11–18.
41. Richard SA, Black RE, Gilman RH, Guerrant RL, Kang G, et al. Wasting is associated with stunting in early childhood. *J Nutr*. 2012 Jul;142(7):1291–1296. https://doi.org/10.394/jn.111.154922

42. Mascarenhas MR, Zemel B, Stallings VA. Nutritional assessment in pediatrics. *Nutrition*. 1998 Jan;14(1):105–115. https://doi.org/10.1016/s0899-9007(97)00226-8
43. Roche AF, Guo SM, Siervogel RM. Grading body fatness from limited anthropometric data. *Am J Clin Nutr*. 1981 Dec;34(12):2831–2838. https://doi.org/10.1093/ajcn/34.12.2831
44. Weber DR, Moore RH, Leonard MB, Zemel BS. Fat and lean BMI reference curves in children and adolescents and their utility in identifying excess adiposity compared with BMI and percentage body fat. *Am J Clin Nutr*, 2013. 98(1):49–56. https://doi.org/10.3945/ajcn.112.053611
45. Nash A, Dunn M, Asztalos E, Corey M, Mulvihill-Jory B, O'Connor DL. Pattern of growth of very low birth weight preterm infants, assessed using the WHO Growth Standards, is associated with neurodevelopment. *Appl Physiol Nutr Metab*. 2011 Aug;36(4):562–569. https://doi.org/10.1139/h11-059
46. Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. *BMJ*. 2000 Apr 8;320(7240):967–971. https://doi.org/10.1136/bmj.320.7240.967
47. Becker P, Carney LN, Corkins MR, Monczka J, Smith E, et al. Consensus statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: indicators recommended for the identification and documentation of pediatric malnutrition (undernutrition). *Nutr Clin Pract*. 2015 Feb;30(1):147–161. https://doi.org/10.1177/0884533614557642
48. Adams PF, Hendershot GE, Marano MA. Current estimates from the National Health Interview Survey, 1996. National Center for Health Statistics. Vital Health Stat 10(200). 1999. U.S. Department of Health and Human Services. Centers for Disease Control and Prevention.
49. Engsner G, Svanberg U, Furst P, Kjellmer I, Magnell O. Brain growth in children with kwashiorkor: a study using head circumference measurement, transillumination and ultrasonic echo ventriculography. *Acta Paediatr Scand*. 1974 Sep;63(5):687–694.https://doi.org/10.1111/j.1651-2227.1974.tb16991.x

50. Schwarzenberg SJ, Georgieff MK. Advocacy for improving nutrition in the first 1000 days to support childhood development and adult health. *Pediatrics*. 2018 Feb;141(2). https://doi.org/10.1542/peds.2017-3716
51. Delano MJ, Moldawer LL. The origins of cachexia in acute and chronic inflammatory diseases. *Nutr Clin Pract*. 2006 Feb;21(1):68–81. https://doi.org/10.1177/011542650602100168
52. Jensen GL, Wheeler D, Scheinkestel C, et al. Malnutrition syndromes: a conundrum vs continuum. *J Parenter Enteral Nutr*. 2009 Nov–Dec;33(6):710–716. https://doi.org/10.1177/0148607109344724
53. Duncan A, Talwar D, McMillan DC, Stefanowicz F, O'Reilly DS. Quantitative data on the magnitude of the systemic inflammatory response and its effect on micronutrient status based on plasma measurements. *Am J Clin Nutr*. 2012 Jan;95(1):64–71. https://doi.org/10.3945/ajcn.111.023812
54. Ingenbleek Y, Young V. Transthyretin (prealbumin) in health and disease: nutritional implications. *Annu Rev Nutr*. 1994;14:495–533. https://doi.org/10.1146/annurev.nu.14.070194.002431
55. Groos AD. Delayed motor development in relation to nutritional status among children under two years of age in two districts of Simbu Province. *PNG Med J*. 1991 Dec;34(4):238–245.
56. Walker SP, Chang SM, Powell CA, Grantham-McGregor SM. Building human capacity through early childhood intervention: the Child Development Research Programme at the Tropical Medicine Research Institute, the University of the West Indies, Kingston, Jamaica. *West Indian Med J*. 2012 Aug;61(4):316–322. https://doi.org/10.7727/wimj.2012.151
57. McCormick MC, McCarton C, Tonascia J, Brooks-Gunn J. Early intervention in low birth weight premature infants: results at 18 years of age for the Infant Health and Development Program. *Pediatrics*. 2006 Mar;117(3):771–780. https://doi.org/10.1542/peds.2005-1316
58. Abdelaal M, le Roux CW, Docherty NG. Morbidity and mortality associated with obesity. *Ann Transl Med*. 2017 Apr;5(7):161. https://doi.org/10.21037/atm.2017.03.107
59. Grossman DC, Bibbins-Domingo K, Curry SJ, et al. Screening for obesity in children and adolescents: US Preventive Services Task

Force recommendation statement. *JAMA*. 2017 Jun 20;317(23):2417–2426. https://doi.org/10.1001/jama.2017.6803

60. Centers for Disease Control and Prevention (CDC). Defining childhood weight status. Overweight & Obesity 2022 [cited January 1, 2023]; Available from: https://www.cdc.gov/obesity/basics/childhood-defining.html.
61. Kelly AS, Barlow SE, Rao G, et al. Severe obesity in children and adolescents: identification, associated health risks, and treatment approaches: a scientific statement from the American Heart Association. *Circulation*. 2013 Oct 15;128(15):1689–1712. https://doi.org/10.1161/cir.0b013e3182a5cfb3
62. Krebs NF, Jacobson MS. Prevention of pediatric overweight and obesity. *Pediatrics*. 2003 Aug;112(2):424–430. https://doi.org/10.1542/peds.112.2.424
63. Flegal KM, Wei R, Ogden CL, Freedman DS, Johnson CL, Curtin LR. High adiposity and high body mass index-for-age in US children and adolescents overall and by race-ethnic group. *Am J Clin Nutr*. 2010 Apr;91(4):1020–1026. https://doi.org/10.3945/ajcn.2009.28589
64. Hampl SE, Carlson JA, Taveras EM, et al. Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents With Obesity. *Pediatrics*. 2023 Feb;151(2). https://doi.org/10.1542/peds.2022-060640
65. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA*. 2013 Jan 2;309(1):71–82. https://doi.org/10.1001/jama.2012.113905
66. Gulati AK, Kaplan DW, Daniels SR. Clinical tracking of severely obese children: a new growth chart. *Pediatrics*. 2012 Dec;130(6):1136–1140. https://doi.org/10.1542/peds.2012-0596
67. CDC. NEW: Centers for Disease Control and Prevetion: Extended BMI-for-age growth charts for very high BMIs. Growthcharts 2022 [cited 2023 25th February]; Available from: https://www.cdc.gov/growthcharts/extended-bmi.htm
68. WHO. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894:i–xii, 1–253.

69. American Academy of Pediatrics, Committee on Nutrition. Pediatric Nutrition, 8th ed. Kleinman R, Greer FK, eds. Itasca, IL: American Academy of Pediatrics; 2019.
70. Ogden CL, Flegal KM, Carroll MD, Johnson CL. Smoothed percentage body fat percentiles for U.S. children and adolescents, 1999–2004. *Natl Health Stat Report*. 2011(43):1–7. Available from: https://stacks.cdc.gov/view/cdc/13173.
71. Lamb MM, Ogden CL, Carroll MD, Lacher DA, Flegal KM. Association of body fat percentage with lipid concentrations in children and adolescents: United States, 1999–2004. *Am J Clin Nutr.* 2011;94(3):877–883. https://doi.org/10.3945/ajcn.111.015776
72. Thibault R, Pichard C. The evaluation of body composition: a useful tool for clinical practice. *Ann Nutr Metab.* 2012;60(1):6–16. https://doi.org/10.1159/000334879
73. Holmes CJ, Racette SB. The utility of body composition assessment in nutrition and clinical practice: an overview of current methodology. *Nutrients*. 2021;13(8):2493. https://doi.org/10.3390/nu13082493
74. WHO. Energy and protein requirements. Report of a joint FAO/WHO/UNU Expert Consultation. *World Health Organ Tech Rep Ser*. 1985;724:1–206.
75. Ziegler EE. Meeting the nutritional needs of the low-birth-weight infant. *Ann Nutr Metab.* 2011;58(Suppl 1):8–18. https://doi.org/10.1159/000323381
76. Embleton ND, Jennifer Moltu S, Lapillonne A, van den Akker CHP, Carnielli V, et al. Enteral nutrition in preterm infants (2022): a position paper from the ESPGHAN Committee on Nutrition and Invited Experts. *J Pediatr Gastroenterol Nutr*. 2023;76(2):248–268. https://doi.org/10.1097/mpg.0000000000003642
77. Aggett PJ, Agostoni C, Axelsson I, De Curtis M, Goulet O, et al. Feeding preterm infants after hospital discharge: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr*. 2006;42(5):596–603. https://doi.org/10.1097/01.mpg.0000221915.73264.c7
78. Tinnion RJ, Embleton ND. How to use . . . alkaline phosphatase in neonatology. *Arch Dis Child Educ Pract Ed*. 2012;97(4):157–163. https://doi.org/10.1136/archdischild-2012-301633

79. Backström MC, et al. Bone isoenzyme of serum alkaline phosphatase and serum inorganic phosphate in metabolic bone disease of prematurity. *Acta Paediatr*. 2000;89(7):867–873. https://doi.org/10.1111/j.1651-2227.2000.tb00395.x
80. Duffy B, et al. The effect of varying protein quality and energy intake on the nitrogen metabolism of parenterally fed very low birthweight (less than 1600 g) infants. *Pediatr Res.* 1981;15(7):1040–1044. https://doi.org/10.1203/00006450-198107000-00013
81. Butte NF, et al. Body composition during the first 2 years of life: an updated reference. *Pediatr Res*. 2000;47(5):578–585. https://doi.org/10.1203/00006450-200005000-00004
82. Mehta NM, Compher C. ASPEN clinical guidelines: nutrition support of the critically ill child. *J Parenter Enteral Nutr*. 2009;33(3):260–276. https://doi.org/10.1177/0148607109333114
83. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. *Hum Nutr Clin Nutr*. 1985;39(Suppl 1):5–41.
84. Kaplan AS, et al. Resting energy expenditure in clinical pediatrics: measured versus prediction equations. *J Pediatr*. 1995;127(2):200–205. https://doi.org/10.1016/s0022-3476(95)70295-4
85. Sentongo TA, et al. Resting energy expenditure and prediction equations in young children with failure to thrive. *J Pediatr*. 2000;136(3):345–350. https://doi.org/10.1067/mpd.2000.103852
86. Firouzbakhsh S, et al. Measured resting energy expenditure in children. *J Pediatr Gastroenterol Nutr*. 1993;16(2):136–142. https://doi.org/10.1097/00005176-199302000-00007
87. Barton RG, et al. Chemical paralysis reduces energy expenditure in patients with burns and severe respiratory failure treated with mechanical ventilation. *J Burn Care Rehabil.* 1997;18(5):461–468; discussion 460. https://doi.org/10.1097/00004630-199709000-00019
88. Carpenter A, Pencharz P, Mouzaki M. Accurate estimation of energy requirements of young patients. *J Pediatr Gastroenterol Nutr.* 2015;60(1):4–10. https://doi.org/10.1097/mpg.0000000000000572
89. Forbes GB, et al. Body composition changes during recovery from anorexia nervosa: comparison of two dietary regimes. *Am J Clin Nutr.* 1984;40(6):1137–1145. https://doi.org/10.1093/ajcn/40.6.1137

90. Spady DW, et al. Energy balance during recovery from malnutrition. *Am J Clin Nutr.* 1976;29(10):1073–1088. https://doi.org/10.1093/ajcn/29.10.1073
91. Feng X. Chemical and biochemical basis of cell-bone matrix interaction in health and disease. *Curr Chem Biol*. 2009;3(2):189–196. PMCID: PMC2790195
92. Wyshak G, Frisch RE. Carbonated beverages, dietary calcium, the dietary calcium/phosphorus ratio, and bone fractures in girls and boys. *J Adolesc Health*. 1994;15(3):210–215. https://doi.org/10.1016/1054-139x(94)90506-1
93. Semrin G, et al. Impaired intestinal iron absorption in Crohn's disease correlates with disease activity and markers of inflammation. *Inflamm Bowel Dis*. 2006;12(12):1101–1106. https://doi.org/10.1097/01.mib.0000235097.86360.04
94. Lynch S. Influence of infection/inflammation, thalassemia and nutritional status on iron absorption. *Int J Vitam Nutr Res*. 2007;77(3):217–223. https://doi.org/10.1024/0300-9831.77.3.217
95. Schade SG, Cohen RJ, Conrad ME. Effect of hydrochloric acid on iron absorption. *N Engl J Med*. 1968;279(13):672–674. https://doi.org/10.1056/nejm196809262791302
96. Nield LS, Stenger JP, Kamat D. Common pediatric dental dilemmas. *Clin Pediatr (Phila)*. 2008;47(2):99–105. https://doi.org/10.1177/0009922807305810
97. Clark MB, Keels MA, Slayton RL. Fluoride use in caries prevention in the primary care setting. *Pediatrics*. 2020;146(6). https://doi.org/10.1542/peds.2020-034637
98. Gaudiani JL, Sabel AL, Mehler PS. Low pre-albumin is a significant predictor of medical complications in severe anorexia nervosa. *Int J Eat Disord*. 2014;47(2):148–156. http://dx.doi.org/10.1002/eat.22233
99. Dunn RL, Stettler N, Mascarenhas MR. Refeeding syndrome in hospitalized pediatric patients. *Nutr Clin Pract*. 2003;18(4):327–332. https://doi.org/10.1177/0115426503018004327
100. Mock DM. Skin manifestations of biotin deficiency. *Semin Dermatol*. 1991;10(4):296–302.
101. Cashman MW, Sloan SB. Nutrition and nail disease. *Clin Dermatol*. 2010;28(4):420–425.

https://doi.org/10.1016/j.clindermatol.2010.03.037
102. Finner AM. Nutrition and hair: deficiencies and supplements. *Dermatol Clin*. 2013;31(1):167–172. https://doi.org/10.1016/j.det.2012.08.015
103. WHO. Obesity and overweight. Newsroom/Fact Sheets 2021. [cited 2022 Sep 11]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

Test Your Knowledge Answers

1. The correct answer is **D**. Growth of children under age 24 months is assessed using WHO growth standard. Patients with growth measurements above the 97th percentile or below the 3rd percentile should have z-scores computed. At age 13 months the growth status was the following: weight 7.3 kg <3rd percentile, z-score −2.7); length 73 cm (5th percentile, z-score −1.62); and weight-for-length <3rd percentile, with a z-score of −2.75. At age 21 months the growth status was the following: weight 8.3 kg <3rd percentile, z-score −2.93); length 81 cm (7th percentile, z-score −1.44);and weight-for-length <3rd percentile, with a z-score of −3.12. Therefore, even though there have been gains in length (cm) and weight (kg), this child's growth has *actually worsened.* The growth pattern is most consistent with wasting. A weight-for-length z-score below −3.0 is associated with a greater than 9-fold risk of mortality.
2. A. The correct answer if **False**. Obesity is defined as a BMI above the 95th percentile. Weight-for-length and BMI are not equivalent. Increased weight-for-length corresponds with overweight.
   B. The correct answer is **True**. The risk of mortality in children with moderate malnutrition is relatively similar to that in children with mild malnutrition[2,38].
   C. The correct answer is **True**. The WHO criteria states that an absolute mid-arm circumference of less than 115 mm corresponds with severe wasting and requires immediate intervention. This has been used as a screening tool to identify children with severe

malnutrition who require comprehensive nutritional rehabilitation.[38]

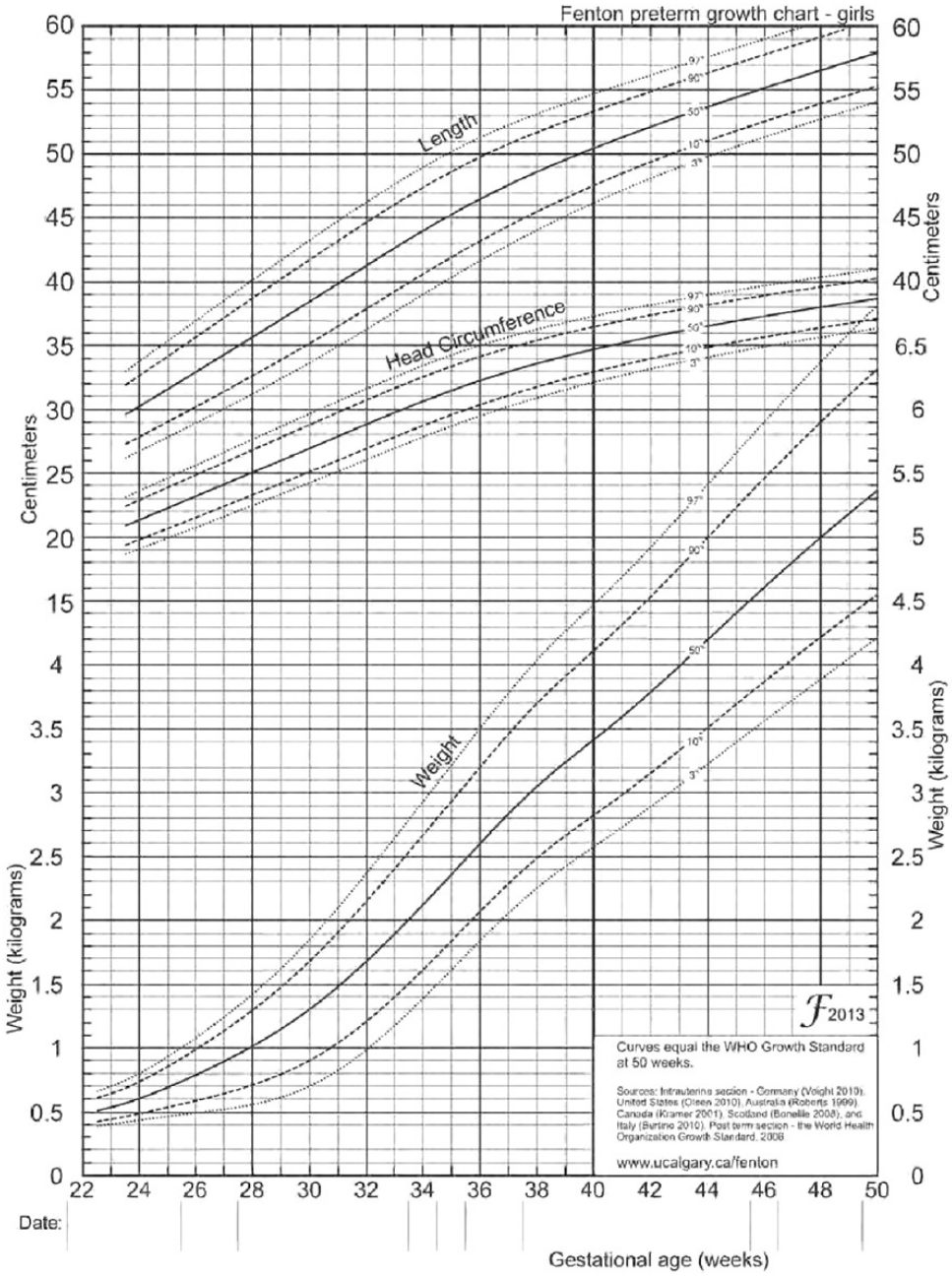
D. The correct answer is **False**. Tall stature is defined as a height z-score greater than 2.0 (97th percentile).

3. Answers:
   A. The correct answer is **F**.
   B. The correct answer is **C**.
   C. The correct answer is **E**.
   D. The correct answer is **D**.
   E. The correct answer is **A**.
   F. The correct answer is **B**.

   For more information, see Table 30-4.
4. The correct answer is **D**. This is a child with cerebral palsy who wears braces but ambulates independently (GMF-CS II). The child has a G-tube indicating some degree of major disability. Appropriate age and gender growth reference is cerebral palsy ages birth to 25 years growth chart for girls with GMF-CS II who are tube fed (see https://www.LifeExpectancy.org/articles/GrowthCharts.shtml).
5. The correct answer is **D**. DEXA is the most reliable of the options.
6. Responses:
   A. The correct answer is **True**. CDC percentage body fat percentile charts are available. For more information see Ogden et al.[70]
   B. The correct answer is **True**. Malnourished patients may have an increased body fat percentage. This demonstrates the limitations of using body fat percentage to diagnosis adiposity. Some chronic diseases may disproportionately deplete lean tissue without necessarily increasing fat tissue, such as juvenile rheumatoid arthritis, Crohn's disease, and end stage renal disease. This phenomenon is also referred to as sarcopenic obesity. Therefore, interpretation of body fat percentage should also consider BMI. Increased body fat percentage in patients with a BMI over the 95th percentile represents obesity and increased risk for dyslipidemia, while increased body fat percentage in the setting of decreased BMI below the 95th percentile represents sarcopenic obesity.

C. The correct answer is **False**. BMI is only correlated with body fat percentage in patients with a BMI above the 95th percentile.

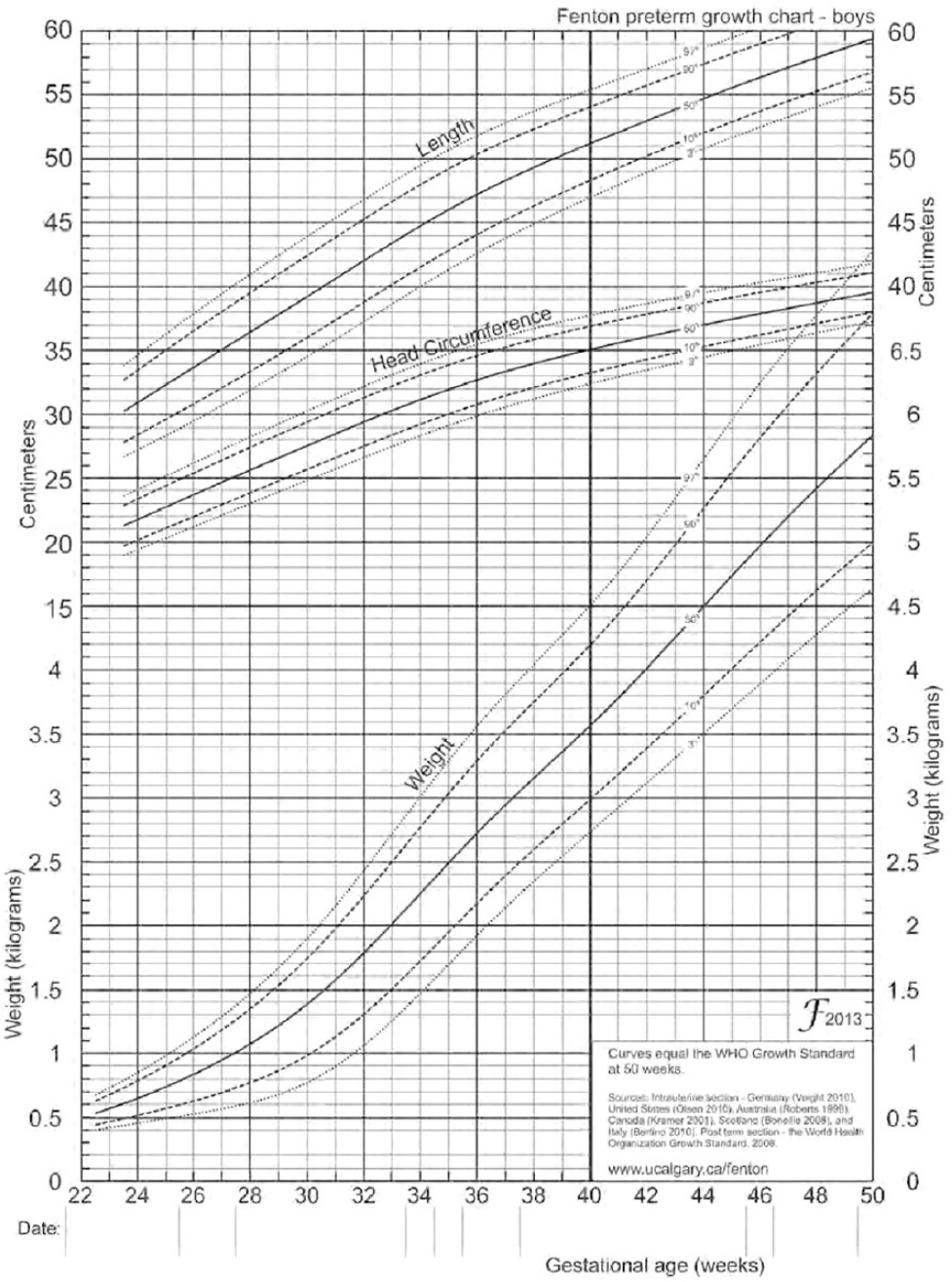
APPENDIX 30-1. Fenton 2013 Growth Charts for Preterm Girls



Reprinted under Creative Commons 2.0 license from Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatrics*. 2013;13:59.

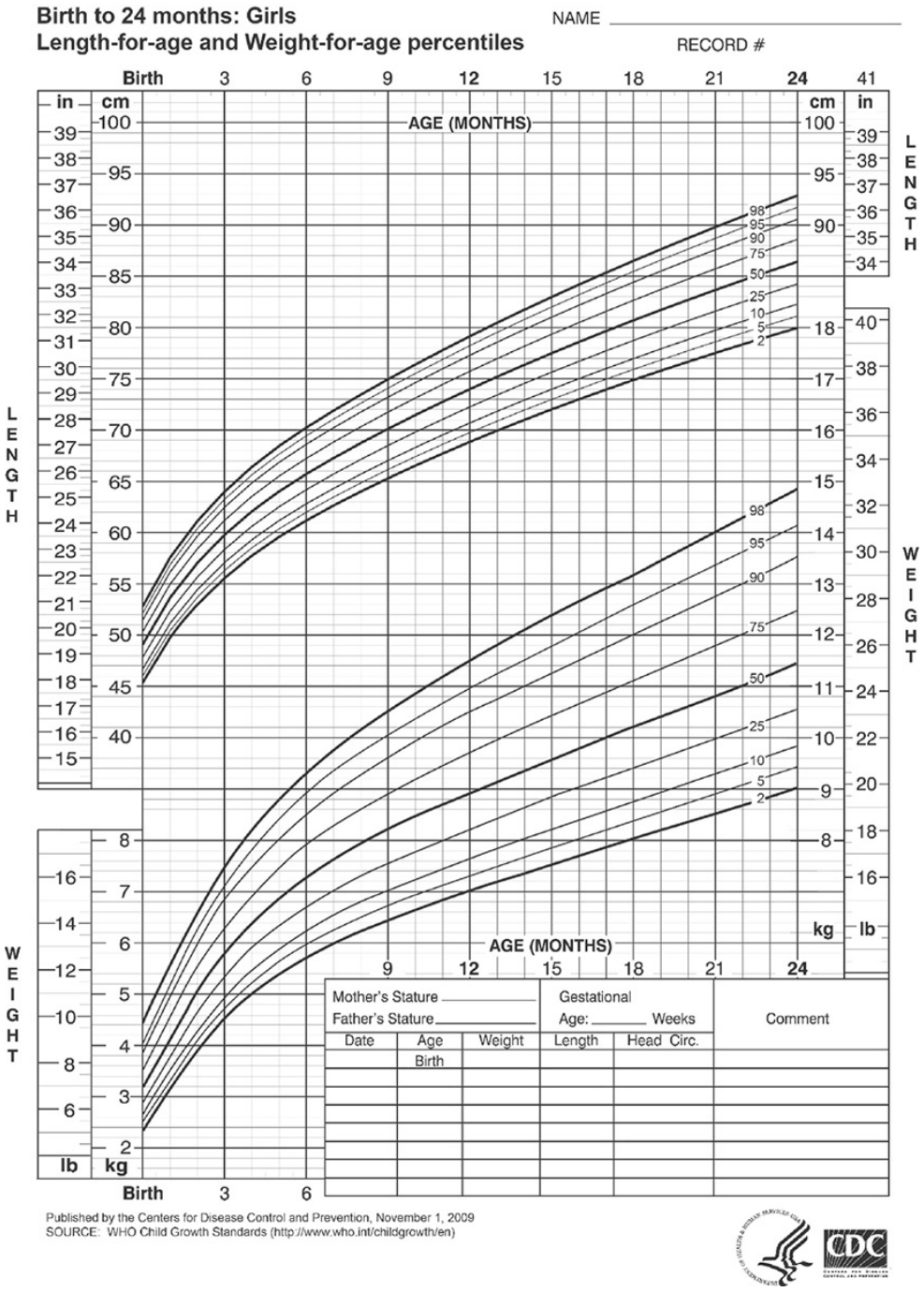
(*continued on next page*)

APPENDIX 30-1. (Continued)
Fenton 2013 Gender-Specific Growth Charts for Preterm Boys



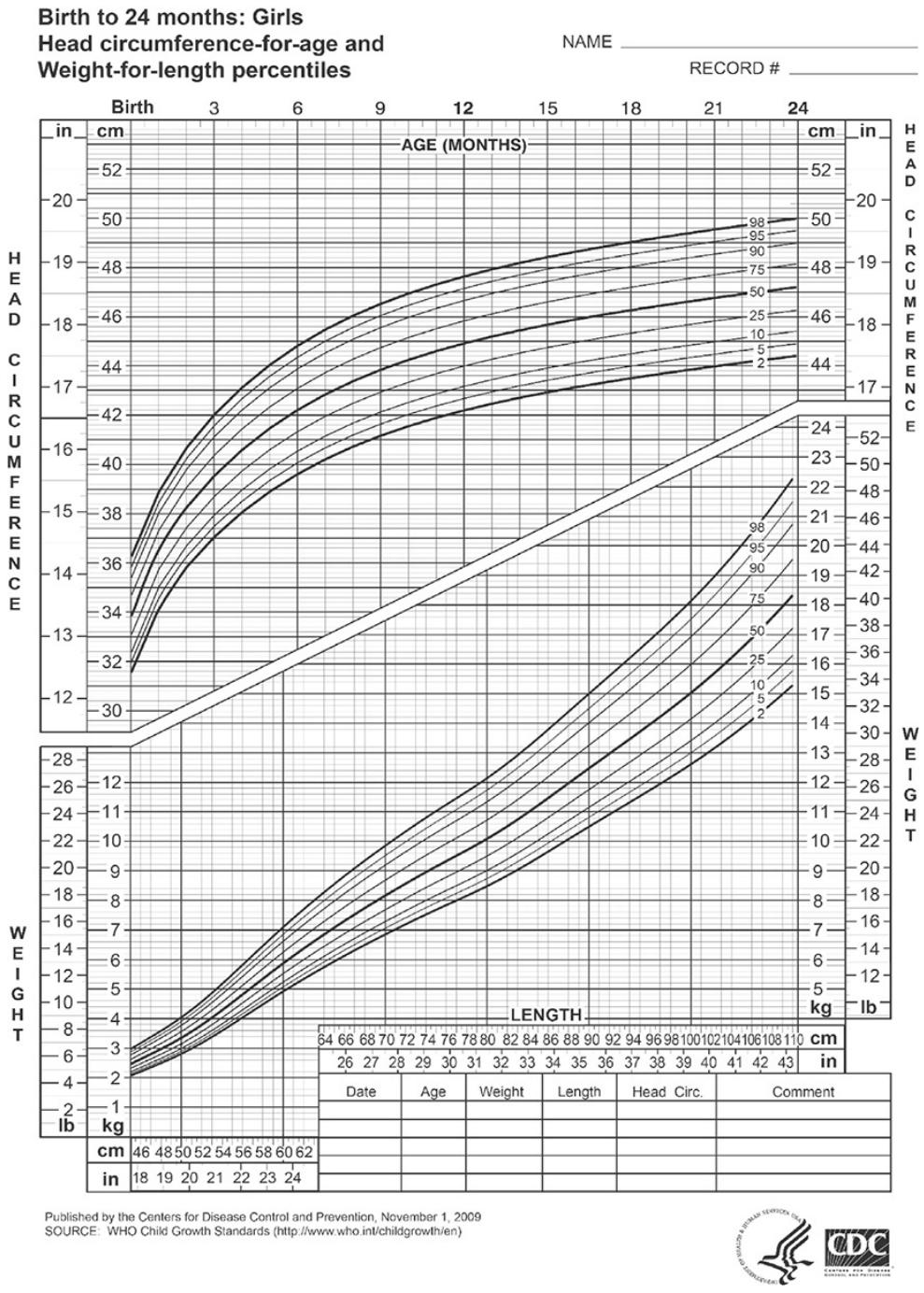
Reprinted under Creative Commons 2.0 license from Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatrics*. 2013;13:59.

APPENDIX 30-2.



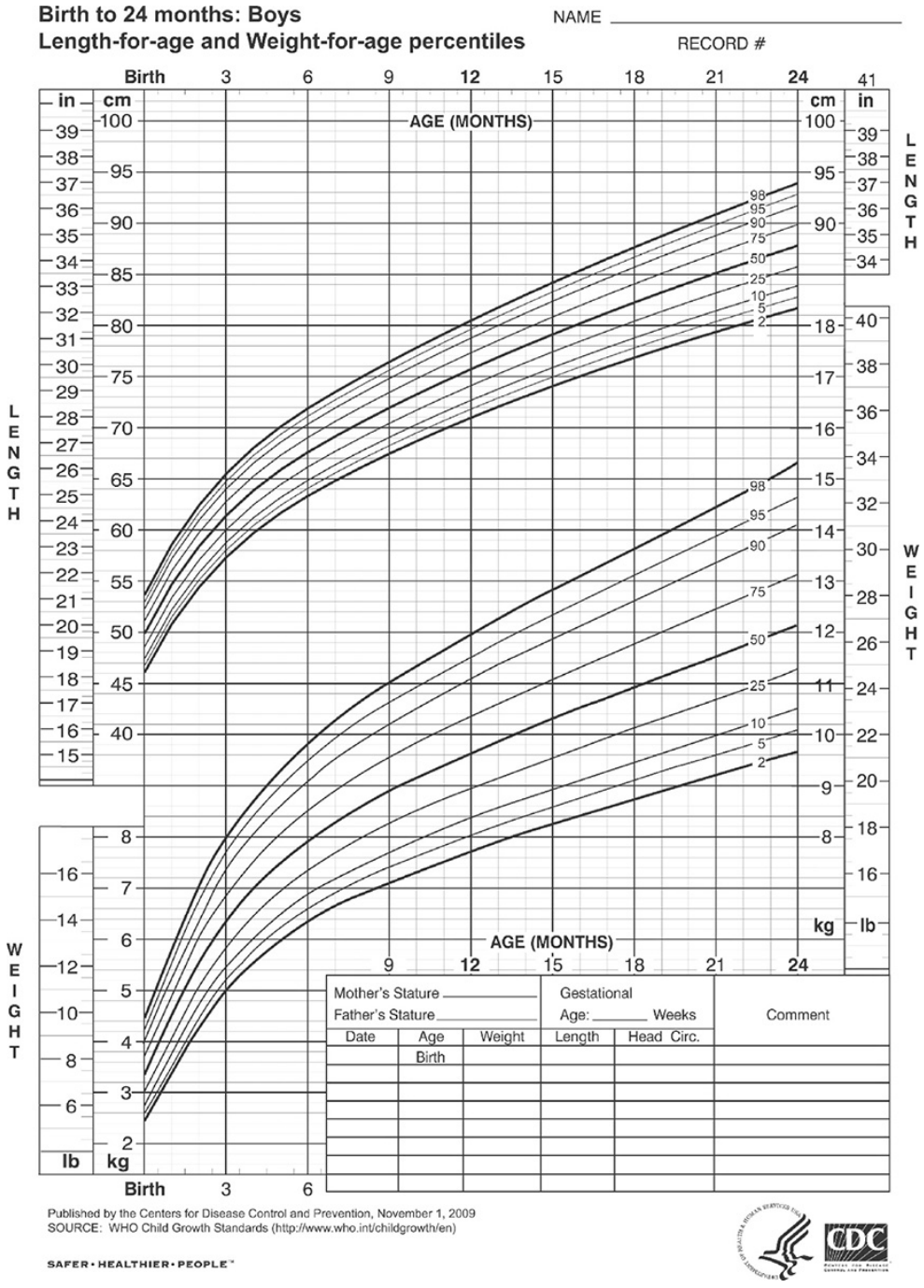
(*continued on next page*)

APPENDIX 30-2. (Continued)



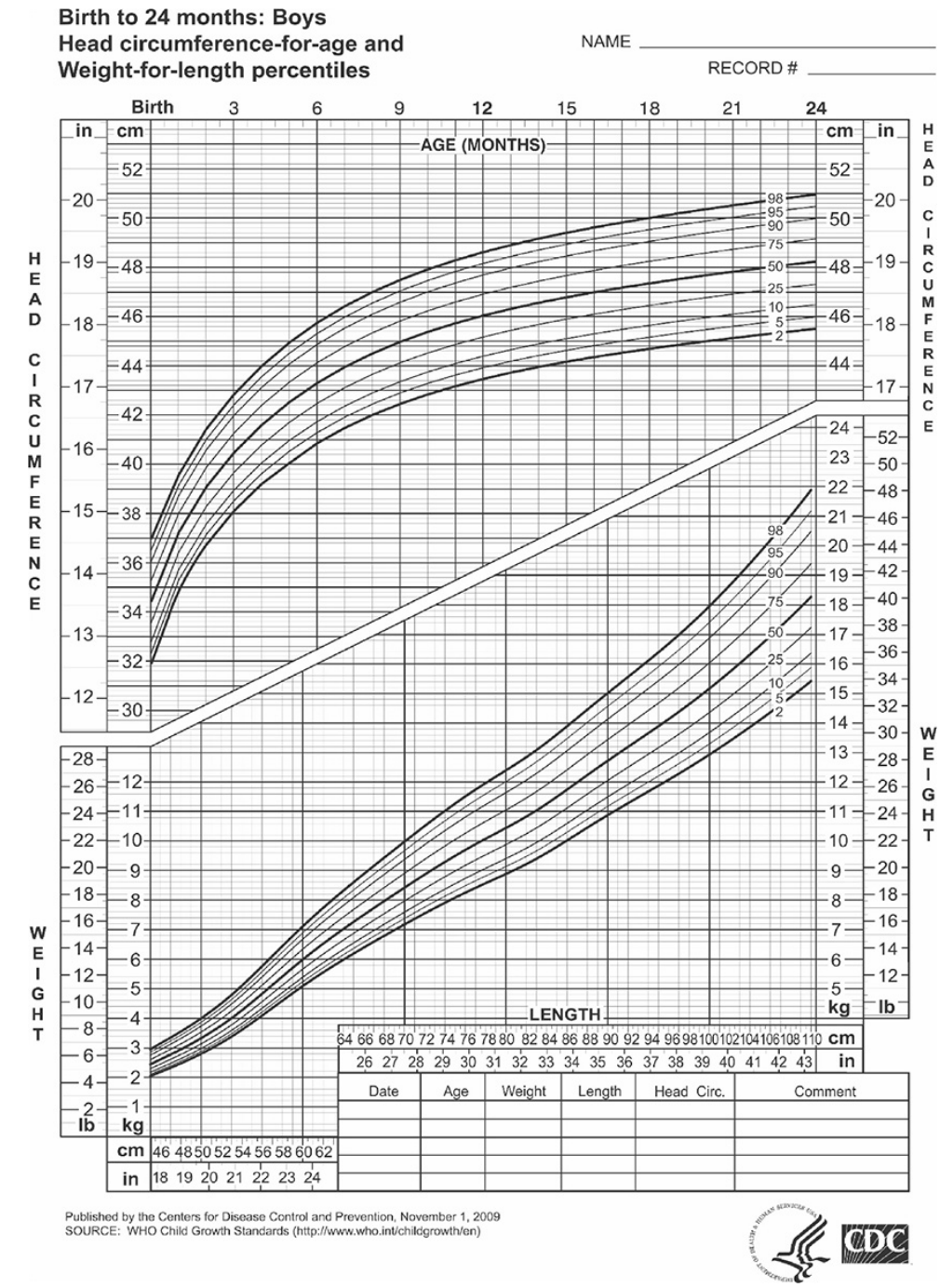
(*continued on next page*)

APPENDIX 30-2. (Continued)



(*continued on next page*)

APPENDIX 30-2. (Continued)



APPENDIX 30-3.a

GIRLS

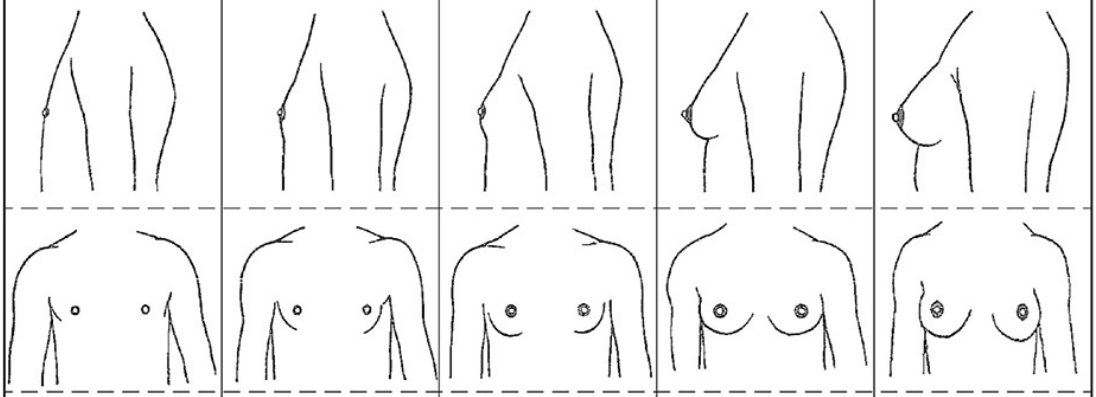
SELECT ONE FROM EACH SET OF DRAWINGS BELOW.

SET ONE: The drawings below show 5 different stages of how the breasts grow. A girl can go through each of the 5 stages as shown. Please look at each drawing and read the sentences that match the drawings. Then, mark an "X" in the box above the drawing that you think is *closest* to your stage of breast growth.

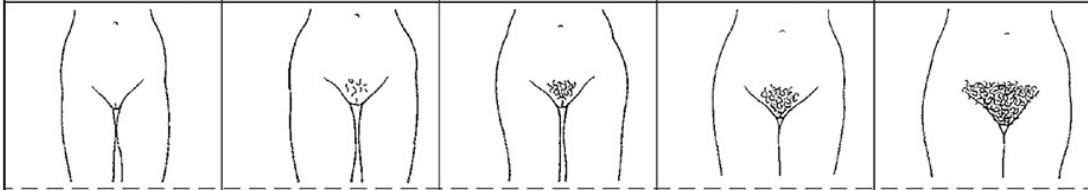
Name _____

D.O.B. _____ Age _____

Medical Record No. _____

Stage 1 ☐	Stage 2 ☐	Stage 3 ☐	Stage 4 ☐	Stage 5 ☐
				
The nipple is raised a little. The rest of the breast is still flat.	This is the breast bud stage. In this stage, the nipple is raised more than in stage 1. The breast is a small mound. The areola is larger than stage 1.	The breast and areola are both larger than in stage 2. The areola does not stick out away from the breast.	The areola and the nipple make up a mound that sticks up above the shape of the breast. NOTE: This stage may not happen at all for some girls. Some girls develop from stage 3 to stage 5 with no stage 4.	This is the mature adult stage. The breasts are fully developed. Only the nipple sticks out in this stage. The areola has moved back in the general shape of the breast.

SET TWO: The drawings below show 5 different stages of female pubic hair growth. A girl goes through each of the 5 stages as shown. Please look at each drawing and read the sentences below that match each drawing. Then, mark an "X" in the box above the drawing that you think is *closest* to the amount of your pubic hair growth.

Stage 1 ☐	Stage 2 ☐	Stage 3 ☐	Stage 4 ☐	Stage 5 ☐
				
There is no pubic hair at all.	There is a little soft, long, lightly-colored hair. This hair may be straight or a little curly.	The hair is darker in this stage. It is coarser and more curled. It has spread out and thinly covers a bigger area.	The hair is now as dark, curly, and coarse as that of an adult female. The area that the hair covers is not as big as that of an adult female. The hair has NOT spread out to the legs.	The hair is now like that of an adult female. It covers the same area as that of an adult female. The hair usually forms a triangular (∇) pattern as it spreads out to the legs.

Adapted from: Morris, N.M., and Udry, J.R., (1980), Validation of a Self-Administered Instrument to Assess Stage of Adolescent Development. *Journal of Youth and Adolescence, Vol. 9 No. 3: 271-280.*

Reprinted with kind permission from Springer Science and Business Media.

(*continued on next page*)

APPENDIX 30-3.b (Continued)

BOYS

SELECT ONE FROM EACH SET OF DRAWINGS BELOW.

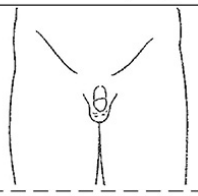
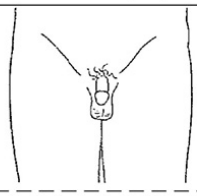
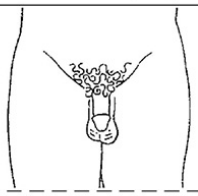
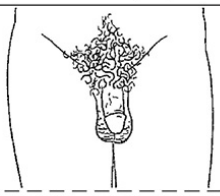
Name _____

D.O.B. _____ Age _____

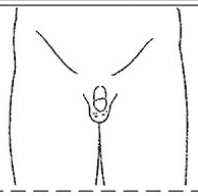
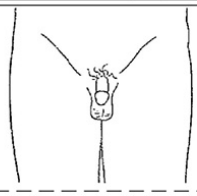
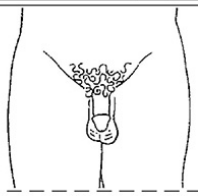
Medical Record No. _____

SET ONE: The drawings below show 5 different stages of testes, scrotum, and penis growth. A boy can go through each of the 5 stages as shown. Please look at each drawing and read the sentences that match the drawings. Then, mark an "X" in the box above the drawing that you think is *closest* to your stage of penis, scrotum, and testes growth.

Do not look at or select for pubic hair growth with this set of drawings.

Stage 1 ☐	Stage 2 ☐	Stage 3 ☐	Stage 4 ☐	Stage 5 ☐
				
The testes, scrotum, and penis are about the same size and shape as they were when you were a child.	The testes and scrotum are bigger. The skin of the scrotum has changed. The scrotum, the sack holding the testes, has gotten lower. The penis has gotten only a little bigger.	The penis has grown in length. The testes and scrotum have grown and dropped lower than in drawing 2.	The penis has gotten even bigger. It is wider. The glans (the head of the penis) is bigger. The scrotum is darker than before. It is bigger because the testes are bigger.	The penis, scrotum, and testes are the size and shape of an adult man.

SET TWO: The drawings below show 5 different stages of male pubic hair growth. A boy can pass through each of the 5 stages as shown. Please look at each drawing and read the sentences below that match each drawing. Then, mark an "X" in the box above the drawing that you think is *closest* to your stage of your pubic hair growth. *Do not look at or select for penis size with this set of drawings.*

Stage 1 ☐	Stage 2 ☐	Stage 3 ☐	Stage 4 ☐	Stage 5 ☐
				
There is no pubic hair at all.	There is a little soft, long, lightly-colored hair. Most of the hair is at the base of the penis. This hair may be straight or a little curley.	The hair is darker in this stage. It is more curled. it has spread out and thinly covers a bigger area.	The hair is now as dark, curley, and coarse as that of an adult man. The area that the hair covers is not as big as that of an adult man. The hair has NOT spread out to the legs.	The hair has spread out to the legs. The hair is now like that of an adult man. It covers the same area as that of an adult man.

APPENDIX 30-4. Percentiles of Mid-Upper Arm Circumference

Percentiles of upper arm circmference (mm) and estimated upper arm muscle circumference (mm) for whites of the United States Health and Nutrition Examination Survey I of 1971 to 1974

Age group	Arm circumference (mm)							Arm muscle circumference (mm)						
	5	10	25	50	75	90	95	5	10	25	50	75	90	95
Males														
1–1.9	142	146	150	159	170	176	183	110	113	119	127	135	144	147
2–2.9	141	145	153	162	170	178	185	111	114	122	130	140	146	150
3–3.9	150	153	160	167	175	184	190	117	123	131	137	143	148	153
4–4.9	149	154	162	171	180	186	192	123	126	133	141	148	156	159
5–5.9	153	160	167	175	185	195	204	128	133	140	147	154	162	169
6–6.9	155	159	167	179	188	209	228	131	135	142	151	161	170	177
7–7.9	162	167	177	187	201	223	230	137	139	151	160	168	177	190
8–8.9	162	170	177	190	202	220	245	140	145	154	162	170	182	187
9–9.9	175	178	187	200	217	249	257	151	154	161	170	183	196	202
10–10.9	181	184	196	210	231	262	274	156	160	166	180	191	209	221
11–11.9	186	190	202	223	244	261	280	159	165	173	183	195	205	230
12–12.9	193	200	214	232	254	282	303	167	171	182	195	210	223	241
13–13.9	194	211	228	247	263	286	301	172	179	196	211	226	238	245
14–14.9	220	226	237	253	283	303	322	189	199	212	223	240	260	264
15–15.9	222	229	244	264	284	311	320	199	204	218	237	254	266	272
16–16.9	244	248	262	278	303	324	343	213	225	234	249	269	287	296
17–17.9	246	253	267	285	308	336	347	224	231	245	258	273	294	312
18–18.9	245	260	276	297	321	353	379	226	237	252	264	283	298	324
19–24.9	262	272	288	308	331	355	372	238	245	257	273	289	309	321
25–34.9	271	282	300	319	342	362	375	243	250	264	279	298	314	326
35–44.9	278	287	305	326	345	363	374	247	255	269	286	302	318	327
45–54.9	267	281	301	322	342	362	376	239	249	265	281	300	315	326
55–64.9	258	273	296	317	336	355	369	236	245	260	278	295	310	320
65–74.9	248	263	285	307	325	344	355	223	235	251	268	284	298	306
Females														
1–1.9	138	142	148	156	164	172	177	105	111	117	124	132	139	143
2–2.9	142	145	152	160	167	176	184	111	114	119	126	133	142	147
3–3.9	143	150	158	167	175	183	189	113	119	124	132	140	146	152
4–4.9	149	154	160	169	177	184	191	115	121	128	136	144	152	157
5–5.9	153	157	165	175	185	203	211	125	128	134	142	151	159	165
6–6.9	156	162	170	176	187	204	211	130	133	138	145	154	166	171
7–7.9	164	167	174	183	199	216	231	129	135	142	151	160	171	176
8–8.9	168	172	183	195	214	247	261	138	140	151	160	171	183	194
9–9.9	178	182	194	211	224	251	260	147	150	158	167	180	194	198
10–10.9	174	182	193	210	228	251	265	148	150	159	170	180	190	197
11–11.9	185	194	208	224	248	276	303	150	158	171	181	196	217	223
12–12.9	194	203	216	237	256	282	294	162	166	180	191	201	214	220
13–13.9	202	211	223	243	271	301	338	169	175	183	198	211	226	240
14–14.9	214	223	237	252	272	304	322	174	179	190	201	216	232	247
15–15.9	208	221	239	254	279	300	322	175	178	189	202	215	228	244
16–16.9	218	224	241	258	283	318	334	170	180	190	202	216	234	249
17–17.9	220	227	241	264	295	324	350	175	183	194	205	221	239	257
18–18.9	222	227	241	258	281	312	325	174	179	191	202	215	237	245
19–24.9	221	230	247	265	290	319	345	179	185	195	207	221	236	249
25–34.9	233	240	256	277	304	342	368	183	188	199	212	228	246	264
35–44.9	241	251	267	290	317	356	378	186	192	205	218	236	257	272
45–54.9	242	256	274	299	328	362	384	187	193	206	220	238	260	274
55–64.9	243	257	280	303	335	367	385	187	196	209	225	244	266	280
65–74.9	240	252	274	299	326	356	373	185	195	208	225	244	264	279

Reprinted with permission from Frisancho AR. New norms of upper limb fat and muscle areas for assessment of nutritional status *Am J Clin Nutr.* 1981;34:2540–2545.

APPENDIX 30-5. Triceps Skinfold Percentiles

Percentiles for triceps skinfold for whites of the United States
Health and Nutrition Examination Survey I of 1971 to 1974

Age group	Triceps skinfold percentiles (mm^2)															
	n	5	10	25	50	75	90	95	n	5	10	25	50	75	90	95
	Males								Females							
1–1.9	228	6	7	8	10	12	14	16	204	6	7	8	10	12	14	16
2–2.9	223	6	7	8	10	12	14	15	208	6	8	9	10	12	15	16
3–3.9	220	6	7	8	10	11	14	15	208	7	8	9	11	12	14	15
4–4.9	230	6	6	8	9	11	12	14	208	7	8	8	10	12	14	16
5–5.9	214	6	6	8	9	11	14	15	219	6	7	8	10	12	15	18
6–6.9	117	5	6	7	8	10	13	16	118	6	6	8	10	12	14	16
7–7.9	122	5	6	7	9	12	15	17	126	6	7	9	11	13	16	18
8–8.9	117	5	6	7	8	10	13	16	118	6	8	9	12	15	18	24
9–9.9	121	6	6	7	10	13	17	18	125	8	8	10	13	16	20	22
10–10.9	146	6	6	8	10	14	18	21	152	7	8	10	12	17	23	27
11–11.9	122	6	6	8	11	16	20	24	117	7	8	10	13	18	24	28
12–12.9	153	6	6	8	11	14	22	28	129	8	9	11	14	18	23	27
13–13.9	134	5	5	7	10	14	22	26	151	8	8	12	15	21	26	30
14–14.9	131	4	5	7	9	14	21	24	141	9	10	13	16	21	26	28
15–15.9	128	4	5	6	8	11	18	24	117	8	10	12	17	21	25	32
16–16.9	131	4	5	6	8	12	16	22	142	10	12	15	18	22	26	31
17–17.9	133	5	5	6	8	12	16	19	114	10	12	13	19	24	30	37
18–18.9	91	4	5	6	9	13	20	24	109	10	12	15	18	22	26	30
19–24.9	531	4	5	7	10	15	20	22	1060	10	11	14	18	24	30	34
25–34.9	971	5	6	8	12	16	20	24	1987	10	12	16	21	27	34	37
35–44.9	806	5	6	8	12	16	20	23	1614	12	14	18	23	29	35	38
45–54.9	898	6	6	8	12	15	20	25	1047	12	16	20	25	30	36	40
55–64.9	734	5	6	8	11	14	19	22	809	12	16	20	25	31	36	38
65–74.9	1503	4	6	8	11	15	19	22	1670	12	14	18	24	29	34	36

Reprinted with permission from Frisancho AR. New norms of upper limb fat and muscle areas for assessment of nutritional status. *Am J Clin Nutr.* 1981;34:2540–2545.

APPENDIX 30-6. Estimating Nutrient Needs

Name of Equation or Formula	Description	Calculations for the Equation or Formula	Applicable to Which Patient Populations?	Source
ENERGY				
1989 Recommended Daily Allowance (RDA)	Based on the median energy intakes of children followed in longitudinal growth studies. It can overestimate needs in non-active populations (eg, bedridden) and does not provide a range of energy needs. Though an outdated reference, still widely used.	**Infants:** 0–0.5 y: 108 × wt (kg) 0.5–1 y: 98 × wt **Children:** 1–3 y: 102 × wt 4–6 y: 90 × wt 7–10 y: 70 × wt **Males:** 11–14 y: 55 × wt 15–18 y: 45 × wt **Females:** 11–14 y: 47 × wt 15–18 y: 40 × wt	Most often used for healthy infants and children	Committee on Dietary Allowances, Food and Nutrition Board, National Research Council. *Recommended Dietary Allowances*. 10th ed. Washington, DC: National Academy Press; 1989.
Estimated Energy Requirements (EER) (new DRI/IOM equation) & Physical Activity (PA) Coefficients	Replaces the 1989 Recommended Dietary Allowances (RDA). Energy needs were determined from children with normal growth, body composition, and activity, and who are also metabolically normal.	EER = TEE + energy deposition **Ages 0-36 mo:** 0–3 mo: (89 × wt [kg] – 100) + 175 4–6 mo: (89 × wt [kg] – 100) + 56 7–12 mo: (89 × wt [kg] – 100) + 22 13–36 mo: (89× wt [kg] –100) + 20 **Ages 3–8 y—Boys:** EER = 88.5 – (61.9 × age [y]) + PA × (26.7 × wt [kg] + 903 × ht[m]) + 20 kcal PA = 1 if PAL is estimated to be > 1 < 1.4 (sedentary) PA = 1.13 if PAL is estimated to be > 1.4 < 1.6 (low active) PA = 1.26 if PAL is estimated to be > 1.6 < 1.9 (active) PA = 1.42 if PAL is estimated to be > 1.9 < 2.5 (very active) **Ages 3–8 y—Girls:** EER = 135.3 – (30.8 × age [y]) + PA × (10 × wt [kg] + 934 × ht [m]) + 20 kcal PA = 1 if PAL is estimated to be > 1 < 1.4 (sedentary) PA = 1.16 if PAL is estimated to be > 1.4 < 1.6 (low active) PA = 1.31 if PAL is estimated to be > 1.6 < 1.9 (active) PA = 1.56 if PAL is estimated to be > 1.9 < 2.5 (very active) **Ages 9–18 y—Boys:** EER = 88.5 – (61.9 × age [y]) + PA × (26.7 × wt [kg] + 903 × ht [m]) + 25 kcal PA = 1 if PAL is estimated to be > 1 < 1.4 (sedentary) PA = 1.13 if PAL is estimated to be > 1.4 < 1.6 (low active) PA = 1.26 if PAL is estimated to be > 1.6 < 1.9 (active) PA = 1.42 if PAL is estimated to be > 1.9 < 2.5 (very active) **Ages 9–18 y—Girls:** EER = 135.3 – (30.8 × age [y]) + PA × (10 × wt [kg] + 934 × ht [m]) + 25 kcal PA = 1 if PAL is estimated to be > 1 < 1.4 (sedentary) PA = 1.16 if PAL is estimated to be > 1.4 < 1.6 (low active) PA = 1.31 if PAL is estimated to be > 1.6 < 1.9 (active) PA = 1.56 if PAL is estimated to be > 1.9 < 2.5 (very active)	Children with normal growth, body composition, and activity, and who are also metabolically normal	National Academy of Sciences, Institute of Medicine, Food and Nutrition Board. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients)*. The National Academies Press; 2005

(*continued on next page*)

APPENDIX 30-6. Estimating Nutrient Needs (Continued)

EER (new DRI/IOM equation) & obesity coefficients/ factors		**Weight Maintenance TEE in Overweight Boys Ages 3–18 y:** TEE = 114 – (50.9 × age [y]) + PA × (19.5 × weight [kg] + 1161.4 × height [m]) PA = 1 if PAL is estimated to be > 1 < 1.4 (sedentary) PA = 1.12 if PAL is estimated to be > 1.4 < 1.6 (low active) PA = 1.24 if PAL is estimated to be > 1.6 < 1.9 (active) PA = 1.45 if PAL is estimated to be > 1.9 < 2.5 (very active) **Weight Maintenance TEE in Overweight Girls Ages 3–18 y:** TEE = 389 (41.2 × age [y]) + PA × (15 × weight [kg] + 701.6 × height [m]) PA = 1 if PAL is estimated to be > 1 < 1.4 (sedentary) PA = 1.18 if PAL is estimated to be > 1.4 < 1.6 (low active) PA = 1.35 if PAL is estimated to be > 1.6 < 1.9 (active) PA = 1.6 if PAL is estimated to be > 1.9 < 2.5 (very active)	Overweight children who are metabolically normal	National Academy of Sciences, Institute of Medicine, Food and Nutrition Board. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients)* The National Academies Press; 2005
Schofield	A predictive equation for calculating basal metabolic rate (BMR) in healthy children that was developed by analysis of Fritz Talbot tables.	**Males:** 0–3 y: (0.167 ×wt [kg]) + (15.174 × ht [cm]) – 617.6 3–10 y: (19.59 ×wt [kg]) + (1.303 × ht [cm]) + 414.9 10–18 y: (16.25 ×wt [kg]) + (1.372 × ht [cm]) + 515.5 > 18 y: (15.057 ×wt [kg]) + (1.0004 × ht [cm]) + 705.8 **Females:** 0–3 y: (16.252 × wt[kg]) + (10.232 × height [cm]) 413.5 3–10 y: (16.969 ×wt [kg]) + (1.618 × ht [cm]) + 371.2 10–18 y: (8.365 ×wt [kg]) + (4.65 × ht [cm]) + 200 >18 y: (13.623 ×wt [kg]) + (23.8 × ht [cm]) + 98.2)	Healthy children, acutely ill patients in the hospital setting	Schofield WN. Predicting basal metabolism rate, new standards and review of previous work. *Hum Nutr Clin Nutr.* 1985;39C:5-91.
FAO/WHO	The "WHO equation" was developed for use in healthy children; however, it is commonly used to predict resting energy expenditure (REE) of acutely ill patients in the hospital setting.	**Males:** 0–3 y: (60.9 ×wt [kg])– 54 3–10 y: (22.7 ×wt [kg]) + 495 10–18 y: (17.5 ×wt [kg]) + 651 **Females:** 0–3 y: (61 ×wt [kg]) – 51 3–10 y: (22.5 ×wt [kg]) + 499 10–18 y: (12.2 ×wt [kg]) + 746	Healthy children who are acutely ill patients in the hospital setting	World Health Organization. *Energy and Protein Requirements. Report of a Joint FAO/WHO/UNU Expert Consultation*. Technical Report Series 724. World Health Organization, 1985.
Estimating calorie needs for developmental disabilities	Children with developmental disabilities (DD) may have a slower basal energy need due to a decreased muscle tone, growth rate, and motor activity. The recommendation to calculate energy needs in children with DD per cm of height is based on the fact that they tend to have a shorter height when compared to children with normal growth.	**Cerebral palsy (age 5–11 y*):** Mild–moderate activity: 13.9 kcal/cm height Severe physical restrictions: 11.1 kcal/cm height Severe restricted activity: 10 kcal/cm height Athetoid Cerebral Palsy: Up to 6000 kcal/d (adolescence) **Down Syndrome (5–12 y*):** Boys: 16.1 kcal/cm height Girls: 14.3 kcal/cm height **Prader-Willi Syndrome (for all children and adolescents):** 10–11 kcal/cm height for maintenance 8.5 kcal/cm height for weight loss **Myelomeningocele (Spina bifida) (over 8 y of age and minimally active):** 9–11 kcal/cm height for maintenance 7 kcal/cm height for weight loss Approximately 50% RDA for age after infancy	Children with developmental disabilities *This reference applies to the specific ages listed. Please refer to another equation for ages outside of the referenced ages and apply an appropriate activity/stress factor.	Rokusek C, Heindicles E. *Nutrition and Feeding of the Developmentally Disabled.* South Dakota University Affiliated Program, Interdisciplinary Center for Disabilities; 1985.
Peterson's Failure to Thrive (FTT)	This calculates nutrients in excess of the requirements of the RDA. Concerns with using this equation include refeeding syndrome.	[RDA for weight age (kcal/kg) × Ideal body weight for height] ÷ Actual weight	Infants and children who present underweight and need to achieve catch-up growth	Peterson KE, Washington J, Rathbun JM. Team management of failure to thrive. *J Am Diet Assoc.* 1984;84:810-815.
FAO/WHO/ UNU	Food and Agriculture Organization, World Health Organization, United Nations University	Boys: 10–18 y BMR = 16.6 weight (kg) + 77 height (m) + 572 Girls: 10–18 y BMR = 7.4 weight (kg) + 482 height (m) + 217	Overweight/ obese adolescents in an outpatient setting	Dietz WH, Brandini LG, Schoeller DA. Estimates of metabolic rate in obese and non-obese adolescents. *J Pediatr.* 1991;118:146-149.

(*continued on next page*)

APPENDIX 30-6. Estimating Nutrient Needs (Continued)

White equation	Developed for use in the pediatric critical care population by including temperature as a gauge of the body's inflammatory response. It is not commonly used in clinical practice, and recent studies have shown decreased accuracy especially in smaller, younger patients. This equation should not be used in patients less than 2 months of age.	EE (kJ/day) = (17 × age [mo]) + (48 × weight [kg]) + (292 × body temperature [C]) – 9677	Pediatric critical care population	White MS, Shepherd RW, McEniery JA. Energy expenditure in 100 ventilated, critically ill children: improving the accuracy of predictive equations. *Crit Care Med.* 2000;28(7):2307-2312.
STRESS FACTORS FOR ENERGY				
Stress Factors	The use of stress factors along with predictive energy equations should be considered for use in hospitalized children whose energy requirements may be altered due to metabolic stress.	Starvation 0.70–0.85 Surgery 1.05–1.5 Sepsis 1.2–1.6 Closed head injury 1.3 Trauma 1.1–1.8 Growth failure 1.5–2 Burn 1.5–2.5	Pediatric hospitalized population	Leonberg B. ADA *Pocket Guide to Pediatric Nutrition Assessment.* Chicago, IL: American Dietetic Association; 2007. Table 8.10
PROTEIN				
ASPEN clinical Guidelines: Nutrition Support of the Critically Ill Child	Metabolic stress increases catabolism and breakdown of lean body mass. To meet the increased demands of metabolic stress and spare the use of endogenous protein stores, a greater amount of protein is needed in this population until the underlying stress has been overcome. Recommendations are based on limited data.	0–2 y: 2–3 g/kg/d 2–13 y: 1.5–2 g/kg/d 13–18 y: 1.5 g/kg/d	Pediatric critical care population	Mehta NM, Compher C, ASPEN. Board of Directors. ASPEN Clinical Guidelines: Nutrition Support of the Critically Ill Child. *JPEN J Parenter Enteral Nutr.* 2009;33(3):260-276.
For the injured child	Metabolic stress increases catabolism and breakdown of lean body mass. To meet the increased demands of metabolic stress and spare the use of endogenous protein stores, a greater amount of protein is needed in this population until the underlying stress has been overcome.	0–2 y: 2–3 g/kg/d 2–13 y: 1.5–2 g/kg/d Adolescents: 1.5 g/kg/d	Pediatric critical/surgical care population	Jaksic T. Effective and efficient nutritional support for the injured child. *Surg Clin North Am.* 2002;82(2):379-391, vii.
Dietary Reference Intake (DRI)	Replaces the 1989 RDA. Protein needs were determined from children with normal growth, body composition, and activity, and who are also metabolically normal.	0–6 mo: 1.52 g/kg/d *This is an Adequate Intake recommendation; not enough research has been conducted to establish an RDA for this age group. 6–12 mo: 1.2 g/kg/d 12–36 mo: 1.05 g/kg/d; 4–13 y: 0.95 g/kg/d 14–18 y: 0.85 g/kg/d >18 y: 0.8 g/kg/d	Children with normal growth, body composition, and activity, and who are also metabolically normal	National Academy of Sciences, Institute of Medicine, Food and Nutrition Board. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients)*The National Academies Press; 2005

(*continued on next page*)

APPENDIX 30-6. Estimating Nutrient Needs (Continued)

1989 Recommended Dietary Allowance (RDA)	Based on the median nutrient intakes of children followed in longitudinal growth studies It can overestimate needs in non-active populations (eg, bedridden) and does not provide a range of energy needs. Though an outdated reference, still widely used.	0–6 mo: 2.2 g/kg/d 6–12 mo: 1.6 g/kg/d 1–3 y: 1.2 g/ kg/d; 4–6 y: 1.1 g/kg/d 7–14 y: 1 g/kg/d 15–18 y (males): 0.9 g/kg/d 15–18 y (females): 0.8 g/ kg/d	Children with normal growth, body composition, and activity, and who are also metabolically normal	Committee in Dietary Allowances, Food and Nutrition Board, National Research Council. *Recommended Dietary Allowances.* 10th ed. National Academy Press; 1989.
Peterson's Failure to Thrive (FTT)	This calculates nutrients in excess of the requirements of the RDA. Concerns with using this equation include refeeding syndrome. It can be calculated using a method similar to the one for calories above.	[Protein Required for Weight Age (g/kg/d) × Ideal Weight for Age (kg)] ÷ Actual Weight (kg)	Infants and children who present underweight and need to achieve catch-up growth	Peterson KE, Washington J, Rathbun JM. Team management of failure to thrive. *J Am Diet Assoc*. 1984;84:810-815.

The authors of this chapter wish to acknowledge Liesje Neiman Carney, RD, CNSD, LDN; and Jennifer Blair, MA, RD, CSP, LDN, for their contributions to the first edition of the chapter.

31

Nutrition Access

Katina Rahe, RN, BSN, CPN

Learning Objectives

1. Describe the indications for appropriate use and management of nutrition access devices, including enteral and venous access devices.
2. Identify the key components of nutrition access management that caregivers need to learn.
3. Formulate an evidence-based care plan for nutrition access devices to guide age-appropriate and patient-specific clinical interventions.

Introduction

Nutrition access devices allow nutrition support clinicians to deliver parenteral and enteral nutrition to patients. These devices include temporary short-term and long-term or permanent products for both enteral and parenteral nutrition delivery. It is within the scope of medical and nutrition support practice to select the appropriate device(s) and insert and maintain the device(s), but it is the patients and their families that will be responsible for managing and maintaining these devices at home. Therefore, decisions about placing a feeding tube or venous access device (VAD) for nutrition support begin with the family and continue to involve them throughout the process of addressing the child's nutritional needs.

Nutrition support clinicians must be able to teach healthcare professionals and families how to use and care for these devices, as failure to do so can have dire consequences for patients. Often a vascular access team assists with peripherally inserted central catheter (PICC) placement and complication management. Similarly, enteral access teams assist with insertion and management of various enteral access devices. Both vascular and enteral access teams can assist nutrition support clinicians with complication management and educating parents or caregivers. When providing caregiver education, consider the health literacy of the individual(s) being taught. Using a teach-back approach is an effective way to evaluate the caregiver's comprehension of the information presented. This chapter addresses indications for use, care, and management of complications related to nutrition access devices.

Types of Tubes

Nasogastric Tube

Nasogastric (NG) tubes are indicated for children who have an intact and functional gastrointestinal tract and will require nutrition through an enteral access device for less than 12 weeks. An exception to this would be an older child who self-inserts an NG tube at night for overnight enteral feeding. NG tubes are indicated for patients who have minimal gastroesophageal reflux, normal gastric emptying, and low aspiration risk.[1] NG tubes are soft, flexible tubes made of silicone or polyurethane, and the typical size range used in pediatric practice is from 5 to 12 French (Fr). The tube diameter (Fr) is chosen based on the patient's age, body size, naris size, and type of enteral nutrition needed. Small-diameter tubes are more comfortable for the patient but can become clogged, particularly if the patient receives a fiber-containing formula or if there are additives to the formula. Medications administered via the tube may also contribute to clogging.

NG tubes can be easily placed by the family. Self-insertion by children as young as 10 years of age allows them to be more active in their care. Using a rewards/consequences system for children who are old enough to understand is a good approach for when tubes are replaced. Instruction for caregivers should cover the following topics:

- Age-appropriate comfort positioning.
- Correct head position.
- Eliciting a startle reflex and immediate swallowing (eg, by blowing into the face).
- Use or avoidance of water to drink during the procedure.
- How far to place the new tube.
- How to secure the tube.

Confirmation of placement of NG tubes in the home is a topic ripe for research because there is no standard recommendation. Institutional policy on this should be followed. An article published in 2018 identified best practice recommendations for pediatric NG tube placement and verification. This article identified that NG tube placement and verification starts with education, which includes competency validation.[2] Written instructions should be provided in the family's language of preference, and caregivers should be supervised performing this task prior to discharge. Always provide contact information for the family in case they need help, and outline what would indicate a life-threatening complication. Tubes can become dislodged as well, especially by an active or agitated child. Nasogastric bridles can be implemented as a securement device to assist in the prevention of malposition and dislodgement. Studies have shown that bridles can result in fewer dislodgements, ED visits, and radiographic exposure.[3] NG tubes should be replaced or changed according to the manufacturer's recommendations. Children with NG tubes can be encouraged to eat orally while receiving NG tube feedings if it is clinically appropriate.

Orogastric Tube

Orogastric (OG) tubes are not used as frequently because they restrict oral feedings. OG tubes are most useful in the neonatal population to avoid nasal obstruction or in children in whom an NG tube cannot be passed (ie, choanal atresia). In a small study published in 2011, no differences in aspiration were indicated when a child had an OG tube and received an oral diet.[4] Another study looking at hypoxemia and bradycardia for neonates who were crossed over to receive enteral feeds via OG and then NG or vice versa found no difference in primary outcome measures using either tube.[5,6]

However, a study published in 2021 found that OG tubes had a higher incidence rate of aspiration and feeding tube displacement compared to NG tubes.[7]

Gastrostomy Tube

Gastrostomy (G) tubes are used for administering long-term enteral nutrition (>3 mo) by allowing direct access to the stomach through the anterior abdominal wall, similar to an NG tube. The benefits of a G-tube over a nasoenteral tube (NG or nasojejunal [NJ]) are added comfort, decreased likelihood of displacement, increased comfort with oral feeding, and easier concealment with clothing.

Gastrostomies can be placed surgically or endoscopically and come in a variety of sizes and types.[8–10] Surgically placed gastrostomies can be placed laparoscopically or through an upper midline incision. The initial gastrostomy placement may be a G-tube or a G-button, which is a low-profile device that sits at skin level. The endoscopically placed gastrostomy is referred to as a percutaneous endoscopic gastrostomy (PEG) tube. After placement, the G-tube or G-button may be used immediately; however, each of these gastrostomy tracts must mature (usually 8−12 weeks) before replacement.[11] After that time, caregivers can be taught how to change the device themselves.

Gastrojejunostomy Tube

Gastrojejunostomy (GJ) tubes are meant for long-term use and are inserted into the wall of the stomach, like a G-tube. There are 2 ports: 1 into the stomach for fluids, medications, feedings, or venting and the other into the jejunum for continuous drip-feeding administration. GJ tubes are recommended for patients requiring long-term enteral nutrition who have demonstrated intolerance to gastric feedings because of delayed gastric emptying, gastroesophageal reflux, or aspiration risk.[12] The most common reasons for GJ tube replacement include accidental dislodgement, clogging, coiling back into the stomach, or a broken tube.[13–15]

Jejunostomy Tube

Jejunostomy (J)-tubes are surgically or endoscopically placed into the jejunum. J-tubes are typically not placed unless a child is going to need the tube for 6 months or longer.[16] J-tubes may be indicated for use when a child is experiencing problems with delayed gastric emptying, gastric reflux, gastrectomy, or a bowel obstruction proximal to the jejunum. The negative aspects of J-tubes include mandatory continuous feedings and surgical emergencies (volvulus) around the tube or the need for urgent surgical replacement.

Caregiver education for NJ, GJ, and J-tubes must include the prevention of clogging by flushing with 10 mL to 20 mL of water every 4 hours during the day; avoiding medications down the tube or careful flushing with water before and after medication administration and avoiding fiber-containing or high-caloric-density formulas in smaller-bore tubes. Education must also cover what to do and whom to contact if the tube is accidentally removed or dislodged.

Tube Insertion

Most NG tubes are placed at the bedside. Attempts are made to make the child as comfortable as possible. Infants or young children should be swaddled for comfort and to prevent their arms from flailing about during insertion. Accurate measurement to estimate how far the NG tube needs to be placed can be done using the NEMU (naris-earlobe-midpoint between xiphoid process and umbilicus) method, which involves placing the tip of the NG tube from the naris to the earlobe, to the xiphoid process, to the umbilicus, and then finding the *midpoint* between the xiphoid process and *umbilicus*. The NEMU compared favorably with an age-related, height-based equation developed by Cigrin-Ellett.[17] Either method is recommended, especially for neonates.

The cervical spine of the child should be slightly flexed but not hyperextended.[13] A small amount of lubricant or water can be used at the tip of the tube for ease of insertion. The tip is inserted into the naris and then slid carefully down the nasopharynx, oropharynx, esophagus, and into the

stomach. It is then secured to the cheek near the naris. Caregivers are taught the technique for NG tube insertion when home use is necessary.

NJ tubes are inserted similarly but require fluoroscopy or an abdominal X-ray for accurate placement or to confirm placement. Bedside placement of these tubes is becoming a more common nursing procedure. Placement mimics that of NG tubes, except that the child may be turned onto their right side. Sterile water or oral electrolyte solution instilled slowly via syringe helps float the tube post-pylorus after confirmation that the tube is in the stomach. A prompt vacuum effect when trying to aspirate contents using an empty syringe is suggestive of post-pyloric tube placement. These tubes cannot be replaced at home. If the tube migrates back into the stomach, it must be replaced.

G, GJ, and J-tubes are placed endoscopically or surgically by a pediatric gastroenterologist, radiologist, or surgeon. If a tube is dislodged, families should be instructed to insert a replacement tube or temporary tube of the same diameter into the tract immediately to avoid premature closure until a more permanent tube can be placed by a healthcare provider.

Verification of Placement

Verifying the correct placement of an enteral tube is imperative before administering enteral nutrition. A retrospective study reviewing 326 X-rays compared NG tube placement and with an assessment of intragastric air done in a neonatal intensive care unit found half of the NG tubes to be mispositioned.[18] Mispositioned tubes were defined as in the esophagus, curled upward in the stomach, or post-pylorus. Another retrospective study using X-rays to assess NG tube placement in neonates found a 59% incidence of mispositioned tubes.[15] In both studies, 6% to 7% of tubes were in the esophagus. A tube accidentally inserted into the respiratory tract would be disastrous or even deadly for the patient and could be life-altering for the individual who placed the tube.[15,18]

Radiology

A chest or abdominal X-ray that identifies the tip of the tube is the gold standard for confirming gastric or post-pyloric tube placement. However, in

a survey of critical care nurses, Metheny documented poor compliance with national organization recommendations to confirm NG tube placement using X-rays.[16] While there is concern regarding increased radiation exposure to pediatric patients from X-rays, the alternative methods for confirming placement all have limitations.[19,20]

Air Insufflation With Auscultation

The method of air insufflation with auscultation for verifying NG tube placement involves instilling air into the tube using a syringe while using a stethoscope to listen for the sound of moving air over the stomach or left upper quadrant. This method is inexpensive and relatively easy to do, but it is the least accurate of all methods. Air instilled into a feeding tube that is mistakenly placed in the lung can be heard in the abdomen. Many case reports in the literature describe the inability of clinicians to determine gastric versus respiratory placement. In 2012, the Child Health Patient Safety Organization recommended discontinuing this method for verifying NG tube placement.[19,21]

Gastric Aspirate/pH Testing

Aspirating gastric contents and confirming pH is an alternative to the gold standard radiograph and is the recommended bedside method to confirm NG placement.[22] A large study (excluding neonates) by Gilbertson found endotracheal pH aspirate to be ≥ 6 and misplaced tubes to have a pH of ≥ 5.5, thus she recommended a pH of ≤ 5 as the cutoff for confirming NG placement.[21] Continuous enteral feedings, acid-suppressing medications, and time of the last bolus feeding are confounding variables in the use of pH measurements to confirm NG tube placement. Also, sterile water has a pH of 6 and is used to lubricate the inside of the NG tube to allow for easy removal of the stylet. To reduce error this water must be removed before checking the pH of the gastric contents. If the gastric pH is >5, if gastric aspirate cannot be obtained, or if the patient clinically deteriorates during placement, or develops low oxygen saturation, an X-ray is necessary to confirm placement.[20]

Nursing Care Related to Feeding Tubes

Aspiration Precautions

Infants and children lying flat are at increased risk of reflux and aspirating enteral nutrition. It is important to position the infant or child to prevent aspiration episodes, with the head of the child elevated at least 30° while receiving a feeding.[1,13] It may also be necessary to feed the child at risk for aspiration via a post-pyloric tube.[23]

Securing the Tube

NG, NJ, and OG tubes can easily be pulled out by an infant or child tugging on the tube, sneezing, or vomiting. To prevent dislodgement, the tube is secured on the child's face. Every effort should be made to use hypoallergenic adhesive products to avoid skin reactions or tearing of the facial skin. A hydrocolloid dressing (eg, Duoderm) on the cheek near the naris can be used as a base layer to place the external portion of the NG or OG tube, and then it can be secured with a transparent dressing or retention tape (eg, Hypafix). It is recommended that the excess tubing be fixed to the back of the infant or child's shirt using tape. This helps to keep the tube out of sight and prevents the child from dislodging it.

J-tubes and G-tubes, including low-profile devices, can also be pulled out, but is less likely. Most of the permanent feeding devices have an internal retaining bolster or water-filled balloon to secure them in place. Caregivers should receive comprehensive education regarding what to do if dislodgement occurs. To prevent loss of stoma patency, the dislodged tube or a temporary tube should be inserted (with the balloon deflated and then reinflated after insertion) in the stoma. Caregivers should be informed that the stoma site may have some trauma and bleeding. Many permanent feeding tubes have an external bolster to prevent migration of the tube into the stomach and possible blockage of the pylorus. G-tubes or J-tubes can be secured to the abdomen with various commercially available products. Consider the product cost, size of the child, and bulkiness of the device when determining how to best secure the tube to the abdomen. For a comparison of nursing care for feeding tubes, see Table 31-1.

TABLE 31-1. Comparison of Feeding Tubes and Troubleshooting Issues

	Gastrostomy	Gastrojejunostomy	Comments
Feeding type	Bolus, gravity, or continuous drip	Continuous drip via pump only	Pay attention to where the port for feeding is located
Medication administration	• Give medications first if patient receives bolus feeds • Avoid giving high volumes of liquid medications at one time	• Use GJ if gastric emptying is known to be poor • Avoid giving high volumes of liquid medications via J-port, as it can cause cramping/diarrhea	• Check with pharmacist or trusted credible medication references to see if medications need to be given via stomach • Medications often given via G-port even when feeds are via J-port • Liquid medications are hyperosmolar
Flushes	Can give water after bolus feeds	• Flush with no more than 20 mL of water for small children • Flush J-port every 4 h while child is awake to prevent clogging	• The smaller the child, the smaller the water bolus • For children with cardiac history, check with provider about water flushes • For developmentally delayed children, water flushes may be liberalized to provide free water
Site care	• Wash skin around stoma site with soap and water • Rotate once or twice daily	• Wash skin around stoma site with soap and water • NEVER ROTATE!	Rotating GJ-tube can twist it out of small bowel and into the stomach
Replacement	• Done by caregivers after first 8	Done by Interventional Radiology or infants, it may need to be done	When in doubt about placement, obtain a dye study

	Gastrostomy	Gastrojejunostomy	Comments
	weeks post-insertion • Verify proper placement by aspirating gastric contents	within a few hours of dislodgement to prevent hypoglycemia	
When to worry	• Pain with feeds could indicate infection or misplaced G-tube • Black drainage could indicate gastric mucosal erosion at stoma • Erosion of epithelial skin layer • Increase in abdominal distention • Signs of increasing reflux • No weight gain with feedings • Respiratory distress during feedings	• Pain with feeds could indicate infection or misplaced G-tube • Black drainage could indicate gastric mucosal erosion at stoma • Erosion of the epithelial skin layer • Vomiting of EN could indicate J-port has migrated back into stomach	• Anything you do not like about how the patient is tolerating feeds • Resize both tubes periodically as child gains weight to avoid pain, gastric ulceration, and epithelial layer erosion • Vent G-tube or gastric port to allow air out if the patient has distention • Try postpyloric feeds for infant with reflux who is not gaining weight. Do this for a short time and reassess • Instruct caregivers to call 911 for respiratory problems • Consider admission for poor/no weight gain when the patient should be receiving adequate calories
Granulation Tissue	Caused by movement of the tube	Caused by movement of the tube	• Abnormal tissue must be treated to prevent local site

	Gastrostomy	Gastrojejunostomy	Comments
			infection and bleeding • Treat with steroid cream, silver nitrate, or other topical product that will shrink the tissue

(*continued on next page*)

TABLE 31-1. Comparison of Feeding Tubes and Troubleshooting Issues (Continued)

	Nasogastric	Postpyloric	Comments
Feeding type	Bolus, gravity, or continuous drip	Continuous drip via pump only	Avoid fiber-containing or highly viscous EN in small-bore tubes
Medication administration	If able, give orally	• If able, give orally • Flush with 3–5 mL of water after medications • Avoid crushed pills if possible	—
Flushes	Not typically necessary unless giving bolus feeds	Pulsatile flush every 4 h while the child is awake to prevent clogging	• The smaller the child, the smaller the water bolus • For children with cardiac history, check with provider about water flushes • For developmentally delayed children, water flushes may be liberalized to provide free water
Skin care	Secure with hypoallergenic products	Secure with hypoallergenic products	For infants, a thin adhesive bandage (ie, Steri-Strip) may be helpful; watch pacifier and make sure it does not catch in securement products
Replacement	May be done in hospital, outpatient clinic, or home depending on institutional policy	Should be done in a healthcare facility by a healthcare provider	For infants, may need to be done within a few hours of dislodgement to prevent hypoglycemia

	Nasogastric	Postpyloric	Comments
When to worry	• Vomiting with feedings • Increase in abdominal distention • Yellow drainage from nare • Signs of increasing reflux • No weight gain with feedings • Respiratory distress during feedings	• Vomiting with feedings that look like EN which could indicate tube has migrated into stomach • Increase in abdominal distention • Yellow drainage from the nare • Signs of increasing reflux • No weight gain with feedings • Respiratory distress during feedings	• Try to vent tube for abdominal distention • Move tube to the opposite nare if there is yellow drainage, and assess for sinusitis • For any signs of clinical deterioration or lack of progress related to nutrition access device, re-evaluate patient • Instruct caregivers to call 911 for respiratory problems

Abbreviations: EN, enteral nutrition; G, gastrostomy; GJ, gastrojejunostomy; J, jejunostomy.

Site Care

Keeping the site clean and dry is the most important aspect of caring for an enteral feeding tube. Washing the nose and face with mild soap and water daily is enough to keep nasoenteric tubes clean.

Ostomy sites should be monitored daily for cleanliness. The skin around the site should be cleaned with mild soap and water, gently scrubbing off any crusted areas. A slit absorbent pad can be placed between the device and the skin to keep the ostomy site dry if there is some leakage. A dressing is not required around a G-tube site. An over-the-counter antibiotic ointment may be needed if the site becomes erythematous and tender; caregivers should be advised to use the ointment for 3 days, and if the site is not better, to contact their provider. If there is improvement, the ointment can be applied 2 to 3 times daily for a total of 10 days.[24]

Checking Residual Volumes

It is not recommended to check residual volumes routinely, as there is much debate over their significance. Checking residuals may be warranted in instances of feeding intolerance. Intolerance to feedings is demonstrated by mood (fussiness), vomiting, retching, or abdominal distention. Residual volumes are influenced by the enteral nutrition used, gastric emptying, gastroesophageal reflux, respiratory compromise, timing of the measurement to the feed, and delivery method. In general, large residuals that are collected should be re-fed to the patient, as this can be a significant source of calorie loss.

Flushing the Tube

Small-bore temporary feeding tubes may clog from enteral nutrition and medication incompatibility. A retrospective study looking at the use of pancreatic enzymes activated with sodium bicarbonate documented a 48% success rate in 53 of 110 occluded tubes. This study involved adult and pediatric patients and used Creon 12,000 units and 650 mg of sodium bicarbonate dissolved in sterile water.[25] In general, routine flushing of enteral tubes after each bolus feeding or interrupting continuous feeding for water flushes should be discussed and determined by the treatment team.[13] If a tube becomes clogged, water is readily available and is the preferred flushing solution. Sterile or purified water is preferred over tap water in hospital populations.[13]

It is important to consider the child's age when flushing an enteral feeding tube with water. Immature kidneys cannot remove excess water, and too much free water can dilute sodium levels, causing seizures related to hyponatremia in worst-case scenarios. For most NG and OG tubes, 3 mL to 5 mL of water is sufficient for flushing. Smaller volumes may be used in preterm neonates or small infants.

Medication Administration

Enteral feeding tubes of all types are often used for medication administration. Some medications can be easily given via an enteral tube, such as liquid suspensions or solutions, crushed solid tablets, and capsules.

More complex formulations, such as extended-release or sustained-release products, are problematic.

Liquid forms of medication are preferred. Some solutions and suspensions may be too viscous to put safely through a small-bore feeding tube, thus these medications must be diluted with sterile water. Suspensions must be shaken thoroughly before administration.[13] Improper medication administration can lead to inaccurate medication provision.

Medications in solid form, such as tablets or capsules, must be crushed or opened and mixed with water before administering through an enteral feeding tube. It is important to mix the medication well to prevent underdosing resulting from the medication adhering to the syringe barrel. After medications are administered through an enteral feeding tube, the tube should be flushed with purified water to prevent clogging and ensure the entire dose was delivered. When formula and medications are given concurrently, flushing with water before, between, and after medications prevents the medications from being mixed.[14]

In the case of GJ tubes, caregivers should be taught about what medication is being given, why it is being given, and where it is to be administered. Certain medications, including vitamins and minerals, require activation in the stomach or are predominantly absorbed in the small intestine. Medications that alter pH may also affect the activity of concomitant medications. A consultation with a pharmacist is warranted when giving medications via J-tube or G-tube. A pharmacist will also provide information about medication compatibility if the decision is made to add it directly to an enteral nutrition.[13]

Feeding Pumps

Enteral feeding pumps are useful for delivering continuous enteral formula or for a regulated rate for bolus feedings. Some feeding pumps are small enough to be worn in a small backpack for ease of mobility and flexibility of schedules. The ideal pediatric pump is not position-sensitive, can be increased in increments of 0.1 mL up to 5 mL/h, and is relatively lightweight. Providers and caregivers need to be aware that enteral feeding pumps are not free of malfunctions. Most manufacturers of feeding

equipment and pumps have safeguards in place to prevent flow errors. Pumps should accurately administer formula within 5% of the ordered amount. Periodic calibration of the pump is important to ensure delivery system accuracy.[13] Clinicians need to be aware of special limitations imposed by manufacturers. For example, an alert was sent out regarding the use of a pump that strongly recommended it not be used to deliver homemade blended diets.[26] When such an alert is sent out, healthcare providers, families, and durable medical equipment companies need to be notified so they can act accordingly.

Venous Access Devices

When an infant or child requires parenteral nutrition (PN), the selection of the most appropriate VAD includes assessing goals of therapy, anticipated length of therapy, and patient-specific considerations such as peripheral venous access options or the need for intermittent rather than daily PN. Other considerations, such as psychosocial concerns, are also part of the decision-making process when longer-term PN is anticipated. In pediatrics, the use of peripheral parenteral nutrition (PPN) may be the initial nutrition intervention. Regardless of the type of VAD used, meticulous care of the skin, device, and catheter hub will decrease complications related to device use.[27,28]

Peripheral Intravenous Catheters

Neonatal and pediatric patients may receive a short course of PPN before the initiation of CPN. Selection of the most appropriate peripheral intravenous (IV) site involves avoidance of antecubital fossa veins in case a PICC is needed and scalp veins in case of accidental catheter dislodgement or infiltration. After appropriate hand hygiene, the use of clean gloves is recommended when inserting a peripheral IV catheter.[29] If the IV catheter becomes dislodged into surrounding tissue, the infiltration should be graded and treated according to severity, including removal of the catheter, elevation of the extremity, and possible antidote administration.[30,31] PPN-related tissue necrosis from an infiltration-related event is caused by IV calcium and requires a cold compress to assist in sequestering the calcium.

An osmolarity of no greater than 900 mOsm is suggested for PPN solutions to prevent irritation of the vein or phlebitis.[32]

Peripherally Inserted Central Catheters

If PN is required for more than 5 to 7 days, a PICC is often placed, with the tip of the catheter located in the superior vena cava just above the veno-atrial junction. A PICC that is in place before initiation of PN may need to have tip placement verified prior to PN use, as PICCs are associated with a higher rate of malposition than other types of VADs.[30] Case reports in the literature document intracranial malpositioning resulting in seizures and stroke in pediatric patients who had a PICC for PN.[33–35] One report in the literature looked at complication rates when PICCs were used for children with intestinal failure. Investigators reported 95 PICCs were placed in 45 infants, with a central line–associated bloodstream infection (CLABSI) rate of 5.3 per 1000 days and a thrombosis rate of 2 per 1000 patient days.[36] The lack of need for anesthesia and smaller-bore catheters were advantageous.

As PICCs are the preferred VAD for neonates receiving PN, it is important to discern the best practices related to PICC placement and use. Using chlorhexidine for bathing neonates with birth weights of ≥ 1000 g but <28 days old resulted in a CLABSI rate of 1.92 per 1000 patient days compared to infants who were bathed with mild soap, who had a CLABSI rate of 6 per 1000 patient days.[37] Axillary PICC placement has been associated with a 12-fold decrease in inflammation, blockage, edema, and infection compared to PICCs placed in other sites.[38] A multicenter cohort study of 3967 neonates who had 4797 PICCs reported an increased risk of CLABSI during the first 2 weeks after PICC placement and being sustained thereafter.[39] Daily evaluation of the ongoing need for a PICC is recommended.

PICCs should be secured to the skin.[28] The use of sutures results in less migration, occlusion, and leakage compared to tape,[40] however, sutures can become inflamed, requiring removal. The use of an adhesive securement device is easier to place but associated with more complications than sutures in pediatric patients.[40] PICCs may be used for home PN

administration, particularly for short-term needs (<6 wk), but they are also often used successfully for longer.

Temporary Venous Access Devices

Critically ill children who require PN will typically have a single-lumen or multi-lumen temporary VAD via the subclavian, internal jugular, or femoral vein. Reduction of CLABSIs continues to be an ongoing focus in all healthcare settings, including critical care units. Antibiotic-impregnated VADs is one approach but it is controversial in pediatrics because of concerns about sensitization and the development of drug resistance. One study using antibiotic-impregnated VADs saw comparable infection rates, but the antibiotic VADs were in place an average of 18 days before infection occurred, compared to 5 days for the nonantibiotic VADs.[41] While it is often thought that femoral VAD placement is more likely to lead to CLABSI because of proximity to fecal contamination, a study by Reyes et al found that this was not the case. In a retrospective study, looking at 4512 pediatric intensive care unit patients, no association was found between the site of temporary VAD and CLABSI.[42] A report on femoral VAD placement found the left femoral vein to be most commonly medial to the femoral artery, compared to the right femoral vein, where there can be some overlap.[43] Investigators recommend using the left femoral vein where possible to avoid inadvertent cannulization of the femoral artery.

Tunneled Venous Access Devices

When it is apparent that a patient will need long-term PN, it is important to plan for the most appropriate VAD. A patient who will go home for up to 6 weeks of PN can often use the same PICC already in place. A tunneled, cuffed catheter is most often used for infants and children who require home PN for an extended or indefinite period. Tunneled catheters can vary by size, number of lumens, and material. The size and number of lumens may be selected based on the patient's age and indications for catheter placement. However, the minimum number of lumens and smallest-diameter catheter to meet the patient's needs should be selected to minimize complications, including thrombosis and venous stenosis. The catheter material (polyurethane vs silicone) does not affect functionality duration,

although fracture rates may vary.[44] However, a polyurethane tunneled VAD cannot be used for ethanol lock therapy. Before discharge, families must be educated on the care of the tunneled VAD, including dressing changes, flushes, and emergency measures.

Implanted Venous Access Devices

Implantable VADs are used when prolonged vascular access is necessary. They come in multiple French sizes—single-lumen or double-lumen—and can be either polyurethane or silicone. They are generally best suited for intermittent therapies given over an extended period. Benefits of implantable devices include patients' ability to participate in most daily activities, less perception of altered body image, decreased dressing changes, and a lower risk of infection. The location of the subcutaneous implantable VAD is often provider-dependent; however, some data demonstrate decreased complications with placement below the clavicle rather than in the inframammary line.[45] Implanted VADs may be accessed immediately after placement without any increased risk of complications.[46] These implantable devices may develop catheter-associated or subcutaneous pocket infections, which require removal of the catheter and device, along with appropriate antibiotic treatment. Since implanted VADs require a needle through the skin to access the device, they are not commonly used for daily long-term PN administration.

Nursing Care Related to Venous Access Devices

Obtaining Laboratory Specimens From a VAD

The VAD is often used to obtain laboratory specimens to avoid venipuncture. Approaches to obtaining laboratory specimens are compared in Table 31-2. Two studies in the literature document the safe and reliable method of blood sampling, which involves repeated pushing and pulling of blood into an empty syringe before obtaining a specimen in a new syringe.[47,48] Nursing staff should have options for specimen collection based on what is best for that patient, and all infusions should be stopped

when using a multi-lumen catheter to ensure accurate laboratory sample results. Using the waste approach, one study validated the safety of 3 mL versus 5 mL of waste when blood samples are obtained from a tunneled or implanted VAD.[49] Other sources recommend a 1−3 mL discard volume or twice the priming volume.

TABLE 31-2. Comparison of Techniques Used to Obtain Blood Samples From a VAD

Type of Technique	Description	Pros	Cons
Traditional	1. Stop infusion 2. Flush vascular access device with normal saline 3. Obtain waste specimen of 3–5 mL 4. Obtain blood needed for labs ordered 5. Flush VAD with NS 6. Restart infusion	• "Gold standard" procedure • When done properly, low risk of infection associated with obtaining labs	• Increases blood loss when doing frequent blood sampling • Increases staff exposure to blood • Potential for confusing waste syringe with sample syringe
Return the waste	1. Stop infusion 2. Flush VAD with NS 3. Obtain waste specimen of 3–5 mL 4. Rotate waste specimen to prevent clotting 5. Obtain blood needed for labs ordered 6. Return waste specimen to patient 7. Flush VAD with NS 8. Restart infusion	Decreases patient blood loss	• Potential for reinfusion of blood clots • Potential for contamination of blood being reinfused
Push-pull method	1. Stop infusion 2. Aspirate 3–5 mL of blood intosyringe 3. Reinfuse blood and repeat aspiration/reinfuse procedure 3 times 4. Place new syringe on VAD and obtain blood needed for ordered labs	Limits patient blood loss from blood sampling	• Potential for hemolysis due to turbulence created by pushing/pulling • May not be feasible for VADs that are difficult to draw from

Abbreviations: NS, normal saline ; VAD, venous access device.

Venous Access Device Site Care

Meticulous and routine site care is essential for the prevention of CLABSI. The 2011 Centers for Disease Control and Prevention (CDC) Guidelines for the Prevention of Intravascular Catheter-Related Infections recommends the use of chlorhexidine for skin antisepsis in children over 2 months of age.[27] Transparent dressings are changed every 7 days, or when nonocclusive or soiled.[27] For children who have a history of CLABSI or have a temporary VAD and are over the age of 2 months, it is recommended that a chlorhexidine-impregnated sponge be placed over the VAD insertion site.[27] This makes it impossible to inspect the insertion site, but it can still be palpated for tenderness. It is also important to protect the VAD using the dressing to help secure the line. Tunneled VADs often have a long external segment that can be looped under the transparent dressing as a stress loop to prevent accidental dislodgement.

Hub Care

Again, meticulous attention to clean or aseptic technique is recommended when the hub of the VAD or the needleless cap is accessed.[27] Doing a 15-second scrub with either 70% alcohol or chlorhexidine before accessing the catheter or adapter is recommended. The CDC recommends changing the needleless adapter when IV fluids are changed or every 72 hours. An additional layer of protection can be obtained by adding an alcohol-impregnated sponge cap over the needleless adapter. One study done at North Shore Hospital in the Chicago area documented a reduction in CLABSI from 4.2 per 1000 patient days to 0.94 per 1000 patient days after implementing this cap.[47] Hub care is part of several practices to prevent CLABSIs.

Routine Flushing

Traditionally, the VAD has been flushed with normal saline and then with heparin of varying concentrations based on the weight of the child, the number of times the line will be accessed intermittently, and the lumen diameter. Increasingly, normal saline alone is being used to maintain the patency of a VAD when used intermittently. A study in Italy of pediatric oncology patients ages infant to 17 years reported occlusion rates of 4%

complete and 23% partial with the use of normal saline flushes. Investigators found that smaller tunneled catheters (4.2 Fr) were more likely to occlude.[50] Use of normal saline alone to maintain VAD patency is appropriate for children who are cycled off PN for a few hours per day when the lumen of the VAD is greater than 4.2 Fr.

Safety Issues

All caregivers of children with VADs need to be aware of the safety issues associated with the child's current age, as well as what to anticipate as the child grows. For example, infants who are teething may need to have a pacifier to prevent them from sucking or chewing on their IV tubing. The IV tubing can also be taped over the shoulder to keep it out of easy reach. "Out of sight, out of mind" works for many infants and toddlers to protect the line. This method will also benefit children with ostomies, who should have the VAD dressing and tubing as far away from the ostomy as possible.

VAD use by parents with Munchausen syndrome by proxy has been heavily documented in the literature.[49] This term is now referred to as pediatric condition falsification and is a form of child abuse in which the caregiver is the perpetrator by insisting on invasive and painful procedures for their child. Because this condition can be life-threatening for the child, any suspicion of this condition needs to be addressed before placement of a VAD for PN. While this form of abuse is difficult to prove, certain typical behaviors seen in caregivers include *doctor shopping* to different healthcare providers and facilities, discrepancies between reported symptoms and what is observed, caregiver reluctance to leave the child while at the hospital, and overzealous attachment to certain healthcare providers.[49] Parents or caregivers should not be allowed to access or care for a VAD unless specifically trained to do so, and then only with the nurse's permission.

Administration Set Changes

Controversy exists about when to change IV tubing that has been used to administer PN and lipid injectable emulsions (ILE). Also, the American Society for Parenteral and Enteral Nutrition (ASPEN) Parenteral Nutrition Safety Consensus Recommendations suggest that IV administration sets should be completely changed every 24 hours, as ILEs are typically co-

infused.[28] The newest CDC Guidelines for the Prevention of Intravascular Catheter-Related Infections also recommend changing IV administration sets for 3-in-1 PN every 24 hours.[27] Additionally, needleless systems are recommended to be used to access IV administration sets, and to change the system no more often than every 72 hours.[27] All IV administration sets should be free of di-2-ethylehxyl phthalate.[28] Hospital performance improvement projects or larger multicenter collaborative projects focusing on bundling of care around VADs and competency validation of nursing practice are recommended to reduce CLABSI risk (see Table 31-3 for a summary of such practices).[27]

TABLE 31-3. Prevention of CLABSIs

Aspect of Care	Action
Hand hygiene	Wash hands with antiseptic skin soap before placing/or accessing a VAD, or use alcohol-based hand sanitizer
Catheter insertion	• Ensure staff Staff involved in central line placement must be competent to do this procedure • Use maximal sterile barriers, including masks, gowns, drapes, sterile gloves, and a kit with all needed supplies • Allow healthcare provider to call “time out” for observed break in sterile technique • Avoid placement of central line in febrile patients • Avoid guidewire replacement of central line
Catheter access	• Clean catheter hub with 70% alcohol or chlorhexidine wipes before entering the line, or use a passive disinfection device • Have a policy on routine injection cap changes • Avoid stopcocks on central lines • Use sterile, prefilled syringes for central line flushing • Limit accessing for labs to 1 time per day if possible
Catheter dressing change	• Use a kit with all supplies needed • Use Chloraprep as the preferred skin disinfectant • Use a mask and gown for PICC dressings • Prefer a transparent dressing over a gauze-and-tape dressing to allow the site to be assessed • Restrain patient as needed to prevent accidental dislodgement • Place a stress loop in VAD tubing or extension tubing
Diagnosis of bloodstream infection	• Obtain peripheral and central blood culture • Staff obtaining blood cultures should be specially trained and competent to avoid contamination • Draw a minimum of 1 mL for a blood culture • Use clinical and other labs to validate diagnosis • Do not necessarily remove the central line
IV tubing changes	• ILE: every 24 h • PN: every 96 h unless a TNA (dextrose, amino acids, lipid injectable emulsion admixture) then every 24 h or if cycled off a few hours per day per CDC recommendations
Other	• Evaluate all VAD supplies for defects that could lead to infection • Surveillance of possible IV fluid–related infections is needed • Have a surveillance plan within the institution to trend infections and look for a root cause

Abbreviations: CDC, Centers for Disease Control and Prevention; CLABSI, central line–associated bloodstream infection; ILE, lipid injectable emulsion; IV, intravenous; PICC, peripherally inserted central catheter; PN, parenteral nutrition; TNA, total nutrient admixture; VAD, venous access device.

Central Line–Associated Bloodstream Infection

Two therapies often discussed to prevent and treat CLABSI are the use of ethanol or antibiotic locks. Ethanol lock therapy involves filling and closing a catheter lumen with 70% ethanol for a minimum of 2 hours, using the fill volume for the VAD. Ethanol locks alone are effective in reducing CLABSI, and when used in conjunction with standard antibiotic therapy, are effective in clearing CLABSI.[50–52] Criteria for starting ethanol lock therapy include the following: more than 1 previous CLABSI, >5 kg weight, silicone VAD, and caregiver ability to appropriately perform the task, with no concerns about the psychosocial situation in the home.

Similarly, antibiotic lock therapy consists of instilling an antibiotic solution into a catheter hub for a specified period. Several antibiotic formulations have been proven to be effective in clearing and reducing the incidence of CLABSI, but the most promising research is using taurolidine, which is not available in the United States.[53–57]

Thrombosis

VAD-related thrombosis has a variable incidence depending on catheter type, therapy duration, and patient-related and disease-related factors. Most VAD-related thrombosis remains asymptomatic in children, but a common question is the role of prophylaxis and surveillance. Routine prophylaxis for thrombosis after placement of a VAD is unnecessary and may be reserved for children at a higher risk for thromboembolism based on patient-related and disease-related factors (ie, history of deep venous thrombosis or known hypercoagulable state).[57–59] Similarly, routine surveillance for VAD-related thrombosis is not recommended because of significant costs and the infrequency with which it results in changes to patient management.[57,60]

Anticipatory Guidance

Some children grow up with a VAD or an enteral access device. As they progress through the various stages of childhood to adolescence, parents and caregivers must be aware of age-appropriate actions to keep the device and child safe. See Table 31-4 for a summary of issues to consider. This table also stresses the importance of raising the child in a loving yet structured environment where appropriate behavior is expected, and discipline is commensurate with infraction.

TABLE 31-4. Intestinal Failure Anticipatory Suggestion Sheet

Age/Stage	VAD	Feeding Tube	Development	Social/School	Village
Infancy	• Tunneled • Prevent ostomy drainage onto hub of catheter • Prevent ostomy getting pulled as infant discovers fingers • Watch for sucking on the VAD or IV tubing • Be prepared for possible hospitalization for infections in VAD	• NG tube: prevent frequent removal by using cloth wraps as arm splints as needed • Tape securely • G-tube: Watch for granulation tissue as infant starts to crawl • Promote tummy time • Watch tapes and skin cleansers; be gentle with skin	• Cognitive: Usually age-appropriate to advanced • Fine motor: Often age-appropriate • Gross motor: Delayed in sitting up, turning over, crawling, and walking • Oral feeding skill development needs to be worked on; very important	• Usually very social and interactive • Usually happy, so pay attention to when infant is not very responsive and interactive • Make sure siblings do not feel neglected • Get grandparents involved if possible	• IR team: physician, dietitian, nurse, pharmacist • OT • PT • Social worker • Check out the Oley Foundation or other parent/caregiver/ patient support groups • Access only credible websites
Toddlers	Prevent accidental pulling as child runs while on PN	• Get a very small backpack for the enteral pump or put it in a toddler play shopping cart so the toddler can push it • Watch tapes and skin cleansers; be gentle with skin	• Cognitive: Can still be quite advanced • Fine motor: Child will want to self-feed • Gross motor: Allow and encourage development but keep safety in mind; play dates with peers need to be monitored closely • Oral: Picky eaters can have IF, too! If an oral aversion exists, this is the time to address it with an inpatient stay if no progress is being made on an outpatient basis • Watch child at family events—may get into food that he/she cannot tolerate • Watch what siblings offer child	• Early childhood education is appropriate so child learns that rules are for everyone; also identifies gaps in learning • At this point, parenting must focus on normal discipline, so the toddler does not become manipulative and poorly behaved • Use a reward/ consequence system for controlling behavior that really matters, like staying still for a VAD dressing change	• Same IR team • OT may/may not be involved; typically, not as involved once oral feeding skills are age-appropriate • PT may not be needed • Social worker is quite important • Parents/ caregivers: Don't neglect your relationships! • Friends and relatives become more involved as the toddler gets older

(*continued on next page*)

TABLE 31-4. Intestinal Failure Anticipatory Suggestion Sheet (Continued)

Age/Stage	VAD	Feeding Tube	Development	Social/School	Village
Early School Years	• Protect VAD while at school • Carefully consider what physical activities your child will be allowed to participate in: soccer? dance? gymnastics? Tball/baseball? swim lessons?	• By this age, a low-profile G-tube will most likely have been inserted if enteral nutrition is still needed • School lunch issues will need to be addressed with the school and child. Expect some cheating • Also, make sure the teacher knows what special treats your child can have during parties; provide them yourself if needed • Watch tape and skin cleansers; be gentle with skin	• Cognitive: Some learning issues may surface depending on the early hospital course in the NICU. This may not relate to IF issues at all • Work on self-esteem: get your child in something they enjoy and are good at, such as music lessons, Scouts, church group, etc. • Fine motor: Not typically a problem for these kids • Gross motor: Watch what playground and sports activities your child enjoys. Soccer is not recommended if a VAD is in place. Gymnastics/tumbling could be problematic if the VAD is in place, as it can come out of place with flips. Dance could be fine • Oral: oral aversions may remain to a limited extent • Mealtimes need to include the child	• Social: Get your child a “circle of friends” • Encourage normal social outings, but make sure friends’ parents are aware of your child’s special needs regarding diet and VAD/G-tube • School: Have a Section 504 plan to address toilet issues, ostomy issues, special food issues, activities, etc. • Meet with the teacher at the beginning of each school year • Make a rule about school attendance that sets a clear message that school is mandatory. No blood at central line site or in stool, no fever, no doctor’s appointment—school must be attended	• Besides healthcare providers and relatives, the village expands to teachers, school aides, school nurses, coaches, and parents/caregivers or friends • Keep a wide circle of close acquaintances including church members and neighbors • Parents/caregivers are still the most important members of the village, and you will transition to the role of care coordinator as time goes on

(*continued on next page*)

TABLE 31-4. Intestinal Failure Anticipatory Suggestion Sheet (Continued)

Age/Stage	VAD	Feeding Tube	Development	Social/School	Village
Tweens	Often the VAD is out or not used nightly. Think about a port-a-cath if using only 3–4 nights per week	• Deal with issues of swimming, etc. based on your healthcare provider's recommendations • Still avoid lakes, oceans, and dirty water if possible • Focus on what the child can do with the G-tube in place • Your child will be hooking and unhooking the feeding delivery set tubing by now • Encourage more and more self-care • Watch tapes and skin cleansers; be gentle with skin	• Cognitive: Should be same as early school years. If your child is hospitalized, set aside time every day to do homework once they are medically stable • This sets up a routine that allows for a smoother transition back to school. It also sends a message that the hospital is not a place to dodge homework and slack off • Fine motor: encourage building of model airplanes, cars, or making jewelry to help a child who cannot be as physically active as peers to feel accomplished • Gross motor: Discuss team sports, more involved dance, or gymnastics with your healthcare provider, especially if a VAD is still in place. Encourage bike riding and physically taxing activities to the level your child is challenged but not exhausted • Oral: Expect cheating; expect your child to tolerate foods that are not on the approved list. Pick your battles carefully • This is the time when children start becoming a bit noncompliant with medications	• Social: What about overnights with friends? – Can the tube feeding be skipped for a night? – This needs to be discussed with the healthcare provider • Do you like your child's friends? • Do they treat your child with respect? If not, try to find some kids you know are nice and work very hard to get friendships going that you know will bring out the best in your child • Self-esteem issues at this age and with these kids can lead to kids accepting ridicule from friends just to avoid being lonely • School: Same as above— – Attendance is mandatory – Good grades are the goal, – Participation in after-school activities should be at the level your child can tolerate • While school attendance is mandatory, school activities are not. Some kids in this age group want to do it all but may not be physically able to do so	• The village becomes wider, and the influence of parents/caregivers begins to wane. This is hard for all parents/caregivers to see and deal with • Testing boundaries within a safe village with teachers and neighbors keeping an eye out can prevent serious accidents or unsafe behaviors • While trying not to be alarmist, make sure people who have your child in their home know the limits and will honor them

(*continued on next page*)

TABLE 31-4. Intestinal Failure Anticipatory Suggestion Sheet (Continued)

Age/Stage	VAD	Feeding Tube	Development	Social/School	Village
Adolescents	• Expect more risk-taking behaviors • Discuss with your healthcare provider when and how much responsibility your child should take for flushing the VAD, starting home PN, dressing changes, etc. • Expect the child to want the VAD out and to work more diligently on enteral feeds and oral diet to accomplish this	• Some adolescents opt for night-time NG tubes because of body-image issues. This is especially true if IF happens during the adolescent years • Allow your child to make these choices. The child will place the tube and often prepare the enteral nutrition load the feeding pump and run it themselves. You still need to make sure this is done • Expect negotiations for tube feeds 5–6 nights/wk to get 1–2 nights off • Watch tapes and skin cleansers; be gentle with skin	• Cognitive: Often these kids excel academically if parents have set expectations in early years • Fine motor: same as above • Gross motor: Expect kids to test limits and engage in risk-taking behaviors • Competitions involving no physical contact tend to be popular, such as cross-country running • Oral: Expect some experimentation with alcohol. Avoid soft drinks. Encourage healthy eating habits and make sure supplements (eg, vitamins, calcium) are taken as directed	• Social: Friends and school activities take center stage • Encourage as much involvement in school activities as your child can tolerate • Set limits and have a curfew just as if your child did not have IF • Focus on normal teen behaviors and have consequences for breaking rules • Being lenient with rules in this age group is a mistake • Watch out for friends who indulge in risk-taking behaviors • Your child may end up in the hospital for something that just gives a friend a headache • School: Same as above. Start a dialogue about college	• The village has parents/ caregivers playing a different role—more of an observer, advisor, clarifier of expectations • Grandparents can often be more influential than parents • Start a dialogue about transitioning to adult providers if appropriate • Consider college location into the mix of proximity to healthcare providers, and the medical stability and maturity of the adolescent

Abbreviations: G, gastrostomy; IF, intestinal failure; IR, intestinal rehabilitation; IV, intravenous; NG, nasogastric; NICU, neonatal intensive care unit; OT, occupational therapist; PN, parenteral nutrition; PT, physical therapist; VAD, venous access device.

Test Your Knowledge Questions

1. An infant with a 3-day history of gastroenteritis with vomiting and diarrhea is most likely to be started on PN using which of the following?
   A. Peripheral vein
   B. Femoral PICC
   C. Tunneled catheter
2. An 8-month-old, 4-kg baby with intestinal failure receives PN via a silicone tunneled VAD, and the decision is made to start an ethanol lock due to repeated CLABSIs. Which of the following statements best describes this decision?
   A. Not wise because the catheter should be polyurethane

B. Worrisome because of exposure to ethanol at such a young age
C. Appropriate standard of care
D. Not wise due to the weight of the child

3. A 4-year-old with a low-profile balloon G-tube inserted 1 week ago accidentally pulls it out with the balloon inflated. Before discharge, which of the following instructions should have been given to the parents?
   A. Place a temporary catheter in the site immediately
   B. Go to the emergency department for replacement.
   C. Do nothing and contact the surgeon on call.
   D. A and B
4. Which of the following is the initial method for inpatient and home verification of NG-tube placement?
   A. pH
   B. Air insufflations and auscultation
   C. Inspection of gastric contents
   D. X-ray

References

1. Boullata JI, Carrera AL, Harvey L, et al. ASPEN safe practices for enteral nutrition therapy. *JPEN J Parenter Enteral Nutr*. 2017;41(1):15–103. https://doi.org/10.1177/0148607116673053
2. Irving SY, Rempel G, Lyman B, Sevilla W, Northington L, Guenter P, and the NOVEL Project Work Group. Pediatric nasogastric tube placement and verification: best practice recommendations from the NOVEL project. *Nutr Clin Pract*. 2018;33(6):921–927. https://doi.org/10.1002/ncp.10189
3. Lavoie JA, Schinder C, Garnier-Villarreal M, Bagli SP, McCarthy DO, Goday PS. Nasogastric bridles are associated with improved tube-related outcomes in children. *JPEN J Parenter Enteral Nutr*. 2022;46(7):1568–1577. https://doi.org/10.1002/jpen.2409
4. Leder SB, Lazarus CL, Suiter DM, Acton LM. Effect of orogastric tubes on aspiration status and recommendations for oral feeding.

Otolaryngol Head Neck Surg. 2011;144(3):372–375. https://doi.org/10.1177/0194599810391726
5. Bohnhorst B, Cech K, Peter C, Doerdelmann M. Oral versus nasal route for placing feeding tubes: no effect on hypoxemia and bradycardia in infants with apnea of prematurity. *Neonatology.* 2010;98(2):143–149. https://doi.org/10.1159/000279617
6. Badran AT, Hashish M, Ali A, Shokeir M, Shabaan A. Nasogastric versus orogastric bolus tube feeding in preterm infants: pilot randomized clinical trial. *Am J Perinatol*. 2021;38(14):1526–1532. https://doi.org/10.1055/s-0040-1713865
7. Akay B, Capizzani TR, Lee AM, et al. Gastrostomy tube placement in infants and children: is there a preferred technique. *J Pediatr Surg.* 2010;54(6):1147–1152. https://doi.org/10.1016/j.jpedsurg.2010.02.079
8. McSweeney ME, Mitchell PD, Smithers CJ, Doherty A, Perkins J, Rosen R. A retrospective review of primary percutaneous endoscopic gastrostomy and laparoscopic gastrostomy tube placement. *J Pediatr Gastroenterol Nutr*. 2021;73(5):586–591. https://doi.org/10.1097/mpg.0000000000003236
9. Buderus S, Adenaeuer M, Dueker G, Bindl L, Lentze MJ. Balloon gastrostomy buttons in pediatric patients: evaluation with respect to size, lifetime in patients, and parent acceptance. *Klin Padiatr.* 2009;221(2):65–68. https://doi.org/10.1055/s-2007-1004538
10. Islek A, Sayari E, Yilmaz A, Artan R. Percutaneous gastrostomy in children: is early feeding safe? *J Pediatr Gastrenterol Nutr.* 2013;57(5):659–662. https://doi.org/10.1097/mpg.0b013e3182a0d171
11. Egnell C, Eksborg S, Grahnquist L. Jejunostomy enteral feeding in children: outcome and safety. *JPEN J Parenter Enteral Nutr.* 2013;38(5):631–636. https://doi.org/10.1177/0148607113489832
12. Al-Zubeidi D, Demir H, Bishop WP, Rahhal RM. Gastrojejunal feeding tube use by gastroenterologists in a pediatric academic center. *J Pediatr Gastrenterol Nutr.* 2013;56(5):523–527. https://doi.org/10.1097/mpg.0b013e318282a8db
13. Bankhead R, Boullata J, Brantley S, et al. Enteral nutrition practice recommendations. *JPEN J Parenter Enteral Nutr.* 2009;33(2):122–167. https://doi.org/10.1177/0148607108330314

14. Fisher C. Clogged feeding tubes: a clinician's thorn. *Pract Gastroenterol.* 2014;127:16–22. https://med.virginia.edu/ginutrition/wp-content/uploads/sites/199/2014/06/Parrish-March-14.pdf
15. Quandt D, Schraner T, Bucher HU, Mieth RA. Malposition of feeding tubes in neonates: is it an issue? *J Pediatr Gastrenterol Nutr*. 2009;48(5):608–611. https://doi.org/10.1097/mpg.0b013e31818c52a8
16. Kemper C, Northington L, Wilder K, Visscher D. A call to action: the development of enteral access safety teams. *Nutr Clin Pract*. 2014;29(3):264–266. https://doi.org/10.1177/0884533614531626
17. Cirgin Ellett ML, Cohen MD, Perkins SM, Smith CE, Lane KA, Austin JK. Predicting the insertion length for gastric tube placement in neonates. *J Obstet Gynecol Neonatal Nurs.* 2011;40(4):412–421. https://doi.org/10.1111/j.1552-6909.2011.01255.x
18. deBoer JC, Smit BJ, Mainous RO. Nasogastric tube position and intragastric air collection in a neonatal intensive care population. *Adv Neonatal Care.* 2009;9(6):293–298. https://doi.org/10.1097/anc.0b013e3181c1fc2f
19. Irving SY, Lyman B, Northington L, Bartlett JA, Kemper C, and the NOVEL Project Work Group. Nasogastric tube placement and verification in children: review of the current literature. *Nutr Clin Pract*. 2014;29(3):267–276. https://doi.org/10.4037/ccn2014606
20. Gilbertson HR, Rogers EJ, Ukoumunne OC. Determination of a practical pH cutoff level for reliable confirmation of nasogastric tube placement. *JPEN J Parenter Enteral Nutr.* 2011;35(4):540–544. https://doi.org/10.1177/0148607110383285
21. National Association of Childrens Hospitals, ECRI Institute. *Blind Pediatric NG Tube Placements Continue to Cause Harm.* Child Health Patient Safety Organization; 2012. Accessed April 12, 2024. https://www.childrenshospitals.org/-/media/files/migration/childhealthpso_blindpediatricngtubeplacements_patientsafetyalert_wattachment_08012012.pdf
22. Metheny NA, Stewart BJ, Mills AC. Blind insertion of feeding tubes in intensive care units: a national survey. *Am J Crit Care*. 2012;21:352–360. https://doi.org/10.4037/ajcc2012549

23. Richardson DS, Branowicki PA, Zeidman-Rogers L, Mahoney J, MacPhee M. An evidence-based approach to nasogastric tube management: special considerations. *J Pediatr Nurs.* 2006;21(5):288–292. https://doi.org/10.1016/j.pedn.2005.09.001
24. Abdelhadi RA, Rahe K, Lyman B. Pediatric enteral access device management. *Nutr Clin Pract*. 2016;31(6):748–761. https://doi.org/10.1177/0884533616670640
25. Stumpf JL, Kurian RM, Vuong J, Dang K, Kraft MD. Efficacy of a creon delayed-release pancreatic enzyme protocol for clearing occluded enteral feeding tubes. *Ann Pharmacother.* 2014;48(4):483–487. https://doi.org/10.1177/1060028013515435
26. *Enteralite™ Infinity™ Ambulatory Feeding Pumps.* Moog Medical Devices Group; 2014.
27. Huang EY, Chen C, Abdullah F, et al. Strategies for the prevention of central venous catheter infections: an American pediatric surgical association outcomes and clinical trials committee systematic review. *J Pediatr Surg.* 2011;46(10):2000–2011. https://doi.org/10.1016/j.jpedsurg.2011.06.017
28. Miller-Hoover S. Pediatric central line: bundle implementation and outcomes. *J Infus Nurs.* 2011;34(1):36–48. https://doi.org/10.1097/nan.0b013e31820233d0
29. O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis*. 2011;52(9):e162–e193. https://doi.org/10.1093/cid/cir257
30. Ayers P, Adams S, Boullata J, et al. A.S.P.E.N. parenteral nutrition safety consensus recommendations. *JPEN J Parenter Enteral Nutr*. 2014;38(3):296–333. https://doi.org/10.1177/0148607113511992
31. Gasior AC, Marty Knott E, St. Peter SD. Management of peripherally inserted central catheter associated deep vein thrombosis in children. *Pediatr Surg Int.* 2013;29(5):445–449. https://doi.org/10.1007/s00383-013-3259-y
32. Dugan S, Le J, Jew RK. Maximum tolerated osmolarity for peripheral administration of parenteral nutrition in pediatric patients. *JPEN J Parenter Enteral Nutr*. 2014;38(7):847–851. https://doi.org/10.1177/0148607113495569

33. DiChicco R, Seidner DL, Brun C. Tip position of long-term central venous catheter devices used for parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2007;31(5):382–387. https://doi.org/10.1177/0148607107031005382
34. Anderson C, Graupman PC, Hall WA. Pediatric intracranial complications of central venous catheter placement. *Pediatr Neurosurg.* 2004;40:28–31. https://doi.org/10.1159/000076574
35. Parikh S, Narayann V. Misplaced peripherally inserted central catheter: an unusual cause of stroke. *Pediatr Neurol.* 2004;30(3):210–212. https://doi.org/10.1016/j.pediatrneurol.2003.09.008
36. Piper HG, deSilva NT, Amaral JG, Wales PW. Peripherally inserted central catheters for long-term parenteral nutrition in infants with intestinal failure. *J Pediatr Gastrenterol Nutr*. 2013;56(5):578–581. https://doi.org/10.1097/mpg.0b013e3182801e7b
37. Quach C, Milstone AM, Perpete C, Bonenfant M, Moorer DL, Perreault T. Chlorhexidine bathing in a tertiary care neonatal intensive care unit: impact on central line-associated bloodstream infections. *Infect Control Hosp Epidemiol.* 2014;35(2):158–163. https://doi.org/10.1086/674862
38. Panagiotounakou P, Antonogeorgos G, Gounari E, Papakakis S, Labadaridis J, Gounaris AK. Peripherally inserted central venous catheters: frequency of complications in premature newborn depends on the insertion site. *J Perinatol.* 2014;34(6):461–463. https://doi.org/10.1038/jp.2014.36
39. Milstone AM, Reich NG, Advani S, et al. Catheter dwell time and CLABSIs in neonates with PICCs: a multicenter cohort study. *Pediatrics*. 2013;132(6):1609–1615. https://doi.org/10.1542/peds.2013-1645
40. Graf JM, Newman CD, McPherson ML. Sutured securement of peripherally inserted central catheters yields fewer complications in pediatric patients. *JPEN J Parenter Enteral Nutr*. 2006;30(6):532–535. https://doi.org/10.1177/0148607106030006532
41. Chelliah A, Heydon KH, Zaoutis TE. Observational trial of antibiotic-coated central venous catheters in critically ill pediatric patients. *Pediatr Infect Dis.* 2007;26(9):816–820. https://doi.org/10.1097/inf.0b013e318123e8bf

42. Reyes JA, Habash ML, Taylor RP. Femoral central venous catheters are not associated with higher rates of infection in the pediatric critical care population. *Am J Infect Control.* 2012;40(1):43–47. https://doi.org/10.1016/j.ajic.2011.02.011
43. Ozbek S, Avdin BK, Apiliogullari S, et al. Left femoral vein is a better choice for cannulation in children: a computed tomography study. *Pediatr Anaesth.* 2013;23(6):524–528. https://doi.org/10.1111/pan.12125
44. Cohen AB, Dagli M, Stavropoulos SW, et al. Silicone and polyurethane tunneled infusion catheters: a comparison of durability and breakage rates. *J Vasc Interv Radiol.* 2011;22(5):638–641. https://doi.org/10.1016/j.jvir.2011.01.433
45. Fallon SC, Larimer EL, Gwilliam NR, et al. Increased complication rates associated with port-a-cath placement in pediatric patients: location matters. *J Ped Surg*. 2013;48(6):1263–1268. https://doi.org/10.1016/j.jpedsurg.2013.03.020
46. Hanley C, Nagel K, Odame I, Fitzgerald P, Husain M. Immediate versus delayed access of implantable venous access devices: does the timing of access make a difference to the frequency of complications? *J Pediatr Hematol Oncol.* 2003;25(8):613–615. https://doi.org/10.1097/00043426-200308000-00005
47. Barton SJ, Chase T, Latham B. Comparing two methods to obtain blood specimens from pediatric central venous catheters. *J Pediatr Oncol Nurs.* 2004;21(6):320–326. https://doi.org/10.1177/1043454204269604
48. Adlard K. Examining the push-pull method of blood sampling from central venous access devices. *J Pediatr Oncol Nurs.* 2008;25(4);200–207. https://doi.org/10.1177/1043454208320975
49. Cole M, Price L, Parry A. A study to determine the minimum volume of blood necessary to be discarded from a central venous catheter before a valid sample is obtained in children. *Pediatr Blood Cancer.* 2007;48:687–695. https://doi.org/10.1002/pbc.20873
50. Buchini S, Scarsini S, Montico M, Buzzetti R, Ronfani L, Decorti C. Management of central venous catheters in pediatric onco-hematology using 0.9% sodium chloride and positive-pressure-valve needleless

connector. *Eur J Oncol Nurs.* 2014;18(4):393–396. https://doi.org/10.1016/j.ejon.2014.03.010
51. New research shows effectiveness of SwabCap. *Infection Control Today.* September 20, 2010. Accessed May 28, 2014. http://www.infectioncontroltoday.com/news/2010/09/new-research-shows-effectiveness-of-swabcap.aspx
52. Feldman KW, Hickman RO. The central venous catheter as a source of medical chaos in Munchausen syndrome by proxy. *Pediatr Surg*. 1998;334:623–627. https://doi.org/10.1016/s0022-3468(98)90329-3
53. Peroni KP, Nespor C, Ng M, et al. Evaluation of ethanol lock therapy in pediatric patients on long-term parenteral nutrition. *Nutr Clin Pract.* 2013;28(2):226–231. https://doi.org/10.1177/0884533612468009
54. Jones BA, Hull MA, Richardson DS, et al. Efficacy of ethanol locks in reducing central venous catheter infections in pediatric patients with intestinal failure. *J Pediatr Surg*. 2010;45(6):1287–1293. https://doi.org/10.1016/j.jpedsurg.2010.02.099
55. Valentine KM. Ethanol lock therapy for catheter-associated blood stream infections in a pediatric intensive care unit. *Pediatr Crit Care Med.* 2011;12(6):292–296. https://doi.org/10.1097/pcc.0b013e318219267c
56. Denaburg M, Patel S. Salvage antibiotic-lock therapy in critically ill pediatric patients: a pharmacological review for pediatric intensive care unit nurses. *Adv Crit Care*. 2013;24(3):233–238. https://doi.org/10.1097/nci.0b013e31829937d8
57. Handrup MM, Moller JK, Schroder H. Central venous catheters and catheter locks in children with cancer: a prospective randomized trial of taurolidine versus heparin. *Pediatr Blood Cancer*. 2013;60(8):1292–1298. https://doi.org/10.1002/pbc.24482
58. Chu HP, Brind J, Tomar R, Hill S. Significant reduction in central venous catheter-related bloodstream infections in children on HPN after starting treatment with taurolidine line lock. *J Pediatr Gastrenterol Nutr*. 2012;55(4):403–407. https://doi.org/10.1097/mpg.0b013e31825bb0ae
59. Haddad H, Lee KS, Higgins A, McMillan D, Price V, El-Naggar W. Routine surveillance ultrasound for the management of central venous

catheters in neonates. *J Pediatr.* 2014;164(1):118–122. https://doi.org/10.1016/j.jpeds.2013.08.048
60. Gorski LA, Hadaway L, Hagle ME, et al. Infusion therapy standards of practice, 8th ed. *J Infus Nurs*. 2019;44(suppl 1):S1-S224. https://doi.org/10.1097/NAN.0000000000000396

Test Your Knowledge Answers

1. The correct answer is **A**. The peripheral vein is the most appropriate venous access option for an infant who cannot seemingly tolerate anything enterally but should turn around in just a few days.
2. The correct answer is **D**. This child is under the recommended weight of >5 kg.
3. The correct answer is **D**. Families should receive a temporary catheter prior to discharge, along with written instructions for what to do in case the G-tube comes out in the first 8 weeks post-insertion.
4. The correct answer is **A**. Ideally pH is used to confirm proper NG tube placements.

The author wishes to thank Beth Lyman, RN, MSN, CNSC; and Sohail R. Shah, MD, MSHA, FAAP for their contributions to previous editions of this text.

32

Enteral Nutrition Support

Jessica Monczka, RD, CNSC and Sarah Simental, MS, RD, CSNC, CSPCC

Learning Objectives

1. Define indications for enteral nutrition support in infants and children.
2. Explain the options for the delivery of enteral nutrition including route of tube placement, site of feeding delivery, and schedule of feeding regimen.
3. Describe the benefits and risks of each enteral nutrition delivery option.
4. Identify complications associated with enteral nutrition, as well as monitoring parameters for tube-fed patients.

Introduction

The term enteral nutrition (EN) refers to the process of providing nutrients via the gastrointestinal tract (GIT). Parenteral nutrition (PN), on the other hand, bypasses the gastrointestinal tract to deliver nutrients directly into the bloodstream. EN plays an important role in cases where pediatric patients cannot meet their nutrient needs via oral intake alone. It has been well established that EN is preferred over the parenteral route whenever possible. When the GIT is functional and safely accessible, this preference is especially marked for several reasons:[1–4]

- Supports normal endocrine, paracrine, and neural function
- Improves mesenteric blood flow
- Decreases GIT permeability and prevents structural and functional alterations of the gut barrier
- Promotes pancreatic and biliary secretions
- Lowers the risk of metabolic complications (glucose and electrolyte disturbances, aluminum toxicity) compared to PN
- Reduces infection risk
- Lowers cost
- Maintains gut-related immune system function
- Reduces rate of intensive care unit (ICU) mortality
- Decreases length of hospital stay
- May decrease mechanical ventilation time

EN delivered at an early stage in the course of an illness is referred to as early enteral nutrition (EEN). The latest literature demonstrates that EEN is associated with the most improved clinical outcomes when it is initiated within the first 24 to 48 hours of critical illness and achieves up to two-thirds of the nutrition goal within the first week.[4] EEN in the pediatric intensive care unit is best supported by a multidisciplinary team and with a protocolized regimen. This approach may also minimize interruptions and increase overall enteral nutrient delivery.[5–7]

Indications for Enteral Nutrition

EN may be the appropriate therapy for infants and children with a variety of diagnoses, for short-term or long-term support. If the GIT is functional, EN is indicated and would be the preferred mode of nutritional support. In situations where the GIT is not fully functional, EN supplemented by PN may be indicated. The indications for EN generally fall into the following categories:[8]

Inadequate Oral Intake

Some medical conditions make it difficult for patients to consume adequate food and hydration by mouth. Intake may be inadequate for several

different reasons:

- medical (eg, intubation/mechanical ventilation)
- developmental (eg, preterm infants, neurologic decline)
- behavioral (eg, feeding aversions, fatigue)
- anatomical (eg, malabsorption, cancer, burns, mucositis)
- environmental (eg, improper formula mixing)

Increased nutritional need is a frequent etiology for inadequate oral intake in children. Infants with congenital heart disease (CHD), for example, experience high metabolic demands coupled with reduced splanchnic blood flow leading to difficulty achieving optimal growth with oral intake alone. Allowing oral feeding attempts of short duration (dictated by the level of tachypnea and tachycardia with feeding) supplemented with EN is common practice for CHD infants who are experiencing malnutrition.

Children with cystic fibrosis (CF) can have nutrient needs of 150% to 200% of healthy, comparable-aged peers because of increased breathing effort and malabsorption. Body mass index (BMI) for age correlates directly with pulmonary function tests and positive outcomes for these patients; therefore, meeting elevated nutrient needs is imperative. Greater than 90% of CF patients also have difficulty absorbing nutrients due to pancreatic insufficiency. Children with CF may benefit from gastrostomy tube placement for long-term EN supplementation.[9]

Infants and children with skin considerations, such as moderate-to-severe burns or Stevens-Johnson syndrome (SJS) also demonstrate increased nutrient needs due to their hypercatabolic and hypermetabolic states. Depending on the total body surface area (TBSA) impacted and burn degree, nutrient needs may be as much as 150% to 200% of resting energy expenditure (REE). While some patients may continue to maintain oral intake, others may be unable to meet their metabolic demands and will require EN support. Detailed information on EN therapy in pediatric burn patients is covered in Chapter 28, “Trauma and Burns.”

In some cases, moderately to severely malnourished infants may require supplemental, if not full EN support. The reasons for neonatal and infant malnutrition due to inadequate energy intake are vast. A clinician’s

intervention approach should include a low threshold to provide EN support while the infant continues to work on oral feedings.

Lastly, patients with underlying neurologic conditions who can consume nutrition orally may experience a progression of their disease state that can impact their oral intake. Some patients may experience early satiety, or conversely, require a lengthy amount of time to consume meals, thus leading to inadequate energy intake over time, possibly resulting in malnutrition. EN support may be indicated depending on the severity of malnutrition and overall oral intake of the patients. Given the complexity of these patients, a multidisciplinary team approach is optimal in this decision.

Swallowing Dysfunction

In some situations, it may not be safe for children to take nutrients orally while they are unable to protect their airway. Preterm infants have immature suck-swallow-breathe coordination until approximately 34 weeks gestation and will require EN for the safe administration of enteral nutrients. Following open heart surgery, infants can develop a paralyzed vocal cord and may have aspiration with attempts to take oral fluid. In these infants, a speech or occupational therapy consult, and an oropharyngeal swallowing study may be indicated to evaluate the safety of oral intake. Similarly, children who have had extended airway intubation may be unable to safely take oral nutrients and could require short-term or long-term EN support.

As mentioned previously, patients with underlying neurologic conditions such as Spinal Muscular Atrophy, Duchenne's Muscular Dystrophy, and cerebral palsy may experience progression in their disease state ultimately requiring EN support. In severe cases, aspiration may be occurring, and a gastrostomy tube placement will be indicated to provide long-term nutrition.

Inadequate Intestinal Function

Children with gastrointestinal dysfunction may require EN. Slow continuous drip feedings may improve nutrient absorption in a child who is unable to meet needs by mouth because of suboptimal bolus assimilation. Specialty formulas with peptide or amino acid-based protein sources, which are less palatable for oral consumption but can be delivered via enteral

feeding tube, may be required for children with poor digestion and absorption. EN may be used as primary therapy in certain conditions including inborn errors of metabolism, gastroparesis, eosinophilic esophagitis, and Crohn's disease (see Table 32-1). Patients with intestinal failure benefit from supplemental EN therapy to enhance intestinal adaptation and healthy microbiota.[10] Detailed recommendations for EN therapy in these patient populations are discussed in those disease-specific chapters.

TABLE 32-1. Indications for Enteral Nutrition

Indication	Diagnoses	Etiology
Inadequate oral intake		
Increased nutrient needs	• Cystic fibrosis • Bronchopulmonary dysplasia • Congenital heart disease • Renal disease • Infection • Surgery • Burn • Trauma • Malnutrition	Unable to meet nutrient needs due to elevated requirements
Developmental	• Preterm • Prolonged intubation in a neonate or infant • Neuromuscular disorders • Neurological impairment	Immature suck-swallow-breathe coordination; unable to safely swallow until ~32–34 wk.
Behavioral	• Feeding aversions • Unpalatable diet • Anorexia nervosa or other feeding disorder	• Multiple or traumatic intubations • Chronic illness • Prolonged EN requirement • Metabolic or GI disorder requiring unpalatable EN formula
Anatomical	• Cancer, burns, mucositis • Congenital malformation • Tracheoesophageal fistula • Oral intubation	Can interfere with adequate intake if oral/esophageal involvement
Swallowing dysfunction		
Anatomical	• Tracheoesophageal fistula • Paralyzed vocal cord • Severe reflux requiring postpyloric EN route	• Congenital malformation • Laryngeal nerve damage during open heart surgery can lead to aspiration with oral fluid attempts.
Developmental	• Neurodevelopmental delay • Cerebral palsy	Unable to safely swallow
Altered intestinal Function		

Indication	Diagnoses	Etiology
Malabsorption	• Short bowel syndrome • High output ostomy • Crohn's disease • Pancreatic insufficiency • Liver dysfunction	Continuous EN infusion may be required to ensure maximum nutrient absorption.

Abbreviations: EN, enteral nutrition; GI, gastrointestinal.

Contraindications to Enteral Nutrition Support

In some situations, providing nutrition support via the GIT is not possible. If the GIT cannot be reached and utilized safely, EN may be contraindicated. Severe mucositis or severe thrombocytopenia in an oncology patient, for example, could lead to further damage with enteral feeding tube placement. Facial or esophageal injuries or burns could also preclude safe access to the GIT. Signs and symptoms that the gut is not functioning properly, such as gastrointestinal bleeding, ileus, free air, or pneumatosis on abdominal imaging, should be considered carefully and may be signs of an unsafe situation for EN support. During episodes of hemodynamic instability, mesenteric blood flow is diminished and the potential for ischemic bowel damage needs to be considered.

Feeding critically ill patients in the pediatric intensive care unit can present challenges. There are a variety of factors that are contraindications for feeding through the GIT, including hemodynamic instability, vasopressor medications (eg, dopamine, dobutamine, epinephrine), or extracorporeal membrane oxygenation (ECMO).[11] In periods of hemodynamic instability, clinicians may be hesitant to feed enterally due to the risk of bowel ischemia. More recent literature suggests that feeding while on vasopressors may be safe,[4] however, there is not enough evidence to suggest recommendations and thus it must be approached cautiously on a case-by-case basis. It should be noted that pediatric patients have been able to tolerate goal EN while receiving cardiovascular medication support (continuous infusion of dopamine, dobutamine, epinephrine, norepinephrine, or phenylephrine).[4,12]

In a study published in 2018, evidence suggested that it is safe and effective to provide EEN while on ECMO; however, the authors noted that advancement should proceed with caution and with close, vigilant monitoring around times of hemodynamic change along with monitoring for signs of feeding intolerance[11,13,14] Because nutrition support is essential to the ECMO patient, if less than goal rate EN is tolerated or delivery remains at a trophic rate within the first few days, a combination of EN and PN support may be warranted to fully meet nutrition needs. The authors acknowledge that it can be difficult to provide adequate nutrition in patients who are fluid-restricted and potentially those with end-organ failure. Nutrition should be optimized as much as clinically feasible with prioritization of protein delivery.

Determining the Appropriate Enteral Nutrition Route and Regimen

When initiating EN in hospitalized children, the route of tube introduction, as well as the site of nutrient administration, are considerations that need to be made by the multidisciplinary team.

Gastric Versus Postpyloric Delivery

Gastric feeding tubes are easier to place and provide a more physiologic feeding method than postpyloric delivery. The gastric route allows for bolus feeding methods and allows a more hyperosmolar formula if needed. When it is safe to do so, gastric provision of EN is recommended. In preterm infants receiving human milk, bolus feedings may reduce losses of fat, calcium, and phosphorus from the milk.[14] It should be noted that intermittent feedings do not place a child at risk for aspiration over continuous gastric feedings.

In some situations, it may not be possible or desired to administer EN into the stomach. Poor gastric emptying may require a postpyloric route to provide adequate nutrients. If the child is at high risk for aspiration and/or has previously demonstrated aspiration with gastric feedings, postpyloric feedings may be the safer method.

Common reasons why hospitalized infants and children with increased risk of aspiration may require postpyloric feedings include the following:

- Neurologic dysfunction (seizure disorders)
- Anatomic problems—cleft palate, laryngeal cleft, esophageal atresia, tracheoesophageal fistula
- Gastroparesis
- Previous surgical interventions to the GIT
- Increased respiratory support (positive airway pressure)
- Severe reflux
- Chronic aspiration
- Persistent gastric feeding intolerance (emesis, worsening abdominal distention)

In children receiving mechanical ventilation, the gastric route is the preferred EN site. As previously stated, patients who are unable to tolerate gastric feeding may require small bowel feeding. In critically ill patients, there is insufficient evidence to make a practice recommendation to provide continuous or intermittent gastric feedings.[4]

If the patient's clinical course does require postpyloric feedings, it is important for the medical team to assess the stability and readiness of the patient to be transitioned back to gastric feedings. If the child's nutrition plan includes long-term EN, the transition to a practical home EN regimen should occur as soon as possible.

With new advances in medical technology, it is now possible to safely place small bowel feeding tubes at the bedside, such as using electromagnetic sensing technology. Even so, postpyloric tube placement requires experienced personnel and careful technique as complications such as pneumothorax and malpositioning can occur. Difficulties associated with postpyloric tubes need to be considered when deciding about tube placement and whether it can be placed at the bedside or if placement by interventional radiology would be better.

There are no clear recommendations for preterm infants regarding the site of EN delivery; however, preterm infants can be fed in the stomach or in the upper small bowel (transpyloric tube feeding).[15] A 2013 Cochrane review of preterm infants given gastric or postpyloric feedings found no

beneficial effect of postpyloric delivery; however, it is common practice to provide physiologic, gastric feedings. An increased rate of gastrointestinal disturbance and mortality occurred in preterm infants with postpyloric feeding tubes.[16] The authors recommended interpreting the results cautiously because the infants who were fed postpylorically were often sicklier and were born more prematurely.

Nasoenteric or Oroenteric Versus Semipermanent Feeding Routes

The tube that will physically deliver the EN can be placed in various locations depending on the desired route of administration, and the type of feeding tube will vary accordingly. While the length of therapy has the most influence on the route that is chosen, some clinical scenarios may dictate one route over another. For instance, trauma or surgery to the upper GIT may require transabdominal tube placement, even for shorter-term enteral access. Conversely, congenital malformations or abdominal surgery may require a nasoenteric feeding route, even in long-term EN. In the neonatal population, it is not uncommon to use an orogastric tube as a nasal placement may compromise respiration, increasing nasal airway resistance and breathing effort; however, the data from the Cochrane review did not provide sufficient evidence to inform practice.[16]

Nasal or oroenterically placed feeding tubes can be done at the bedside by trained personnel. Correct placement should be confirmed before each use. This route is relatively simple, does not require sedation, and leaves no permanent scarring. Fine bore feeding tubes (silicone and polyurethane) are flexible and less likely to cause erosions, inflammation, or strictures. Fine bore tubes can be left in place for up to 8 weeks, depending on the manufacturer.[17] However, nasal or orally placed feeding tubes may significantly contribute to oral feeding aversion and local irritation for chronically ill infants and young children. Oral tubes may also be more prone to displacement.[15]

When long-term EN is anticipated (>6–12 weeks), semipermanent access via the transabdominal route (gastrostomy, often called a G-tube) should be considered by the multidisciplinary team. These tubes require

sedation for placement and when removed will leave a small abdominal scar. Caregiver input should be included in the decision-making process.

There are three techniques for semipermanent feeding-tube placement: (1) endoscopic (percutaneous endoscopic gastrostomy; PEG), (2) radiologic, and (3) surgical.

PEG insertion is the most common technique because of lower complication rate and cost. Patients can receive a PEG feeding tube and be discharged home within 1to 2 days if there are no complications or problems with EN tolerance. The timing of EN commencement varies widely, generally 4 to 24 hours post-PEG. Studies have not shown any increased complications when EN started 3 to 4 hours post-PEG.[18,19,20] See Chapter 31, "Nutrition Access," for a more in-depth discussion on placement techniques.

Initiation and Advancement

When initiating EN, the first step is to consider which delivery of feeding would best fit the clinical picture. Intermittent or bolus feeding more closely matches what an oral diet would entail and is therefore more physiological. Bolus feedings should not be given over a shorter period than the time a child would be expected to consume an oral feeding and should not be spaced out beyond their normal between-meal times. For example, infants are generally fed every 3 to 4 hours for a total of 6 to 8 feedings per day, while older children may tolerate their full daily volume with 4 to 5 bolus feedings per day. Maximum volumes for continuous and bolus feedings are determined by the child's response to the regimen, weight gain and growth, and overall GI status.[21–23] In situations such as severe diarrhea, malabsorption, or reduced splanchnic blood flow in CHD patients, continuous feeding may increase absorption of enteral nutrients and improve growth.[24]

Appropriate initiation and advancement of EN is dependent on the patient's age and weight as well as the enteral access device type. Whether working with an EN feeding protocol or not, advancement may be dependent on the patient's current clinical condition, risk of refeeding syndrome, underlying disease state, or other complications and may need to

be individualized. In some cases, the child may be unable to tolerate or be advanced beyond the trophic rate of EN, and PN support may be indicated. Providing a combination of EN and PN support will support GIT mucosal integrity and motility while simultaneously supporting the nutrient needs of the patient.

Complications and Monitoring

Successful delivery of the EN prescription can be complicated by various mechanical and metabolic abnormalities.[21] For developing infants or young children, lack of oral stimulation during prolonged periods of EN support can have profound effects on feeding success after the child recovers and has been deemed ready to safely attempt an oral diet. Early involvement with speech and occupational therapists is paramount for optimal oral recovery. Infectious, gastrointestinal, pulmonary, metabolic, or tube-related mechanical complications can occur. Before initiating an EN regimen, the child's medical and nutrition history should be considered (including *nil per os* [NPO] status prior to EN) as well as any preexisting physical or biochemical abnormalities.

Mechanical

Although generally less severe than the complications associated with the parenteral route, enteral tube–related complications can occur.

Nasoenteric Tubes

Modern feeding tubes are smaller, more flexible, and are associated with fewer problems than their predecessors. Correct placement should be confirmed before initial feeding. Although obtaining an abdominal x-ray is one way to confirm placement, it may not be ideal for pediatric patients given the accumulating exposure to radiation. In addition, pediatric patients infusing EN at home via nasogastric tube may frequently have the tube replaced by the caregiver without access to radiology. While radiographic confirmation remains the gold standard for determining appropriate placement, measurement of the acidity or pH of the gastric aspirate may also be used.

Pediatric nasogastric tube placement and verification best practice recommendations have been published by the ASPEN NOVEL project.[25] Parents and caregivers are taught to measure using the nose-earlobe-xiphoid process-midline of the umbilicus (NEMU) method to determine insertion length, and then obtain an aspirate of gastric pH with a value between 1 and 5.5, indicating correct placement.

A nasally placed feeding device can migrate from its intended position; for instance, a postpyloric tube may be inadvertently pulled back into the stomach, putting a child at risk for aspiration. Similarly, a nasogastric tube can migrate into the small bowel. Tubes should be monitored for correct positioning. Tube occlusion can occur when medications are given without adequate water flushes or when added directly to the EN, causing viscous or curdled formula.

Gastric Tubes

Semipermanent gastric tubes can be fitted too loose or too tight, causing chronic inflammation at the stoma site or leakage of gastric contents. Tubes can be placed improperly with the bumper or balloon inflated inside the abdominal cavity, with subsequent EN infusion into the peritoneum. Chronic irritation at the stoma site can lead to granulation tissue. Excessive pain at the tube site and inability to twist the tube in its tract can indicate buried bumper syndrome, which is a rare but serious late complication of gastric tube placement. For more detailed information regarding feeding-tube problems and troubleshooting ideas, see Table 31-1 in Chapter 31, "Nutrition Access."

Gastrointestinal

Abdominal distension, cramping, nausea, vomiting, and diarrhea can occur with EN. Symptoms may be associated with acute gastroenteritis, side effects of medications, rapid administration of bolus feedings, formula intolerance, or malabsorption. Liquid formulations of pediatric medications often contain sugar or sugar substitutes that can contribute to loose stools. Antibiotics diminish healthy gut flora and can cause diarrhea.

Constipation is also common among infants and children. Inadequate fluid intake, limited mobility, and narcotic administration can contribute to

constipation as well as an underlying medical condition, gastric dysmotility, or small bowel obstruction. Monitoring stooling patterns in hospitalized children and prescribing adequate softeners or motility agents can help prevent constipation-related intolerance of EN.

Hypertonic feedings delivered postpylorically or rapid gastric emptying may lead to dumping syndrome in some patients. For the latter, cornstarch is sometimes included in the feeding regimen to try to minimize the hypoglycemia that can be associated with dumping.[26]

Stool studies checking for reducing substances, inflammatory markers, guaiac, or bacterial cultures can help differentiate the cause of gastrointestinal distress. Careful evaluation of the tube location, EN prescription, and medication regimen can help identify potential problems. Small bowel bacterial overgrowth should be considered in the differential diagnosis in patients with a history of gastrointestinal problems.

Oral-Motor Deficit

Pediatric patients receiving EN for an extended period may have difficulty resuming oral feeding. Infants who are kept NPO for prolonged periods do not receive normal oral motor stimulation and cannot achieve their developmental milestones for feeding. Preterm infants should receive oral stimulation therapy throughout their hospitalization, with nonnutritive sucking encouraged at approximately 30 weeks gestation. They should begin to develop coordinated suck-swallow-breathe patterns between 32 weeks and 34 weeks gestation. Older children should be evaluated for safe swallowing function, with appropriate ongoing oral motor interventions to minimize declines during EN therapy. Involving the speech-language or occupational therapist early and prioritizing oral skills throughout EN therapy will help achieve successful reintroduction of oral nourishment in children able to wean off EN.

Refeeding Syndrome

Malnourished patients at risk for refeeding syndrome should be monitored closely when initiating and advancing EN. This is covered in depth in Chapter 17, “Eating Disorders.”

Drug–Nutrient Interactions

Medication compatibility is important to consider when creating a nutrition plan for initiation, advancement, and goal feeds. The EN regimen may need to be adjusted to account for nutrient–medication incompatibilities. Certain medications may require EN to be held for a predetermined time around each dose. Table 32-2 provides examples of drug–nutrient interactions. Working with the multidisciplinary team to develop the EN plan will ensure medication compatibility is taken into consideration.

TABLE 32-2. Examples of Drug-Nutrition Interactions

Precipitating Factor	Object	Examples
Drug	Nutrient	• Carbamazepine lowers biotin status • Isoniazid impairs vitamin B6 status
Drug	Nutrition status	• Quetiapine increases weight gain • Sorafenib is associated with sarcopenia
Drug	Metabolic status	• Capecitabine may cause hypertriglyceridemia • Olanzapine may cause hyperglycemia
Nutrition status	Drug	• Obesity results in lower ertapenem levels • Vitamin C deficiency prolongs pentobarbital action
Specific nutrient	Drug	• Vitamin D reduces atorvastatin concentrations. • Iron supplements reduce doxycycline concentrations.
Food component	Drug	• Calcium reduces ciprofloxacin absorption. • Protein interferes with levodopa absorption.
Food	Drug	• Grapefruit juice increases simvastatin toxicity. • Enteral nutrition impairs ciprofloxacin absorption.

Reproduced with permission from the American Society for Parenteral and Enteral Nutrition from Boullata JI, ed. *Guidebook on Enteral Medication Administration*, 2019:22.

Micronutrient Deficiency

Many pediatric diagnoses will alter the energy needs of children, causing them to require much more or much less of a given EN product than the standard reference child of the same age and size. The majority of available EN products are formulated in a fixed ratio to meet energy needs in a predetermined volume. Since feedings are primarily provided to meet energy and protein needs, children with hypermetabolic or hypometabolic needs may not have their needs met by a single enteral formula product.

Children with severe developmental delays may have significantly decreased energy expenditure than the recommended dietary reference intake for age and, therefore, will receive considerably less EN than another child of the same size. This can lead to deficiencies in vitamins, minerals, electrolytes, protein, and fluid. The specific micronutrient intake provided by the nutrition prescription should be calculated, and supplements given to ensure nutrient needs are met.

Close monitoring of biochemical markers or clinical signs of micronutrient deficiencies or abnormalities will help identify problems and guide treatment. When realizing that supplements and modulars may be needed in a patient's feeding regimen, pay special attention to providing adequate protein, fluid, and micronutrients.[26,27]

Chronically ill children are often vitamin D deficient and potentially at greater risk for osteopenia or metabolic bone disease. In at-risk patients, 25-hydroxy-vitamin D (25[OH]D) levels should be checked at least once per year; however, patients who may be at greater risk or are receiving high-dose therapy may need levels monitored as frequently as every 8 to 12 weeks. Risk factors for vitamin D deficiency are as follows:[28–30]

- Antiepileptic medication use
- Antiretroviral medication use
- Obesity
- Malabsorption syndromes (eg, CF, inflammatory bowel disease, Crohn's disease)
- Nonambulatory status
- Exclusively breastfed infants
- Hypo-metabolically fed infants/children
- Preterm infants born <32 weeks

In summary, patients receiving EN should be monitored for complications. GI complications may manifest clinically as abdominal distension, vomiting, or diarrhea. Tube-related mechanical problems should be evaluated and treated appropriately to avoid serious complications. Biochemical indices should be monitored to avoid micronutrient deficiencies or refeeding syndrome in at-risk patients. If respiratory symptoms occur with feedings, aspiration should be ruled out. EN regimens should be frequently reassessed to ensure complications are addressed, macronutrient and micronutrient needs are met, and the optimal nutrition plan is in place.

Enteral Nutrition Formula Selection

Human milk and infant and pediatric formulas are covered in detail in Chapters 11 ("Human Milk"), 12 ("Infant Formulas and Complementary Feeding"), and 13 ("Enteral Formulas"). Fortunately, a wide variety of commercial formulas are available to suit patient needs. Age-appropriate enteral formulas should be thoughtfully chosen, with options for condition-specific or disease-specific formulations, along with the patient's medical needs, such as fluid restriction. If the patient has no known prior concerns or conditions, a standard formula should be tried before providing a specialized formula. Once a child shows an inability to tolerate a standard formula, it is customary to trial a peptide-based formula before moving to an elemental formula. For patients who may be fluid-restricted, providing a concentrated formula may be indicated until fluid delivery can be liberalized.

The American Academy of Pediatrics recommends that all newborns, including very low birth weight (VLBW) infants, receive human milk as their source of EN. When mother's own milk is not available, infant formula will be needed. For some preterm infants, pasteurized donor human milk may be indicated. Fortification for term infants is not needed, but human milk fortification is a standard of care for very preterm/VLBW infants to support adequate growth and body composition, including bone mineralization.[17,31–35]

Enteral Nutrition Formula Safety

Microbial contamination of EN formulas is common.[36–42] Powdered formulas are not sterile and have been implicated in infections leading to meningitis and necrotizing enterocolitis.[43] When clinically acceptable sterile liquid formulations are commercially available, they should be used instead of powdered formula. Closed-system enteral products are commercially available. Closed-system containers can be directly spiked to the tube feeding line rather than opening formula containers and pouring them into a feeding bag. With the introduction of closed enteral feeding systems, EN safety has improved for adolescent patients and adults, and the length of the safe hang time has increased. Closed enteral feeding systems are generally 1 liter and larger, and therefore may not be practical for use with infants and young children because of waste. Table 32-3 provides the room temperature formula stability or hang time for various formulas, administration systems, and care settings.

TABLE 32-3. Room Temperature Formula Stability[21]

Hang Time (h)	Formula Type
4	Sterile formula in an open system (neonate)
	Nonsterile powdered formula
	Nonsterile powdered additives
	Human milk
8	Sterile formula in an open system for inpatient administration
12	Sterile formula in an open system for home administration
24–48	Sterile formula in a closed system

Formula manipulation with powdered products is common in pediatrics and can be another source of contamination. For hospitalized infants, formula should be prepared by specialized personnel using aseptic technique and sterile water for reconstitution of powdered formulas to minimize contamination.[44] When mixing powdered infant formula at home, tap water that has been boiled for at least 1 minute and then cooled or

bottled water may be used. Purified or distilled water may also be used to avoid excessive fluoride administration. For home EN, parents/caregivers should be instructed on good hand washing and cleaning techniques to minimize contamination risk. Education on room temperature formula stability should also be provided (see Table 32-3).

Administration sets for open-system EN should be changed at least every 24 hours. More information is available as part of the ASPEN Enteral Nutrition Practice Recommendations.[21,44]

Preparing for Home Enteral Nutrition

Pediatric patients dependent on EN, who are otherwise stable for discharge, can receive their continuous or intermittent feeds at home via pump or syringe. To prepare for the shift to home EN, the healthcare care team must provide thorough education and training to parents/caregivers, which should begin as early as possible during the hospital stay. Learning small amounts of information at the bedside throughout the hospitalization will make parents/caregivers feel more prepared for home. Parents/caregivers should also be involved in decision making around the home regimen, including schedules and administration methods. It is important to ensure the home regimen developed by the healthcare team will work with the patient's daily activities at home, including school and childcare. Prior to discharge, home caregivers must demonstrate competence in the safe and effective preparation and administration of home EN.

Table 32-4 describes the components of home enteral nutrition education.

TABLE 32-4. Components of Home Enteral Nutrition Education

Educational Component	Description
Information about nasal feeding device	• Identification of tube type: nasogastric, nasoduodenal, nasojejunal • Tube size (French) and presence of tube adapter • Manufacturer and access to manufacturer information • Instructions for reinsertion (if being done at home or by a healthcare professional) • Site care and maintenance: checking position, securing tube, and cleaning nostrils • Steps for providing feeding through nasal tube via gravity bolus feeds or using a pump for continuous feeds • Trouble-shooting information: intolerance of feeds, breakdown or issues with skin surrounding securement of tube, contact numbers for emergent and urgent issues • Information for reordering supplies: company name and phone number • Primary contact name, phone number, and patient portal contact for questions
Information about gastric feeding device	• Identification of size (French), date of placement, and clinical information (eg, procedure documentation) • Manufacturer and access to manufacturer information • Skin care around insertion site • Instruction for securing tube • Instructions for use of feeding tube during feedings (eg, flushing with water) • For low-profile EADs: instruction on feeding tube extension type (continuous vs bolus) and cleaning the feeding tube extension after feeds • Information for reordering supplies: company name and phone number • Troubleshooting information: intolerance of feeds, breakdown or issues with skin surrounding G-tube, instructions if G-tube comes out, contact numbers for emergent and urgent issues • Primary contact name, phone number, and patient portal contact for questions
Other general information	• Proper clothing with enteral feeding device • Bathing and swimming • Securing and positioning during feeding • Prevention of dislodgement

Educational Component	Description
	• Allow for physical activity as tolerated; more rigorous activity to be guided by physician • Primary contact name, phone number, and patient portal contact for questions • Outpatient resources and peer support groups (eg, Oley Foundation or Feeding Tube Awareness Foundation) to provide up-to-date information, outreach services, conference activities, and emotional support for home EN patients and families

Abbreviations: EAD, enteral access device; EN, enteral nutrition; G-tube, gastric tube.

Adapted with permission from Sevilla et al.[45]

Once the patient has been discharged home on enteral nutrition, an appropriate long-term follow-up plan is important to reduce the incidence of complications, growth failure, emergency room or urgent clinic visits, readmissions, and costs. Clinical complications such as vomiting, diarrhea, aspiration pneumonia, and constipation; enteral access device–related complications such as tube clogs or dislodgement; and site complications such as leakage, erythematous, or granulation tissue are common.[46] Patients should also be monitored for appropriate growth and development, and advancement of oral intake with weaning of EN when appropriate. Children who have undergone lengthy hospital admissions and multiple procedures at a young age often have difficulty with oral skills and require significant therapeutic interventions to optimize oral intake.[47]

Conclusion

Utilizing and feeding via the GIT is the preferred method for pediatric patients, and a multidisciplinary team approach is needed to optimize nutrition. Evidence suggests that a feeding protocol may aid in providing EN sooner to critically ill children. Regardless, every child should be evaluated to determine optimal nutrition to promote metabolic support and recovery from critical illness, and growth and development in the stable patient. The patient's nutrition prescription should continue to be

reevaluated throughout their hospital stay, and regularly at home to ensure appropriate nutrient delivery and optimal growth and development. Ongoing research and data provide safe recommendations for feeding hospitalized pediatric patients.

When determining the home nutrition plan, the entire family must be considered, and regimens should account for the child's school and activities to ensure that quality of life is not negatively affected. What works for one child and caregiver may not work for another. Factors to consider may include the patient's baseline nutrition status, GIT functionality, access options, administration schedule, and modality. It is essential to be flexible and supportive when working with caregivers to develop a nutrition plan of care that is best for their child and their lives.

Test Your Knowledge Questions

1. DB, a 9-year-old boy with CF was admitted with pulmonary exacerbation. The BMI for age plots below the 10th percentile (z score –1.3). He consumes a high-calorie, high-protein diet and takes pancreatic enzymes with every meal and snack. He has undergone nutritional counseling during previous visits and has incorporated liquid supplements by mouth. Which of the following would be the most appropriate initial recommendation?
   A. Encourage a high-calorie, high-protein diet with snacks between each meal.
   B. Evaluate the pancreatic enzyme dosing to determine if they are receiving optimal replacement therapy and ask about the stooling pattern to evaluate for malabsorption.
   C. Encourage liquid nutrition supplements at least 3 times daily.
   D. Recommend a G tube for supplemental EN.
   E. Check vitamin levels and adjust supplements as needed.
2. You are rounding in the pediatric cardiac intensive care unit on a 15-day-old infant with hypoplastic left heart syndrome s/p palliative surgery, tolerating a small amount of human milk given via nasogastric feeding tube but unable to advance to goal rate and wean off PN because of worsening tachypnea, tachycardia, and cool extremities. The

patient's healthcare team would like your input on the nutrition plan. Which of the following would be the most appropriate initial recommendation?

A. Advance the EN and wean the PN off because double-blinded, randomized controlled trials have shown clear benefits of EN over PN in pediatric patients.
B. Continue the EN plus PN combination nutrition support to ensure 100% of the infant's estimated nutritional needs are met.
C. Hold the EN and increase PN back to goal rate since the child does not seem to be tolerating enteral feeds.
D. Change to elemental formula, which is better tolerated in hemodynamically unstable infants.

3. SPN is a previously healthy boy who was admitted to the pediatric intensive care unit following a motor vehicle collision, requiring intubation/mechanical ventilation. The patient's healthcare team would like to start EEN but consult you for formula and feeding route recommendations. Which of the following would be the most appropriate initial recommendation?

A. Place a nasogastric tube and use a standard formula.
B. Place a nasogastric tube and use a peptide formula.
C. Place a nasojejunal tube and use a standard formula.
D. Place a nasojejunal tube and use a peptide formula.
E. None of the above, it is not safe to start EN; start PN.

4. A 10-year-old child with cerebral palsy, tracheostomy, and ventilator dependence was admitted from home with respiratory illness. The child has very low energy needs and is concerningly over-nourished as evidenced by your nutrition-focused physical exam and is receiving 50% of the dietary reference intake for age from the home EN regimen. Which of the following would be the most appropriate initial recommendation?

A. Reassess the home feeding regimen, consider decreasing total caloric delivery, and add a protein modular.
B. Calculate the maintenance fluid needs and adjust the fluid boluses if needed.
C. Add sodium chloride to maintain at least 1 to 2 mEq/d from the daily nutrition prescription.

D. Check vitamin and mineral levels and supplement as needed.
E. All of the above

References

1. Baker S, Baker R, Davis A. *Pediatric Nutrition Support*. Jones & Bartlett; 2007.
2. McClave SA, Heyland DK. The physiologic response and associated clinical benefits from provision of early enteral nutrition. *Nutr Clin Pract*. 2009;24(3):305–315. https://doi.org/10.1177/0884533609335176
3. Matarese LE, Mullin GE, Raymond JL. Enteral nutrition. In: *The Health Professional's Guide to Gastrointestinal Nutrition.* Academy of Nutrition and Dietetics; 2014:235–257.
4. Mehta NM, Skillman HE, Irving SY, et al. Guidelines for the provision and assessment of nutrition support therapy in the pediatric critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition. *JPEN J Parenter Enteral Nutr*. 2017;41(5):706–742. https://doi.org/10.1177/0148607117711387
5. Martinez EE, Bechard LJ, Mehta NM. Nutrition algorithms and bedside nutrient delivery practices in pediatric intensive care units: an international multicenter cohort study. *Nutr Clin Prac*. 2014;29(3):360–367. https://doi.org/10.1177/0884533614530762
6. Mehta NM. Approach to enteral feeding in the PICU. *Nutr Clin Prac*. 2009;24:377–387. https://doi.org/10.1177/0884533609335175
7. Braegger C, Decsi T, Dias JA, et al. Practical approach to paediatric enteral nutrition: a comment by the ESPGHAN committee on nutrition. *JPEN J Pediatr Gastroenterol Nutr*. 2010;51:110–122. https://doi.org/10.1097/mpg.0b013e3181d336d2
8. Shimmin D, Lowdon J, Remmington T. Enteral tube feeding for cystic fibrosis. *Cochrane Database of Systematic Reviews*. 2019;7:1465–1858. https://doi.org/10.1002/14651858.cd001198.pub5
9. Channabasappa N, Girouard S, Nguyen V, et al. Enteral nutrition in pediatric short-bowel syndrome. *Nutr Clin Pract.* 2020;35(5):848–854. https://doi.org/10.1002/ncp.10565

10. Toh TSW, Ong C, Mok YH, Mallory P, Cheifetz IM, Lee JH. Nutrition in pediatric extracorporeal membrane oxygenation: a narrative review. *Front Nutr*. 2021;8:666464. https://doi.org/10.3389/fnut.2021.666464
11. Panchal AK, Manzi J, Connolly S, Christensen M, Wakeham M, Goday PS, Mikhailov TA. Safety of Enteral Feedings in Critically Ill Children Receiving Vasoactive Agents. *JPEN J Parenter Enteral Nutr*. 2016;40(2):236–41. https://doi.org/10.1177/0148607114546533
12. Jaksic T, Hull MA, Modi BP, Ching YA, George D, Compher C; American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. Nutrition support of neonates supported with extracorporeal membrane oxygenation (ECMO). *JPEN J Parenter Enteral Nutr*. 2010;34(3):247–253. https://doi.org/10.1177/0148607110369225
13. Farr BJ, Rice-Townsend SE, Mehta NM. Nutrition support during pediatric extracorporeal membrane oxygenation. *Nutr Clin Pract.* 2018;33(6):747–753. https://doi.org/10.1002/ncp.10212
14. Wang Y, Zhu W, Luo BR. Continuous feeding versus intermittent bolus feeding for premature infants with low birth weight: a meta-analysis of randomized controlled trials. *Eur J Clin Nutr.* 2020;74(5):775–783. https://doi.org/10.1038/s41430-019-0522-x
15. Koletzko B. *Nutritional Care of Preterm Infants: Scientific Basis and Practical Guidelines*. Karger; 2014.
16. Watson J, McGuire W. Transpyloric versus gastric tube feeding for preterm infants. *Cochrane Database Syst Rev*. 2013;(2):CD003487. https://doi.org/10.1002/14651858.CD003487.pub3
17. Braegger C, Decsi T, Dias JA, et al. Practical approach to paediatric enteral nutrition: a comment by the ESPGHAN committee on nutrition. *J Ped Gastro and Nutr.* 2010;51(1):110–122. https://doi.org/10.1097/mpg.0b013e3181d336d2
18. Shahmanyan D, Lawrence JC, Lollar DI, et al. Early feeding after percutaneous endoscopic gastrostomy tube placement in patients who require trauma and surgical intensive care: a retrospective cohort study. *JPEN J Parenter Enteral Nutr.* 2021;46(5):1160–1166. https://doi.org/10.1002/jpen.2303
19. Corkins MR, Fitzgerald JF, Gupta SK. Feeding after percutaneous endoscopic gastrostomy in children: early feeding trial. *J Pediatr*

Gastroenterol Nutr. 2010;50(6):625–627. https://doi.org/10.1097/mpg.0b013e3181bab33d
20. Islek A, Sayar E, Yilmaz A, Artan R. Percutaneous endoscopic gastrostomy in children: is early feeding safe? *J Pediatr Gastroenterol Nutr*. 2013;57(5):659–662. https://doi.org/10.1097/mpg.0b013e3182a0d171
21. Bankhead R, Boullata J, Brantley S, et al. Enteral nutrition practice recommendations. *JPEN J Parenter Enteral Nutr*. 2009;33(2):122–167. https://doi.org/10.1177/0148607108330314
22. Koletzko B, Goulet O, Hunt J, et al. Guidelines on paediatric parenteral nutrition of the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), supported by the European Society of Paediatric Research (ESPR). *J Pediatr Gastroenterol Nutr*. 2005;41;S28–S32. https://doi.org/10.1097/01.mpg.0000181841.07090.f4
23. Lord L, Harrington M. Enteral nutrition implementation and management. In: Merritt R, ed. *The ASPEN Nutrition Support Practice Manual*. 2nd ed. American Society for Parenteral and Enteral Nutrition; 2005:76–89.
24. Axelrod D, Kazmerski K, Iyer K. Pediatric enteral nutrition. *JPEN Parenter Enteral Nutr*. 2006;30(1):S21–S26. https://doi.org/10.1177/01486071060300s1s21
25. Irving SY, Rempel G, Lyman B, et al. Pediatric nasogastric tube placement and verification: best practice recommendations from the NOVEL project. *Nutr Clin Pract.* 2018;33(6):921–927. https://doi.org/10.1002/ncp.10189
26. Della Pepa G, Vetrani C, Lupoli R, et al. Uncooked cornstarch for the prevention of hypoglycemic events. *Crit Rev Food Sci Nutr*. 2022;62(12):3250–3263. https://doi.org/10.1080/10408398.2020.1864617
27. Da Silva JS, Seres DS, Sabino K, et al. ASPEN consensus recommendations for refeeding syndrome. *Nutr Clin Pract.* 2020;35(2):178–195. https://doi.org/10.1002/ncp.10474
28. McGowan JE, Fenton TR, Wade AW, Branton JL, Robertson M. An exploratory study of sodium, potassium, and fluid nutrition status of

tube-fed nonambulatory children with severe cerebral palsy. *Appl Physiol Nutr Metab*. 2012;37(4):715–723. https://doi.org/10.1139/h2012-050
29. National Research Council. *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate*. The National Academies Press; 2005.
30. Sentongo TA, Semaeo EJ, Stettler N, Piccoli DA, Stallings VA, Zemel BS. Vitamin D status in children, adolescents, and young adults with Crohn disease. *Am J Clin Nutr*. 2002;76(5):1077. https://doi.org/10.1093/ajcn/76.5.1077
31. Pappa HM, Langereis EJ, Grand RJ, Gordon CM. Prevalence and risk factors for hypovitaminosis D in young patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2011;53(4):361. https://doi.org/10.1097/mpg.0b013e3182250b3e
32. Shellhaas RA, Joshi SM. Vitamin D and bone health among children with epilepsy. *Pediatr Neurol*. 2010;42(6):385–393. https://doi.org/10.1016/j.pediatrneurol.2009.12.005
33. Johnston M, Landers S, Noble L, Szucs K, Viehmann L. Breastfeeding and the use of human milk. *Pediatrics*. 2012;129(3):827–841. https://doi.org/10.1542/peds.2011-3552
34. Sullivan S, Schanler RJ, Kim JH, et al. An exclusively human milk-based diet is associated with a lower rate of necrotizing enterocolitis than a diet of human milk and bovine milk-based products. *J Pediatr*. 2010;156:562–567. https://doi.org/10.1016/j.jpeds.2009.10.040
35. Quigley MA, Henderson G, Anthony MY, McGuire W. Formula milk versus donor breast milk for feeding preterm or low birth weight infants. *Cochrane Database Syst Rev*. 2007;(4):CD002971. https://doi.org/10.1002/14651858.CD002971.pub2
36. Patchell CJ, Anderton A, MacDonald A, et al. Bacterial contamination of enteral feeds. *Arch Dis Child*. 1994;70:327–330. https://doi.org/10.1136/adc.70.4.327
37. Roy S, Rigal M, Doit C, et al. Bacterial contamination of enteral nutrition in a pediatric hospital. *J Hosp Infect*. 2005;59:311–316. https://doi.org/10.1016/j.jhin.2004.09.026
38. Kim H, Ryu JH, Beuchat LR. Attachment of and biofilm formation by *Enterobacter sakazakii* on stainless steel and enteral feeding tubes.

Appl Environ Microbiol. 2006;72:5846–5856. https://doi.org/10.1128/aem.00654-06
39. Doherty T, Coutsoudis A, McCoy D, et al. Is the US infant formula shortage an avoidable crisis? *Lancet.* 2022;400(10346):83–84. https://doi.org/10.1016/s0140-6736(22)00984-9
40. Warren CM, Gupta RS, Nowak-Wegrzyn A. The 2022 US infant formula shortage: Perspectives on a nutritional crisis. *Ann Allergy Asthma*. 2023;130(4):427–428. https://doi.org/10.1016/j.anai.2023.01.011
41. Anderton A, Nwoguh CE, McKune I, Morrison L, Grieg M, Clark B. A comparative study of the numbers of bacteria present in enteral feeds prepared and administered in hospital and the home. *J Hosp Inf*. 1993;23:43–49. https://doi.org/10.1016/0195-6701(93)90129-n
42. Bott L, Husson MO, Guimber D, et al. Contamination of gastrostomy feeding systems in children in a home-based enteral nutrition program. *J Pediatr Gastroenterol Nutr*. 2001;33:266–270. https://doi.org/10.1097/00005176-200109000-00007
43. Centers for Disease Control and Prevention. *Enterobacter sakazakii* infections associated with the use of powdered infant formula—Tennessee, 2001. *MMWR*. 2002;51:297–300.
44. Boullata JI, Long Carrera A, Harvey L, et al. ASPEN safe practices for enteral nutrition therapy. *J Parenter Enter Nutr.* 2017;41(1):15–103. https://doi.org/10.1177/0148607116673053
45. Sevilla WM, McElhanon B. Optimizing transition to home enteral nutrition for pediatric patients. *Nutr Clin Pract.* 2016;31(6):762–768. https://doi.org/10.1177/0884533616673348
46. Diamanti A, Ciommo V, Tentolini A, et al. Home enteral nutrition in children: a 14-year multicenter survey. *Eur J Clin Nutr*. 2013;67:53–57. https://doi.org/10.1038/ejcn.2012.184
47. Edwards S, Davis A, Bruce A, et al. Caring for tube-fed children: a review of management, tube weaning, and emotional considerations. *J Parenter Enteral Nutr.* 2016;40(5):616–622. https://doi.org/10.1177/0148607115577449

Test Your Knowledge Answers

1. The correct answer is **D**. All choices are possible interventions that could be made, but this child is in nutritional failure and at this point, a G-tube would be recommended to supplement the oral diet. Intermittent nocturnal feeds could provide additional nutrients while the child sleeps.
2. The correct answer is **B**. While EN is certainly preferred if the GIT is functional, hemodynamically unstable infants may not tolerate goal EN. There is a lack of high-quality evidence comparing EN to PN, particularly in pediatric patients, so you would not be able to state this as a reason to wean off PN. If the infant can tolerate a small amount of enteral human milk, giving a combination of EN and PN support would be preferred over withholding EN altogether. Elemental formula would not be indicated over human milk in this patient at this time.
3. The correct answer is **A**. In a previously healthy child, with an otherwise functioning GIT and protected airway, it is safe to trial gastric feedings using a standard formula. As the patient's course continues, and if intolerance arises, switching formulas or advancing the feeding tube into the small bowel may be of consideration.
4. The correct answer is **E.** Fluids should be evaluated in children with low energy needs as they are at high risk for constipation. If receiving standard enteral formula in a fixed ratio dosed for energy needs, they will not meet their fluid needs via formula alone. Electrolytes may also be deficient. Sodium and potassium should be evaluated to ensure minimum needs are met. In addition to electrolytes, vitamin and mineral needs may not be met by the low volume of enteral formula. Vitamin D is often deficient in chronically ill children due to medications (antiseizure therapies), inadequate supply in the enteral formula, poor sunlight exposure with chronic illness, and malabsorption.

33

Parenteral Nutrition Support

Kathleen M. Gura, PharmD, FASHP, FPPA, FASPEN, FMSHP, BCNSP; and Catherine M. Crill, PharmD, FCCP, BCPS, BCNSP

Learning Objectives

1. Determine the appropriateness of parenteral nutrition therapy for a given pediatric patient.
2. Describe the typical macronutrient and micronutrient makeup of both central and peripheral parenteral nutrition formulations for neonates (preterm and term), infants, children, and adolescents.
3. Identify common pediatric parenteral nutrition complications and describe how they are assessed and can be prevented and managed.
4. Identify ways to increase the safety of the parenteral nutrition process—from ordering to administration—in institutions and at home.

Introduction

The ability to provide nutrition intravenously, known as parenteral nutrition (PN), has been lifesaving in pediatric patients, such as preterm neonates and patients with short bowel syndrome (SBS). Without PN, these patients would not have been able to sustain themselves on an enteral diet alone. PN is a complex solution of macronutrients, micronutrients, fluid, electrolytes, and additives. The clinician's role in providing safe and effective PN

support to pediatric patients requires knowledge of appropriate indications and access for PN, optimal macronutrient and micronutrient provision, and assessment for and management of complications. Safety in PN support must be ensured throughout the PN process, from prescribing to compounding and administration to transitioning to home PN.

Indications for PN

PN is indicated in patients when the gastrointestinal (GI) tract is not functional or cannot be accessed, or when nutrient needs exceed what can be provided through enteral nutrition (EN).[1] PN is routinely used in preterm neonates and patients with congenital heart disease, congenital anomalies of the GI tract, necrotizing enterocolitis (NEC), SBS, and other GI conditions. It is also routinely used in critically ill patients and patients receiving extracorporeal membrane oxygenation.

Prematurity

Preterm and low birth weight infants need a source of nutrition immediately after birth because of low nutrient reserves, increased energy expenditure, immaturity of the GI tract, and their increased propensity for acute and chronic illness.[2,3] Preterm infants may be unable to digest nutrients enterally due to immature intestinal development and low digestive enzyme production.[4] Early PN administration in low birth weight preterm neonates results in improved outcomes in growth.[2,3,5] Thus, PN should be initiated in these patients within the first 24 to 48 hours of life and continued until adequate EN is tolerated.

Starter PN solutions are often used in institutions with newborn intensive care units to provide early protein provision until an individual PN solution can be prescribed, compounded, and available for administration. These starter solutions contain dextrose and amino acids and may also contain a minimum amount of additives such as calcium and heparin.

Preterm infants, particularly those weighing <1500 g, are also prone to reflux, generalized GI dysmotility, and delayed gastric emptying.[6] Organized gut motility does not begin until 32 to 34 weeks of gestation.[7]

PN is weaned slowly as EN intake, oral intake, or both increase so that the overall nutrient intake remains optimal during this transition.

Other neonates and infants should receive PN if it is anticipated that they will be unable to receive enteral feedings for more than 2 to 3 days. Infants have limited fat and glycogen stores, and when these are depleted, infants begin to catabolize protein stores for energy. EN is commonly withheld if the following conditions are present:

- Severe respiratory failure associated with hypoxia and acidosis.
- Hypotension treated with vasopressors.
- Perinatal asphyxia with signs of organ involvement.
- Clinical signs of NEC or intestinal obstruction.
- Congenital heart disease with decreased left-sided outflow.
- Patent ductus arteriosus with left to right shunt or requiring indomethacin or surgical ligation.
- Sepsis-associated paralytic ileus.

In addition, red blood cell transfusion has been associated with decreased tissue perfusion in preterm infants receiving enteral feedings.[8] Because of concerns for the development of NEC, some clinicians will hold enteral feedings and give PN support for 24 to 48 hours in preterm infants receiving blood transfusions.

GI conditions

Several congenital anomalies of the GI tract (eg, esophageal or intestinal atresias, tracheoesophageal fistula, malrotation with volvulus, Hirschsprung's disease, anorectal malformations, abdominal wall defects) generally require short-term PN support while the patient is on bowel rest before and after surgical correction. In addition, children who develop GI disorders that temporarily prohibit the use of EN (eg, appendicitis, chronic or intractable diarrhea or vomiting, malrotation, intussusception, severe inflammatory bowel disease, acute pancreatitis, obstruction, pseudoobstruction, motility disorders, or severe gastroesophageal reflux disease) are given PN support to maintain nutrition status during illness while the GI tract is inaccessible.

NEC, a condition primarily affecting preterm infants, is characterized by GI ischemia and necrosis. NEC is managed with bowel decompression and rest, systemic antibiotic therapy, and potential surgical resection of necrotic bowel. NEC in infants requires PN because enteral feedings are withheld for 10 to 21 days to support bowel healing and recovery.[9]

PN support is required following major small bowel resection resulting in SBS. Common causes of SBS in pediatric patients are intestinal atresias, gastroschisis, NEC, Hirschsprung's disease, and volvulus.[10] Functional SBS may occur without resection and is the result of obstruction, dysmotility, or disease-associated loss of absorptive capacity. PN is always indicated for SBS in the immediate postoperative period; however, many individuals with SBS can adapt to enteral feeds and be successfully weaned from PN over time.[10,11] Individuals with intestinal failure—reduction of functional intestinal mass resulting in the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance enterally—usually require long-term PN for a minimum of 60 days within a consecutive 74-day period.[12]

Critical Illness

Patients with a critical illness are at risk for malnutrition primarily because of protein catabolism that is directly related to the severity of their illness or injury.[13] While EN is the preferred method of feeding critically ill pediatric patients with a functioning GI tract, clinical factors such as hemodynamic instability and feeding intolerance often necessitate the use of PN support.[13] In infants and children with congenital heart disease, PN may be used until tolerance to EN is established, especially preoperatively and postoperatively due to increased nutrient needs to support recovery.

In patients who are receiving vasopressor medications (eg, dopamine, dobutamine, or epinephrine), EN may be withheld because of concerns about bowel ischemia and the potential risk for NEC. PN is occasionally needed to treat individuals with chyle leaks (ie, chylothorax, chylous effusion, chylous ascites, or chylopericardium) who do not respond to enteral diets restricted in long-chain triglycerides and high in medium-chain triglycerides.[14] Because the injectable lipid emulsion (ILE) is infused directly into the bloodstream and bypasses the lymph system, it does not affect the volume of chyle produced.

Extracorporeal Membrane Oxygenation

Treatment with extracorporeal membrane oxygenation (ECMO) and the use of vasopressor support may not be absolute contraindications to enteral feedings; however, many clinicians are hesitant to enterally feed these patients. Concerns about the possible effect of hypoxia on the gut during ECMO have led to the use of PN as the main source of nutrition support. A study in infants on ECMO receiving vasopressors compared PN to full-strength, continuous EN via either nasogastric or postpyloric feeding tubes.[15] No cases of NEC or intestinal perforation were documented. Although the PN group achieved goal calories more rapidly (3.07 ± 2.1 d vs 4.25 ± 2.6 d for the EN group), the benefits of EN outweighed the risks of PN. The authors concluded that vasoactive drug infusions should not be considered a contraindication to enteral feeding.[15] The American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines recommend that nutrition support be initiated expeditiously in pediatric patients on ECMO. Generally, this is accomplished with PN initiation within 24 hours of ECMO cannulation; EN may be initiated when patients have stabilized clinically.[16]

Other indications

Malnourished children, especially those with diarrheal losses, are commonly given PN to allow bowel rest and promote weight gain until the etiology of the malnutrition can be determined and adequate tolerance of EN can be established. Other indications for PN support in pediatric patients include the following:

- High output fistulas.
- Graft-vs-host disease.
- Severe GI side effects of chemotherapy including radiation enteritis, cancer cachexia, diaphragmatic hernia, meconium aspiration, and organ failure (liver, renal, pulmonary, pancreas) when EN is contraindicated, and the child is catabolic.
- In preparation for organ transplant in malnourished patients.[17,18]

While severely malnourished patients with anorexia nervosa who require urgent nutrition rehabilitation may more readily accept PN over EN

support, PN should be considered as a last resort therapy in eating disorders.[19]

Parenteral Access

Vascular access is not defined by the initial point of entry but rather by the position of the catheter tip. With central venous access devices (CVADs), the catheter tip should be in the distal portion of the superior vena cava or at the junction of the superior vena cava and the right atrium.[1] If central access is not obtained, PN can be administered through a peripheral vein; however, the final osmolarity is limited to 900 mOsm/L to minimize the risk of phlebitis and infiltration.[20] The PN components that impart the greatest osmolarity to a solution are protein (100 mOsm/%), dextrose (50 mOsm/%), and sodium and potassium salts (2–3 mOsm/mEq). With peripheral PN (PPN) solutions, dextrose concentration is limited to 10%–12.5%. This limitation means that the PPN requires a relatively large volume to adequately administer nutrients. In critically ill infants or children, nutrient requirements often cannot be met with PPN because of fluid restriction. If PN support will be needed for more than 7 to 10 days, central access should be obtained.[1] Adequate PN support requires a CVAD and allows for the administration of a solution with a high osmolarity (ie, >900 mOsm/L).

Macronutrients

For recommendations regarding macronutrient initiation and advancement in PN for pediatric patients, see Table 33-1.[17,20–23]

TABLE 33-1. Recommendations for Initiation and Advancement of Macronutrients in Parenteral Nutrition[17,20–23,a,b]

Macronutrient	Initiation		Advance by		Goals	
	Preterm	Term	Preterm	Term	Preterm	Term
Infants (<1 y)						
Protein[c] (g/kg/d)	1–3 (max 3.5)	2.5–3	—	—	3–4	2.5–3
Dextrose (mg/kg/min)	6–8	6–8	1–2	1–2	10–14 (max 14–18)	10–14 (max 14–18)
SO-ILE[d] (g/kg/d)	0.5–1	0.5–1	0.5–1	0.5–1	3 (max 0.15 g/kg/h)	2.5–3 (max 0.15 g/kg/h)
OO,SO-ILE[e] (g/kg/d)	0.5−1	0.5−1	0.5–1	0.5–1	3	3
SO,MCT,OO,FO-ILE (g/kg/d)	0.5−1	0.5−1	0.5−1	0.5−1	3	3
FO-ILE[f] (g/kg/day)	1	1	1	1	1	1
Children (1–10 y)						
Protein[c] (g/kg/d)	1.5–2.5		—		1.5–2.5	
Dextrose (mg/kg/min)	3–6		1–2		8–10	
SO-ILE[d] (g/kg/d)	1–2		0.5–1		2–2.5	
OO,SO-IL[e]e (g/kg/day)	1–2		0.5–1		3	
SO,MCT,OO,FO-ILE (g/kg/d)	1 −2		0.5− 1		2.5−3	
FO-ILE[f] (g/kg/day)	1		1		1	
Adolescents[g] (11−17 y)						
Protein[c] (g/kg/d)	0.8–2		—		0.8–2	
Dextrose (mg/kg/min)	2.5–3		1–2		5–6	
SO-ILE[d] (g/kg/d)	1		1		1–2 (max 2−2.5)	
OO,SO-IL[e]e (g/kg/day)	1		1		2.5	
SO,MCT,OO,FO-ILE (g/kg/d)	1		0.5−1		2−2.5	
FO-ILE[f] (g/kg/day)	1		1		1	

Abbreviations: FO-ILE, fish oil ILE; ILE, lipid injectable emulsion; OO,SO-ILE, olive oil, soybean oil ILE; SO-ILE, soybean oil ILE; SO,MCT,OO,FO-ILE, soybean oil, medium-chain triglycerides, olive oil, fish oil ILE.

[a] Adapted with permission from the American Society for Parenteral and Enteral Nutrition from ASPEN Recommendations on Appropriate Parenteral Nutrition Dosing for Neonatal and Pediatric Patients. 2019. Updated November 17, 2020. Accessed April 29, 2024. https://www.nutritioncare.org/uploadedFiles/Documents/Guidelines_and_Clinical_Resources/PN%20Dosing%201-Sheet-Nov%202020-FINAL.pdf

[b] Glucose infusion rate (mg/kg/min) = (dextrose [g/d] × 1000) / (24 [h/d] × 60 [min/h] × weight [kg]).

[c] Protein does not need to be titrated; protein needs will be increased with critical illness.

[d] Lipids should account for ~25%−50% of nonprotein calories.

[e] Dosing for OO,SO-ILE are considered off-label, as not approved by the U.S. Food and Drug Administration for pediatrics.

[f] 1.5 g/kg/d has been used off-label for FO-ILE.

[g] For older children in this age range, dosing adjustments may be necessary in response to clinical conditions.

Protein

Protein is administered as a crystalline amino acid solution, which provides 4 kcal/g. Specialized amino acid solutions (see Table 33-2) are available for infants and young children; these include TrophAmine 6% and 10% (B. Braun), Premasol 6% and 10% (Baxter Healthcare), and Aminosyn-PF 7% and 10% (ICU Medical, Inc). These specialized solutions contain increased concentrations of essential amino acids, including histidine and tyrosine, and low concentrations of phenylalanine, methionine, and glycine. They also contain glutamic acid, aspartic acid, taurine, and N-acetyl-L-tyrosine (TrophAmine, Premasol), which are not present in standard amino acid products. The pediatric amino acid products have a lower pH, which allows higher concentrations of calcium and phosphorus to be added to the solution. The addition of cysteine lowers the pH further, thereby optimizing calcium and phosphorus solubility within PN solutions.

TABLE 33-2. Comparison of Commercially Available Pediatric Amino Acid Products[a]

Company	B. Braun	ICU Medical	Baxter
Product	TrophAmine	Aminosyn PF	Premasol
Introduction date (FDA approval date)	July 20, 1984	Sept. 6, 1985	June 23, 2003
Amino acid content (g/100 mL)			
Essential amino acids	0.820	0.760	0.820
Isoleucine	1.400	1.200	1.400
Leucine	0.820	0.677	0.820
Lysine	1.200	—	—
(added as lysine acetate)	0.340	0.180	0.340
Methionine	0.480	0.427	0.480
Phenylalanine	0.420	0.512	0.420
Threonine	0.200	0.180	0.200
Tryptophan	0.780	0.673	0.780
Valine	<0.016	—	<0.016
Cysteine	<0.024	—	—
(as cysteine HCl H2O)	0.480	0.312	0.480
Histidine	0.240	0.044	0.240
Tyrosine	0.044	—	—
(added as tyrosine and N-acetyl-L-tyrosine)	0.240	—	—
Nonessential amino acids			
Alanine	0.540	0.698	0.540
Arginine	1.200	1.227	1.200
Proline	0.680	0.812	0.680
Serine	0.380	0.495	0.380
Glycine	0.360	0.385	0.360
l-Aspartic acid	0.320	0.527	0.320
l-Glutamic acid	0.500	0.820	0.500
Taurine	0.025	0.070	0.025

Company	B. Braun	ICU Medical	Baxter
Sodium metabisulfite NF (as an antioxidant)	0	0	0
pH adjusted with glacial acetic acid USP			
Average pH (range)	5.5 (5.0–6.0)	5.5 (5.0–6.5)	5.5 (5.0–6.0)
Calculated osmolarity (mOsmol/L)	875	788	865
Total amino acids (g/L)	100	100	100
Total nitrogen (g/L)	15.5	15.2	15.5
Protein equivalent (g/L)	97	100	—
Electrolytes (mEq/L)			
Sodium	5	None	—
Acetate	96.2	46	94
Chloride	<3	None	<3

Source: Manufacturer's package inserts.

[a] 10% pediatric amino acid formulations.

[b] TrophAmine reformulated and manufacturing moved to Melsungen, Germany in October 2020.

TrophAmine and Aminosyn PF were designed to replicate plasma amino acid patterns of breastfed infants. Premasol, introduced in 2003, was formulated to be similar to TrophAmine. None of these formulations contain sulfites and may be used in patients with sulfite allergy. The use of TrophAmine compared with Aminosyn PF in infants has been associated with a decrease in intestinal failure-associated liver disease (IFALD).[24]

Dextrose

Carbohydrate calories are supplied in PN through the use of dextrose, which provides 3.4 kcal/g. Final concentrations of dextrose in PN solutions used in pediatric patients range from 10% to 12.5% for PPN and up to 25% or higher for central PN. In general, the dextrose content in PN should not exceed the maximum glucose oxidation rate (see Table 33-1). Exceeding the glucose oxidation or glucose infusion rate results in fat production, a

consequence that may be desired in the short term for some patients, such as very low birth weight preterm neonates.[25] However, excess glucose provision has been associated with hepatic steatosis and should be avoided in long-term PN patients at risk for IFALD.[23,25,26]

Injectable lipid emulsion

The availability of ILE products in the United States has changed over the last several years (see Table 33-3).[27–28] While products containing soybean oil or a combination of safflower and soybean oils used to be all that was available, currently, 5 ILE products are available with 4 different formulations, each with different dosing, clinical, and safety issues. All are approved for use in infants and children except for the olive oil/soybean oil ILE. The 20% products are preferred when infusing ILE with a 2-in-1 PN solution; 30% products should be reserved for use in total nutrient admixtures (TNAs). The 10% pure fish oil ILE is used in infants and children with a history of IFALD. While a gram of fat provides 9 kcal, the caloric content of ILE is slightly greater per gram (2 kcal/mL for 20% ILE products) because of the additional calories from the egg phospholipids (emulsifier) and glycerin. The labeling for ILE products contains a warning about pulmonary fat accumulation and deaths in preterm infants associated with ILE infusion; the infusion rate should be as slow as possible and should not exceed 0.15 g/kg/h.[28–30] Because of their high calcium and phosphorus requirements, the use of TNAs in neonates and infants is not recommended.[20]

TABLE 33-3. Composition and Properties of ILE Products[a]

Category	Component	OO,SO-ILE	SO-ILE	SO-ILE	FO-ILE	SO,MCT,OO,FO-ILE
Source oil (%)	SO FO MCT OO	20 0 0 80	100 0 0 0	100 0 0 0	0 100 0 0	30 15 30 25
Additives	Egg phospholipid (g/100 mL) Glycerin (g/100 mL) α-Tocopherol (mg/100 mL) Sodium oleate (g/100 mL)	1.2 2.25 3.2 0.03	1.2 2.25 0 0	1.2 2.5 0 0.03	1.2 2.5 15–30 0.03	1.2 2.5 16.3–22.5 0.03
ω-3 (%)	Linolenic acid EPA DHA	0.5–4.2 0 0	4–11 0 0	4–11 0 0	1.1 (mean) 13–26 14–27	1.5–3.5 1–3.5 1–3.5
ω-6 (%)	Linoleic acid Arachidonic acid	13.8–22 0	44–62 0	48–58 0	1.5 (mean) 0.2–2	14–25 NR
ω-7 (%)	Palmitoleic acid	0	0	0	4–10	NR
ω-9 (%)	Oleic acid	44.3–79.5	19–30	17–30	4–11	23–35
Saturated fatty acids	Caprylic acid (%) Capric acid (%) Palmitic acid (%) Stearic acid (%) Myristic acid (%) ω-6:ω-3 ratio	0 0 7.6–19.3 0.7–5 0 9:1 208.8 ± 39.4	0 0 7–14 1.4–5.5 0 7:1 422.4 ± 130.5	0 0 9–13 2.5–5 0 7:1 NR	0 0 4–12 0 2–7 1:8 0	13–24 5–15 7–12 1.5–4 NR 2.5:1 142.2 ± 15.3

Category	Component	OO,SO-ILE	SO-ILE	SO-ILE	FO-ILE	SO,MCT,OO,FO-ILE
	Phytosterols (mg/L)					
Energy (kcal/mL)		2	2	2	1.12	2

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentanoic acid; FO-ILE, fish oil ILE (Omegaven [Fresenius Kabi]); ILE, lipid injectable emulsion; NR, not reported; OO,SO-ILE, olive oil, soybean oil ILE (Clinolipid [Baxter Healthcare Corporation]); SO-ILE, soybean oil ILE (Intralipid [Baxter Healthcare Corporation]); Nutrilipid (B. Braun Medical Inc); SO,MCT,OO,FO-ILE, soybean oil, medium-chain triglycerides, olive oil, fish oil ILE (SMOFLipid [Fresenius Kabi]).

[a] Reproduced with permission from the American Society for Parenteral and Enteral Nutrition from Cober MP, Gura KM, Mirtallo JM, et al.[29]

Administration of ILE in pediatric patients presents challenges to clinicians. Since the majority of ILE products are not manufactured in units smaller than 100 mL, they are commonly repackaged into syringes to provide smaller unit volumes (consistent with daily doses of ILE for neonates and infants) via syringe pump technology.[31] While this practice decreases the risk of inadvertent administration of large amounts of ILE to small patients,[32,33] repackaged ILE has resulted in bacterial and fungal contamination during compounding or infusion.[31,34–37] Shorter hang times for repackaged ILE (eg, 12 h) should be considered to decrease the potential for infusing contaminated ILE into small patients.[31,38,39] If two syringes are needed, the unused syringe should be refrigerated until administration time and then brought to room temperature before infusion, for patient comfort. Enough volume of ILE should be dispensed to allow for priming of the intravenous tubing (ie, 10–25 ml depending on infusion set). The use of non-DEHP infusion sets and containers is recommended.[29]

ILE not only supplies a concentrated source of calories but also provides essential fatty acids for cell membrane integrity and brain development. The lower osmolarity of ILE also helps prolong the integrity of peripheral lines. It is crucial to provide infants and children with a minimum amount of pure soybean ILE (0.5–1 g/kg/d) to prevent essential fatty acid deficiency (EFAD).[21,30] Because of the different amounts of oils in each ILE product,

higher ILE doses must be used when administering a mixed oil ILE. While biochemical EFAD has historically been defined as a triene to tetraene ratio ≥ 0.2, with clinical signs and symptoms appearing at ratios ≥ 0.4,[40] individual laboratories may have different criteria for determining deficiency. For example, Mayo Clinical Laboratories has developed a new set of standards for assessing the triene-to-tetraene ratio for various age groups. Clinicians should refer to the individual laboratory's reference ranges for specific essential fatty acids when assessing for EFAD.[29]

Micronutrients

Electrolytes

Close monitoring of electrolyte status is essential. In newborns, the addition of electrolytes to PN may be deferred until the second day of life in some cases. Potassium is generally added once normal kidney status and good urine output are established, and sodium is often added once diuresis begins. In infants at risk for refeeding syndrome, phosphorus may be added on the first day of PN, but the salt form needs to be considered as it is available as both a sodium and potassium salt. Daily adjustments to electrolyte intake are often necessary. The electrolyte requirements of preterm and term infants are generally similar, except for calcium and phosphorus. Prescribing electrolytes as the amount per kilogram per day is recommended in pediatric patients (see Table 33-4).

TABLE 33-4. Parenteral Nutrition Electrolyte and Mineral Dosing Guidelines[a]

Electrolyte	Preterm Neonates	Infants/Children[b]	Adolescents/Children >50 kg
Sodium	2–5 mEq/kg	2–5 mEq/kg	1–2 mEq/kg
Potassium	2–4 mEq/kg	2–4 mEq/kg	1–2 mEq/kg
Calcium	2–4 mEq/kg	0.5–4 mEq/kg	10–20 mEq/d
Phosphorus	1–2 mmol/kg	0.5–2 mmol/kg	10–40 mmol/d
Magnesium	0.3–0.5 mEq/kg	0.3–0.5 mEq/kg	10–30 mEq/d
Acetate Chloride	As needed to maintain acid base-balance		

Adapted from ASPEN Recommendations on Appropriate Parenteral Nutrition Dosing for Neonatal and Pediatric Patients (https://www.nutritioncare.org/PNResources/)

[a] Assumes normal organ function and losses.

[b] For older children in this age range, dosing adjustments may be necessary in response to clinical conditions.

Calcium and phosphorus

The provision of adequate calcium and phosphorus in an optimal ratio is important for bone mineralization in neonates and infants, particularly those born preterm since maximum calcium and phosphorus accretion rates occur over the last 6 weeks of gestation. While solubility limits within PN solutions prohibit the supply of minerals provided in utero during the last trimester (6–7.5 mEq/kg/d calcium and 2.3–2.7 mmol/kg/d phosphorus), providing calcium and phosphorus in a ratio of 1.7 mg calcium to 1 mg phosphorus optimizes bone accretion of both minerals and minimizes urinary losses.[38,41] In neonates at risk for refeeding syndrome, calcium to phosphorus ratios of 1:1 or 1.3:1 have been suggested.[42] When dosing in milliequivalents per kilogram per day and millimoles per kilogram per day for a preterm neonate, this ratio would be consistent with giving 3.5 mEq/kg/d calcium gluconate and 1.4 mmol/kg/d phosphorus (as either sodium or potassium phosphate).

Calcium and phosphorus solubility is enhanced by an acidic solution pH and decreased solution temperature. Solution pH is decreased by using pediatric amino acid products, the addition of cysteine, and higher amino acid and dextrose concentrations. Calcium gluconate is the preferred salt for

use in PN solutions since it is more stable and disassociates less rapidly than calcium chloride. While visual assessment of the solution will detect macroprecipitates, calcium phosphate microprecipitates can form that cannot be seen by the naked eye. To prevent potentially fatal pulmonary emboli from a systemic infusion of calcium phosphate precipitates, the recommendation is to calculate the amount of calcium and phosphate in PN solutions, utilize solubility checks during compounding, and filter PN solutions with a 1.2-micron filter during administration.[43] In addition, the use of TNAs is not recommended in neonates and infants.[29]

Vitamins

Parenteral multivitamin products are available for pediatric patients (<11 years of age) and are dosed based on weight (see Table 33-5).[44–46] In children and adolescents >11 years, the adult parenteral multivitamin product (dose = 10 mL) should be used. While Greene et al[44] explored the need for changes to parenteral vitamin and trace element products in 1988, parenteral multivitamins for infants and children (<11 years of age) have not been reformulated since their inception.[47] ASPEN convened the Novel Nutrient Task Force in 2009 to recommend what changes, if any, were needed in currently available multivitamin and trace elements products.

TABLE 33-5. Dosing Recommendations[a] for Pediatric Parenteral Multivitamins[42–44]

Weight (kg)	Dose (mL)
Manufacturer Recommendations[b]	
<1	1.5
≥1 to <3	3.25
≥3	5
NAG-AMA Recommendations	
<2.5	2 mL/kg
≥2.5	5 mL

Abbreviation: NAG-AMA, Nutrition Advisory Group-American Medical Association.

[a] Assumes normal organ function.

[b] Infuvite Pediatric (Baxter)

Concerning vitamins, the Novel Nutrient Task Force noted the need for potentially increased daily vitamin D supplementation, in addition to daily carnitine and choline supplementation. They also recommended the need for a parenteral choline product (either as a single entity or incorporated into a multivitamin product), as well as a parenteral cholecalciferol or ergocalciferol product (for PN-dependent patients with vitamin D deficiency unresponsive to enteral supplementation).[47]

Trace elements

The Nutrition Advisory Group of the American Medical Association has recommended that 5 trace elements (chromium, copper, manganese, selenium, and zinc) be supplemented in patients receiving PN.[44] Two of these trace elements, chromium and manganese, accumulate in patients receiving prolonged PN.[48–50] Chromium is a contaminant of large- and small-volume parenteral products used in PN compounding; thus, deficiency is rare in PN patients.[47,48] Chromium is eliminated renally and may also accumulate in patients with renal failure[48] If deficiency occurs, it may present as glucose intolerance, hyperlipidemia, peripheral neuropathy, or encephalopathy.[48,51] Manganese is a cofactor for several enzymatic

processes; it is eliminated via the biliary system.[49,52] Like chromium, it has also been reported as a contaminant in PN components.[50] It has also been found to accumulate in patients with or without liver disease receiving long-term PN, which raises concerns about neurotoxicity.[47,49,53] Manganese deficiency in PN patients is not common; deficiency has only been reported in a single child with SBS.[49]

Serious micronutrient deficiencies have been documented when copper, selenium, and zinc have not been supplemented in patients receiving PN; recent reports have surfaced during times of PN product shortages.[44,47,53–60] Copper is an important component for hemoglobin synthesis, neurologic development, and bone and connective tissue function.[54,61] Clinical manifestations of copper deficiency include hypochromic, microcytic anemia that is unresponsive to iron therapy; neutropenia; leukopenia; bone demineralization or osteoporosis; loss of hair and skin pigmentation; and cardiac and nervous system abnormalities.[54,61] Preterm infants may be at greater risk for deficiency.[54,61] Conditions requiring higher copper intake include increased biliary losses due to jejunostomy output or via external biliary drainage and persistent diarrhea or GI fluid losses.[54] Since copper undergoes biliary elimination, it has been withheld from PN in patients with cholestasis; however, cases of copper deficiency have been reported.[57] In patients with cholestasis, it is recommended to reduce supplementation by 50% of the amount typically provided for age, monitor serum copper levels and ceruloplasmin, and adjust supplementation accordingly.[54,62]

Selenium is critical for antioxidant capacity, primarily through glutathione peroxidase, for immune function, and as a cofactor for thyroid hormone production and regulation; needs may be increased with critical illness and thermal injury.[55,63] Selenium deficiency may present as cardiomyopathy (ie, Keshan disease), myalgias, myositis, hemolysis, and impaired cellular immunity.[55,63]

Zinc offers antioxidant properties, has been associated with immune competence and wound healing, and is critical for growth in infants and children.[56,64] In addition, zinc is primarily eliminated via the GI tract and adequate supplementation becomes increasingly more important in patients with excessive fluid losses from wounds, stool, and ostomy output.[56,64]

Patients with severe burn injury have greater zinc needs due to skin losses.[47] Zinc deficiency may result in dermatitis, alopecia, anorexia, growth failure, delayed sexual maturation, reduced taste, poor night vision, immune compromise, and impaired wound healing.[56,64] Some conditions that require additional zinc intake include elevated urinary zinc excretion (eg, high-output renal failure) and increased GI excretion (eg, high-volume stool loss, fistula/stoma losses).

Parenteral multitrace element products that contain zinc, copper, manganese, and selenium are available (see Table 33-6); single-entity products exist for copper, chromium, manganese, molybdenum, selenium, and zinc.[65,66] Dosing of pediatric multitrace element products is problematic in that the weight-based dosage recommendations underestimate the recommended daily intake for some trace elements such as zinc, while intake is excessive for others like manganese that are contaminants in PN solutions and can accumulate in patients receiving long-term PN support (see Table 33-7).

TABLE 33-6. Comparison of Multitrace Element Products[a]

	Multrys	**Tralement**
Manufacturer	American Regent	American Regent
Preservative	None	None
Trace elements (per 1 mL) Zinc, mg Copper, mcg Manganese, mcg Selenium, mcg	 1 60 3 6	 3 300 55 60
Recommended dosage	Pediatric patients weighing 0.4−0.59 kg: 0.2 mL every other day; daily supplementation of zinc, copper, and selenium needed to meet daily requirements	• Adults/pediatric patients weighing at least 50 kg: 1 mL/d • Pediatric patients weighing 10−49 kg: dosage is based on body weight, ranging from 0.2−0.8 mL/d • Pediatric patients weighing 10−49 kg: additional zinc (in heavier patients in some weight bands), copper, and selenium may be required to meet the recommended daily dose

[a] Data from American Regent.[65]

TABLE 33-7. Pediatric Trace Element Requirements[a]

Trace Element	Preterm Neonates <3 kg (mcg/kg/d)	Term Neonates 3–10 kg (mcg/kg/d)	Children 10–40 kg (mcg/kg/d)	Adolescents >40 kg/d
Zinc	500[b]	50–250	50–125	2–5 mg
Copper	40	20	5–20	200–500 mcg
Manganese[b]	1	1	1	40–100 mcg
Chromium[b]	0.05–0.2	0.2	0.14–0.2	5–15 mcg
Selenium[c]	7	2	1.0–2	40–60 mcg

Adapted with permission from the American Society for Parenteral and Enteral Nutrition from Mirtallo J, Canada T, Johnson D, et al.[20]

[a] Assumes normal organ function and losses.

[b] Consider removing from PN since adequate amounts provided through contamination of other additives.

[c] Commercially available multi-trace element products will not meet needs; additional supplementation required with single entity products.

Important trace elements may also be neglected in the currently available products. Iodine, fluoride, and molybdenum are routinely supplemented in multitrace element preparations available outside the United States. Although iodine supplementation is not needed in patients on short-term PN, deficiency may occur in patients receiving chronic therapy especially since topical povidone-iodine is rarely used in dressings anymore.[67] Deficiency of molybdenum has not been reported in pediatrics; however, one adult case of deficiency has been documented.[47]

Revised recommendations for multitrace element products have been made multiple times, primarily advocating for increased selenium, decreased copper and chromium, and decreased or no manganese in commercially available products.[20,53] The ASPEN Novel Nutrient Task Force recommended decreasing manganese to 1 mcg/kg/d in neonates, and no chromium, and the addition of selenium at 2 mcg/kg /d in all pediatric products.[47]

Recently, 2 new trace element products received U.S. Food and Drug Administration (FDA) approval. However, until an optimal multitrace element product is developed, one mechanism for dose-adjusting trace elements based on age-specific or disease-specific needs is to supplement PN solutions with copper, selenium, and zinc using the single-entity products instead of the multitrace element products. Thus, accumulation of chromium and manganese can be avoided. For institutions using multitrace element products, supplemental zinc may be required in certain patients, such as preterm infants and those with increased GI losses. In addition, routine monitoring of copper in patients with cholestasis and of chromium and manganese in all patients is advised.

PN Additives

Medications

Heparin is commonly added to PN solutions to reduce central line–associated bloodstream infections (CLABSIs), catheter thrombus, or central vein thrombosis, as well as to maintain or increase longevity of a peripheral access device.[38,68] In addition, heparin has been proposed to improve lipid clearance by activation of lipoprotein lipase.[17] Typical heparin doses used are 0.5 units or 1 unit per mL PN solution.[17,38,68] Current ASPEN clinical guidelines do not support adding heparin to PN solutions to decrease the risk of central vein thrombosis.[38] Heparin is also a high-alert medication and the Institute for Safe Medication Practices (ISMP) recommends avoiding using heparin as an additive to PN solutions to decrease the potential for adverse events.[69] While heparin is compatible with dextrose/amino acid solutions, its addition to TNAs has been found to destabilize the formulation.[38,70] Other medications that may be added to PN solutions include histamine-2 receptor antagonists (eg, famotidine) and regular human insulin.

Carnitine

Carnitine is responsible for the transport of long-chain fatty acids into the mitochondria for oxidation and energy production.[71] Carnitine may be

considered a conditionally essential nutrient in preterm neonates and infants receiving PN because of the lack of placental carnitine transfer in the third trimester and enzymatic immaturity in the biosynthetic pathway of carnitine from lysine and methionine.[71] Decreased carnitine concentrations have been reported in infants and children on PN without supplemental carnitine.[71] In addition, patients with SBS or other GI conditions affecting absorption may not be carnitine sufficient despite significant enteral intake.[71] Potential benefits of carnitine supplementation include improved fatty acid oxidation, improved lipid tolerance, and positive nitrogen balance and weight gain.[71]

Carnitine is available for supplementation via PN. Recommended doses in PN have ranged from 10 to 20 mg/kg/d[71]; however, a study in preterm neonates receiving 20 mg/kg/d found carnitine concentrations that exceeded the reference range.[72] Lower starting doses of 10 to 15 mg/kg/d and assessing carnitine status periodically in long-term PN patients seems prudent. The ASPEN Novel Nutrient Task Force recommends routine carnitine supplementation of 2 to 5 mg/kg/d to neonatal PN if no enteral source was provided.[47]

Cysteine

Cysteine has been considered a conditionally essential amino acid in neonates and infants because of the enzymatic immaturity of the transsulfuration pathway responsible for the conversion of methionine to cysteine and ultimately to taurine.[73] Cysteine is not a component of crystalline amino acid solutions because it is unstable and will form an insoluble precipitate.[21] Common dosing for L-cysteine hydrochloride is 30 to 40 mg/g of pediatric amino acids; however, 20 mg/g may be adequate.[74] In general, current practice suggests supplementation with L-cysteine hydrochloride for the first year of life, although actual practice varies widely.[20] Riedijk et al[75] have suggested that cysteine requirements are satisfied in 1-month-old preterm infants born at 32 weeks of gestation or older who are on a full enteral diet. In addition, the ASPEN Cysteine Product Shortage Considerations[74] state that cysteine supplementation is not needed under normal feeding and growth situations if patients are

receiving a minimum of 3 g/kg/d protein. It is important to note that a benefit of the addition of L-cysteine hydrochloride to PN is decreased solution pH, which increases the solubility of calcium and phosphorus.

Monitoring

Before initiation of PN support, checking the following biochemical indices is recommended:

- serum electrolytes (sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus)
- serum glucose
- liver function (ie, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase)
- total bilirubin
- conjugated or direct bilirubin
- prealbumin
- albumin
- triglyceride
- renal function (blood urea nitrogen, serum creatinine)
- complete blood count

In addition, weight and height, fluid status, and clinical status should be assessed. Following the initiation of PN, patients require close biochemical monitoring (serum electrolytes, glucose, triglyceride) in addition to assessment of growth (daily for neonates and infants) and clinical status. Monitoring is then slowly decreased in frequency depending on the patient's clinical status and demonstration of stable parameters. In addition to routine comprehensive chemistry, liver function, and complete blood count assessment, patients on long-term PN (such as those with SBS) require continual assessment for growth (weight/height, body mass index at ≥2 y of age) to include plotting on Centers for Disease Control and Prevention/World Health Organization growth charts, and periodic assessment of micronutrient status (iron studies, trace elements, vitamins), carnitine status, thyroid studies, fatty acid panel (if receiving intermittent or low-dose ILE), vitamin D, and bone density (every 5 y). For a more

detailed discussion about monitoring and assessment of PN patients, see Chapter 34, "Evaluation and Monitoring of Pediatric Patients Receiving Specialized Nutrition Support."

Complications

The provision of PN to pediatric patients is associated with unique potential risks and calls for a diligent interprofessional team approach to prevent, monitor for, and manage complications effectively. Initiating EN as soon as medically appropriate is the key to minimizing the potential adverse effects of PN. Complications of PN can be mechanical (eg, issues with infusion devices, PN bags, or administration sets, catheter leaks or breaks, catheter tip migration, or pneumothorax), infectious (CLABSIs), metabolic (eg, hyperglycemia, hypertriglyceridemia, fluid and electrolyte abnormalities, acid-base disorders, IFALD, metabolic bone disease, refeeding syndrome, or EFAD), and nutritional (micronutrient toxicity or deficiency). Many of these complications are discussed in greater detail in other chapters (see Chapter 7, "Water-Soluble Vitamins and Related Compounds," Chapter 8, "Fat-Soluble Vitamins," Chapter 9, "Fluids and Electrolytes," Chapter 24, "Hepatic Disease," Chapter 25, "Intestinal Failure," and Chapter 31, "Nutrition Access"). In addition, trace element (ie, chromium, copper, manganese, selenium, zinc) toxicity and deficiency have been reviewed in the "Micronutrients" section of this chapter. The following sections will focus on the assessment and management of metabolic bone disease, CLABSIs, aluminum toxicity, and iron deficiency.

Metabolic bone disease

Bone disease in patients receiving PN is multifactorial; however, the use of PN and aluminum contamination are predisposing risk factors.[76] Preterm neonates and infants are at the greatest risk because of rapidly growing bone and the inability to provide similar amounts of calcium and phosphorus (either enterally or parenterally) that are provided in utero. Routine assessment for bone disease should include serum calcium and phosphorus and alkaline phosphatase. Normal serum calcium concentrations do not equate with adequate bone mineralization; the body's

homeostatic mechanisms maintain normal serum calcium in the calcium-deprived state via renal calcium conservation, increased intestinal calcium absorption, and utilization of calcium from bone. Metabolic bone disease may present with hypercalcemia or hyperphosphatemia. Other assessment methods include radiographs (often ordered for other purposes) that can be reviewed for signs of demineralization, and parathyroid hormone and vitamin D assessment.

In patients on long-term PN, bone density testing should be conducted periodically. Prevention and management of metabolic bone disease centers around optimizing adequate minerals via PN; decreasing aluminum exposure; supplementing additional calcium, phosphorus, and vitamin D enterally (when indicated); encouraging weight-bearing exercise; and instituting pharmacotherapy when bone disease is unresponsive to additional mineral and vitamin D supplementation. In preterm neonates receiving PN, decreased bone disease was seen with high-dose (75 mg/kg/d [3.74 mEq/kg/d] calcium and 44.1 mg/kg/d [1.42 mM/kg/d] phosphorus) compared with low-dose (45 mg/kg/d [2.25 mEq/kg/d] calcium and 26.5 mg/kg/d [0.85 mM/kg/d] phosphorus) calcium and phosphorus in PN.[77]

Central line-associated bloodstream infections

CLABSIs are a common complication in patients receiving PN. Risk factors include poor central line care, use of the central line for blood draws, bacterial overgrowth, and contamination of the central line with ostomy or stool output. Preventing initial and repeat CLABSIs is important to improve patient morbidity and decrease the risk of developing IFALD. Assessment for CLABSIs is conducted when a patient receiving PN has documented fever; blood cultures are drawn from the periphery and the central line. Systemic antibiotics are initiated empirically after blood cultures are drawn and then adjusted based on microorganism growth and pathogen identification. In patients receiving long-term PN, catheter salvage is desired to preserve access sites; however, this is not always possible. Retention or removal of the catheter is determined by the patient's clinical status, pathogen identified, and type of access device. Antimicrobial lock therapy has offered additional support to the armamentarium of systemic antibiotics in assisting with the clearance of identified pathogens from

catheters, as well as catheter salvage. Lock therapy involves having an antimicrobial agent, typically vancomycin, gentamicin, or ethanol (70% solution), dwell in the catheter for a period of time. Ethanol lock therapy has been found to effectively prevent catheter-related infections in PN patients.[78] ASPEN guidelines suggest using ethanol lock in pediatric intestinal failure patients to prevent CLABSIs and to reduce catheter replacements.[79]

Typical ethanol lock protocols utilize at least once weekly (and up to daily) locks for a minimum period of 2 hours up to the entire period that the patient is cycled off PN. Protocols also differ on whether the ethanol is flushed through or withdrawn after dwell time is complete. Ideally, the ethanol would be flushed through the catheter to avoid coating the catheter with proteins from blood; however, little is known about the effects of chronic ethanol exposure in small patients. Research is needed to determine the best approach for number of days per week, length of dwell time, and whether the ethanol should be instilled or withdrawn.[79] Of note, ethanol is incompatible with heparin. Catheters should be flushed well with normal saline before and after ethanol locks. In addition, ethanol administration with metronidazole can result in a disulfiram-like reaction. Until more information is available about the likelihood of reactions in patients receiving concomitant ethanol lock and metronidazole therapies, withdrawal of ethanol from the catheter in patients on metronidazole is advised.

Aluminum toxicity

Large and small volume parenteral products utilized during PN compounding are commonly contaminated with aluminum, which can be especially dangerous for infants and children. Preterm infants are extremely vulnerable to aluminum toxicity due to immature renal function and the likelihood of long-term PN.[20]

The FDA mandated in 2004 that products used in compounding PN should state the aluminum content at the end of the product's shelf life on the label. The FDA identified 5 mcg/kg/d as the maximum amount of aluminum that can be safely tolerated; amounts exceeding this limit may be associated with central nervous system or bone toxicity.[20] The mandate has

resulted in decreased aluminum contamination in marketed products. While aluminum content can be reduced by using products with the least amount of contamination and using them earlier in their shelf lives, it is still difficult to achieve levels below the recommended maximum limit set by the FDA in pediatric PN.[80–82] Clinicians should attempt to lower aluminum doses by choosing products with the least contamination when feasible and safe for patients. An acceptable substitution would be to use the least contaminated product when multiple manufacturers produce the same product. An unsafe substitution would be to use calcium chloride instead of calcium gluconate. Despite its higher aluminum content, calcium gluconate remains the preferred calcium salt for PN compounding since it is considerably more stable and poses a significantly lower risk for calcium phosphate precipitation.[20,83]

Iron deficiency

Iron is an essential nutrient for numerous body processes (eg, neurotransmitter production, cell replication, and oxidative metabolism). Iron-deficiency anemia is characterized by progressive depletion of iron stores resulting in a microcytic hypochromic anemia.[84] Blood loss (including phlebotomy), iron intake, and erythropoiesis (including erythropoietin use) can influence iron stores. When routine complete blood count monitoring suggests iron-deficiency anemia, assessment of serum ferritin concentrations reveals the body's iron stores. Low serum ferritin concentrations are an accurate reflection of iron deficiency; however, inflammatory states, iron overload, or a recent red blood cell transfusion can result in elevated serum ferritin concentrations. Iron sufficiency can also be determined by measuring the zinc protoporphyrin to heme ratios, which reflect the availability of iron that can be incorporated into the protoporphyrin molecule to form heme. In states of iron deficiency, zinc is incorporated instead. An elevated ratio suggests iron deficiency, although it may also be seen in patients receiving erythropoietin due to the increased erythropoiesis.

Since parenteral multivitamin products do not contain iron, patients on PN must receive an exogenous source of iron to prevent deficiency. Patients who receive frequent blood transfusions will often not require additional

iron because a typical transfusion will provide approximately 3 months' worth of iron.[85] Oral iron is the preferred route of supplementation in patients who can tolerate and absorb enteral therapy; however, parenteral iron supplementation is warranted in patients with severe iron-deficiency anemia who fail to respond to oral therapy. Children with intestinal failure who initially require parenteral iron may eventually be transitioned to enteral iron as their bowel adapts. The oral iron absorption test is used to assess GI iron absorption. A low dose of 5 to 20 mg of elemental iron as ferrous sulfate is given to detect mild iron deficiency.[86] A minimal rise in serum iron will occur in iron-sufficient patients, while a 100 mcg/dL rise in serum iron can be seen within 1 to- 2 hours after administration in patients with iron deficiency.[87]

Parenteral iron preparations include iron dextran, sodium ferric gluconate, iron sucrose, and ferumoxytol. Table 33-8 summarizes dosing, administration, safety, and adverse effects for each of these products.[88–93] Because of anaphylactic and other adverse reactions associated with iron dextran, practitioners have been reluctant to use it. However, a benefit of iron dextran is that it can be given as a total dose infusion (TDI) or as intermittent infusions. While some adverse reactions appear to be dose-related, studies have demonstrated the overall safety and efficacy of larger TDIs.[94–96] These results, along with the convenience and cost-effectiveness of a single infusion, have made TDI the preferred method of administration of iron dextran.

TABLE 33-8. Comparison of Parenteral Iron Products[85–90]

		Iron Dextran (INFeD) LMW	Sodium Ferric Gluconate (Ferrlecit)	Iron Sucrose (Venofer)	Ferumoxytol (Feraheme)
FDA-approved indications	Adults	IDA when oral therapy failed	IDA (HD + EPO)	IDA in CKD (nondialysis ± EPO; dialysis + EPO)	IDA in CKD
	Pediatrics	IDA when oral therapy failed	Children ≥ 6 y: IDA (HD + EPO)	Children ≥ 2 y: IDA in CKD (nondialysis ± EPO; dialysis + EPO)	No
Dosage (replacement)		TDI: dose in milliliters [50 mg/mL] = 0.0442 × LBW [kg] × (desired Hgb − observed Hgb) + (0.26 × LBW [kg]). • Dilute dose in 250–1000 mL NS and infuse over 4–6 h (max rate 50 mg/min) Or • Sequential daily doses up to the total replacement dose as individual, undiluted injections: – Infants < 5 kg: 25 mg – Children 5–10 kg: 50 mg – Children >10 kg and adults: 100 mg (max rate 50 mg/min)		• Adult: cumulative dose of 1000 mg • Nondialysis: 200 mg on 5 different occasions • HD: 100 mg during consecutive dialysis sessions (up to 1000 mg total) • PD: 3 doses, each 14 days apart, totaling 1000 mg (300 mg day 1, 300 mg day 14, 400 mg day 28) • Pediatric: 0.5 mg/kg slow IV injection or infusion	• Adult: 510 mg (17 mL) as a single dose, followed by a second 510 mg dose 3–8 days after initial dose • Recommended doses may be re-administered with persistent or recurrent IDA • Pediatric: no dosing recommendations available
Dosage (maintenance) when enteral not an option	Neonate	• Serum ferritin <40 mg/L: 2 mg/kg, 3 times per wk • Serum ferritin 40–100 mg/L: 2 mg/kg twice per wk • Serum ferritin 100–400 mg/L: 1.5 mg/kg twice per wk; if serum ferritin remains low, increase dose 2 mg/kg/d IV	Contraindicated	• AOP: 1 mg/kg/d infused over 2 h • Serum ferritin <40 mg/L: 2 mg/kg 3 times per wk • Serum ferritin 40–100 mg/L: 2 mg/kg twice per wk • Serum ferritin 100–400 mg/L: 1.5 mg/kg twice per wk; if serum ferritin remains low, increase dose to 2 mg/kg twice per wk	
	Child		• Children ≥ 6 y: 8 doses of 1.5 mg/kg (0.12 mL/kg) repeated at sequential dialysis sessions • Maximum dose: 125 mg/dose	• Children >2 y: 0.5 mg/kg, not to exceed 100 mg per dose, every 2 wk for 12 wk; may be repeated if necessary or • Children ≥ 2 y and adolescents <15 y: 1 mg/kg/dialysis	
	Adult		Adults may receive up to 125 mg (10 mL) per dose during HD to achieve a cumulative dose of 1 g over 8 sequential sessions		

(*continued on next page*)

TABLE 33-8. Comparison of Parenteral Iron Products[85–90] (Continued)

		Iron Dextran (INFeD) LMW	Sodium Ferric Gluconate (Ferrlecit)	Iron Sucrose (Venofer)	Ferumoxytol (Feraheme)
Administration	IV push	Not recommended; infusion preferred	Not recommended; infusion preferred	Yes, 20–0 mg/min or 40–100 mg/min (indication dependent)	Not recommended; infusion preferred
	IV infusion	• See above for TDI • Neonates: Dilute dose in 10 mL D10W and infuse over hours • Intermittent doses: Doses may be injected undiluted at a rate not to exceed 50 mg/min; large or total replacement doses may be diluted and infused over 1–6 h at a maximum rate not to exceed 50 mg/min	125 mg/100mL NS over 1 h	• Preterm neonates: Infusion: Infuse over at least 1–2 h • Infants, children, and adolescents: – For doses ≤100 mg, infuse over at least 30 min – For doses >100 mg and ≤200 mg, infuse over at least 60 min – For doses >200 mg and ≤ 300 mg, infuse over at least 90 min – Doses ≤ 200 mg may be administered undiluted or diluted in a maximum of 100 mL NS – Doses >200 mg should be diluted in a maximum of 250 mL NS – Do not dilute to concentrations <1 mg/mL	No
	IM injection	Yes, ≤ 100 mg by Z-Track technique	No	No	No
Safety	Anaphylaxis warning	Yes (boxed)	Yes	Yes	Yes
	Test dose	Yes, over 30 s followed by 1 h observation Recommended test dose: • Infants <10 kg: 10 mg • Children 10–20 kg: 15 mg • Children >20 kg/adults: 25 mg	No	No	No
	PN compatibility	Yes, non-ILE PN only	No	No	No
Common adverse reactions	CV	Hypotension, flushing, chest pain	Hypotension, chest pain	Hypotension, hypertension, chest pain	Hypotension, hypertension, chest pain
	CNS	Headache, weakness, dizziness	Syncope, dizziness, headache	Headache, dizziness, fatigue	Headache, dizziness
	GI	NVD	NVD	NVD	NVD
	MSK	Arthralgia	Muscle cramps	Muscle cramps	Back pain
	Other	Malaise	Edema	Edema	Edema Hypophosphatemia
Other	Preservative	No	Benzyl alcohol	No	No

Abbreviations: AOP, anemia of prematurity; CKD, chronic kidney disease; CNS, central nervous system; CV, cardiovascular; D10W, 10% dextrose in water; EPO, erythropoietin; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; HD, hemodialysis; Hgb, hemoglobin; IDA, iron-deficiency anemia; ILE, lipid injectable emulsion; IM, intramuscular; IV, intravenous; LMW, low molecular weight; MSK, musculoskeletal; NS, normal saline; NVD, nausea, vomiting, diarrhea; PD, peritoneal dialysis; TDI, total dose infusion.

Life-threatening hypersensitivity reactions are characterized by acute respiratory failure and cardiovascular collapse, including hypotension, bronchospasm, oral or pharyngeal edema, loss of consciousness, severe pain, and muscle spasms. This response appears to be due to both the toxic effects of and the high antigenicity of free dextran molecules, similar to the types of reactions seen with contrast media or opiates.[97] In some cases, the acute onset of chest and back pain or tightness without hypotension, tachypnea, tachycardia, wheezing, stridor, or periorbital edema can occur. The immunologic basis of allergic hypersensitivity to parenteral iron is still not known, although both antibody-mediated and non-antibody-mediated, dose-dependent mechanisms have been observed in patients after an anaphylactic event.[98,99] Based on information in the FDA's adverse events reporting database, adverse events are greatest with iron dextran formulations and less with the newer iron products.[100] Other experts, including representatives from the FDA, have cautioned that it is not possible to conclude the comparative risks from the different iron products using this database.[101,102]

Of the various parenteral iron products, only the iron dextran products carry boxed warnings in the product labeling about the risk for anaphylactic-type reactions. Reports of patients reacting to subsequent doses of iron dextran despite tolerating test doses prompted the expansion of the box warning in September 2009.[103] This modified warning cautioned prescribers that fatal reactions have occurred even after the test dose was tolerated; the reactions may be delayed in onset. The warning also states that patients with a history of drug allergy are more susceptible, especially with large doses. There does not appear to be cross-reactivity between the parenteral iron formulations because large studies have shown that patients who have experienced anaphylactic-type reactions to iron dextran have been subsequently able to tolerate other iron preparations.[104,105] However, the rate of ferric gluconate intolerance was noted to be higher in patients who had a prior history of iron dextran intolerance.[104] Moreover, patients with multiple drug allergies may similarly be at an increased risk of hypersensitivity reactions.[97,106] Anaphylactic reactions are still a risk with the newer parenteral iron products since reports of adverse events have emerged during post-marketing surveillance. When any of the parenteral

iron preparations are being administered, a system should be in place for patient monitoring and emergency equipment, and rescue medications should be readily available.

Hypotension has been reported with the administration of iron sucrose and may be linked to the rate of infusion or total dose given. In comparison with other parenteral iron products, ferumoxytol has negligible free iron release; this may account for the decreased incidence of free iron–like reactions such as GI symptoms and hypotension.[107] Recently, iron-induced hypophosphatemia has emerged as a serious complication associated with parenteral iron.[108] The highest risk for the development of hypophosphatemia appears to be associated with ferric carboxymaltose, iron polymaltose, and saccharated iron oxide. Possible risk factors include renal phosphate wasting mediated by increased fibroblast growth factor 23 that results in hypophosphatemia after iron therapy. Interestingly, impaired renal function may be protective against hypophosphatemia. The most severe and greatest incidence of cases of iron-associated hypophosphatemia has been reported in patients in whom the underlying cause of iron deficiency cannot be corrected.

Iron dextran is the only formulation with extensive compatibility in non-ILE-containing PN. Iron dextran is physically compatible when added to a non-ILE-containing PN at a concentration of 100 mg/L for 18 hours at room temperature or 10 mg/L for 48 hours when the amino acid concentration is ≥ 2%.[109]Adding iron preparations to ILE-containing PN is not recommended because of the potential for coalescence of small lipid particles due to destabilization of negative surface charges by the iron cations. The labeling for iron sucrose warns that the product should not be mixed with other medications, nor should it be added to PN. However, one study found that iron sucrose at concentrations up to 0.25 mg/dL in non–ILE-containing PN (using neonatal amino acid and cysteine doses) was chemically and physically stable for 24 hours.[110] Iron sucrose concentrations ≥ 1 mg/dL are chemically, but not physically, stable and therefore not compatible with PN.[110]

For years, practitioners have been cautious about using parenteral iron in septic patients, citing its potential to fuel bacterial growth. Bacteria require iron to replicate. High intake of parenteral iron can lead to transferrin

oversaturation resulting in the formation of catalytically active iron within 3.5 hours after an intravenous (IV) injection. Given that catalytically active iron can be potentially toxic and may promote bacterial growth, lower doses should be used to prevent transferrin oversaturation.[111] In one pediatric study, the incidence of neonatal sepsis was greater in a group of infants who received intramuscular (IM) iron dextran injections in comparison to those who did not.[112] It was thought that IM iron dextran impaired the immunity of the treated infants, thus making them more susceptible to *Escherichia coli* sepsis. Another prospective, multicenter, cohort-controlled observational trial conducted in dialysis patients suggested there might be a slightly increased risk of bacteremia in patients given high-frequency, high-dose IV iron.[113] Based on these findings, it may be prudent to hold doses of parenteral iron in septic patients, especially those with gram-negative bacteremia, until the sepsis has resolved.

PN Safety

PN is considered a high-alert medication by the ISMP. Ensuring the safe provision of PN within healthcare institutions and at home requires knowledgeable and skilled clinicians involved in the practice of nutrition support and the development and continual review of policies, protocols, and procedures that support practice that minimize errors with PN therapy. The increased incidence of PN product shortages has further affected the safety of the PN process and has negatively impacted patient care.[110] While there have been numerous adverse outcomes related to PN product shortages, the most extreme example resulted in multiple patient deaths associated with contaminated PN solutions that were traced back to amino acids made from powders during an amino acid product shortage.[114] Clinicians must work together to adequately address PN product supply issues and create protocols to manage shortages as well as develop safeguards within the system to prevent patient injury.

The ASPEN PN Safety Consensus Recommendations were published in 2014 to suggest practices that minimize errors throughout the PN process (eg, prescribing, order review/verification, compounding, administration). Recommendations on PN product shortages and home PN support are also

provided.[39,113] Table 33-9 provides a summary of key recommendations from this document.

TABLE 33-9. Recommendations From ASPEN Parenteral Nutrition Safety Consensus[39,111]

General	Prescription	Order review/verification	Labeling
• Clinicians (interprofessional) with expertise in nutrition support, annual competencies • Develop policies and procedures for all parts of PN process • Education to nonnutrition clinicians on policies and procedures • Perform PN process during daylight hours • Avoid distractions • QI programs to report, track, analyze errors in PN process	• Standardized PN order format and review process for all patients within institution • Educate prescribers on PN prescribing and monitoring • Confirm access • Ideally, CPOE with current patient information (eg, laboratory) displayed, clinical decision support, and limits • When CPOE not available, PN should be prescribed using a standardized order template as an editable electronic document (avoid handwritten) • Follow ASPEN guidelines for inclusion on PN order form • Avoid handwritten, verbal, telephone orders • Order in amount per kilogram per day for neonatal and pediatric orders (amount per day for adults) • Order electrolytes as complete salt form • Use full generic names • Abbreviations consistent with ISMP • Include nutrition-related orders • Avoid prescribing with nonnutrient medications • Reorder PN in its entirety	• Order review by skilled and knowledgeable pharmacists • Ideally, CPOE fully integrated with ACD • When CPOE to ACD integration not possible, standardized editable electronic order form • Avoid verbal and telephone orders • Avoid manually transcribing into ACD; if must be done, use pharmacist double-check • Pharmacist double-check after PN transcribed and before compounding • When compounding outsourced, electronically transmit PN orders to avoid transcription errors • Perform clinical review of order, compare order to previous day, double check calculations and conversions • Perform safety review (compatibility, calcium phosphate precipitation risk, stability) • Modifications communicated to prescriber and documented	• Standardized labeling for PN formulations • Follow ASPEN guidelines for inclusion on PN label • Sequence of order templates and PN labels should match

(*continued on next page*)

TABLE 33-9. Recommendations From ASPEN Parenteral Nutrition Safety Consensus[39,111] (Continued)

Compounding	Administration	PN Shortages	Home
• Operate/comply with USP <797> • Consider outsourcing or using standardized, commercially available PN when USP <797> compliance not possible • Conduct in-depth education/training on CSPs and ACD for all staff participating in compounding process with ongoing competency assessment/verification • Certify pharmacy technicians involved in making CSPs/PNs • Have policy/procedures for use of standardized commercially available PNs • Minimize additions outside pharmacy ACD • Use hard/soft limits • Use weight-based limits • Limit access to ACD database • Permit only pharmacists to override alerts; double-check by another pharmacy staff (ideally pharmacist) • Have appropriate additive sequence • Have a checklist for new product entry • Use barcode technology • Have independent double-check process for initial daily ACD setup • Trace tubing sets daily and with each change in source container • Limit manual compounding • If multiple containers used for single additive, present all containers to pharmacist for verification • Verify manual additives by including inspection of actual vials and syringes, not proxy methods (eg, syringe pullback) • Use a verification process: after order entry, before manually injecting into PN, and after PN compounded	• Conduct education and ongoing validation of competency in PN administration • Ensure hand hygiene • Use sterile technique/CVAD care • Inspect PN container/formulation • Verify PN label against PN order • Verify patient identity • Trace administration tubing at initiation and handoff • Double-check process of infusion pump settings before PN infusion • Filter PN • Maintain prescribed rate (double check) • Institute monitoring protocol • Avoid verbal orders • Institute administration safeguards • Have policy and procedure for PN extravasation • Have a protocol for safe operation of infusion pumps • Review compatibility and stability by pharmacist prior to co-infusion of medications with PN • Discontinue inpatient PNs prior to discharge to home or transfer to another facility	• Institute conservation, allocation, and substitution strategies/protocols for PN product shortages • Communicate shortages and management strategies to prescribers and staff • Have processes to evaluate compounding pharmacies and product compounded by compounding pharmacies • Modify PN order/label/ACD software to reflect shortages • Report, track, and evaluate errors associated with shortages • Monitor patients for nutrient deficiencies during product shortages • Seek out other sources of PN components • Develop drug conservation policy on handling and disposition of PN components (while maintaining sterility and integrity)	• Create a home PN process • Create a separate standardized home PN order template and label • Have a standardized pharmacy review and verification process • Ensure that home PN labels and materials are patient-centered, emphasize patient instructions, use simple language, give explicit instructions, include purpose, limit auxiliary information, address limited English proficiency, and improve readability • Do not use home PNs in acute care facilities • Print copy of initial PN order and any changes to patient/caregiver for review with formulation label

Abbreviations: ACD, automated compounding device; ASPEN, American Society for Parenteral and Enteral Nutrition; CPOE, computerized physician order entry; CSP, compounding sterile products; CVAD, central venous access device; ISMP, Institute for Safe Medication Practices; PN, parenteral nutrition; QI, quality improvement; USP, United States Pharmacopeia.

In addition to the consensus recommendations, ASPEN has developed a PN safety toolkit (www.nutritioncare.org/pnsafety) that offers clinicians and institutions the following:

- Safety checklists for prescribing, order review/verification, compounding, and PN administration.
- Materials to improve PN safety within institutions (eg, PN Safety Preparation Checklist, PowerPoint presentation, example order and label templates).
- Current information on PN product shortages.
- Links to educational opportunities on PN safety, related publications, and the PN adverse event reporting program (a collaboration between ASPEN and ISMP).[114]

Photoprotection of PN

When PN is exposed to ambient light, hydrogen peroxide and lipid peroxides are generated.[115] There is an approximate 50% reduction in the amount of hydrogen peroxide generated when the entire PN solution and delivery system (ie, amino acid/dextrose bag, ILE syringe, tubing) is protected from ambient light.[116,117] This interaction was first reported in the early 1980s when it was observed that light exposure might cause vitamin instability, but most practitioners still choose not to cover solutions, especially when adding the multivitamins immediately before infusing.

Multivitamins, however, are not the only component of PN that may be impacted by light. The amino acids tryptophan and tyrosine undergo photo-oxidation to form free radicals with hepatotoxic properties.[118] Other amino acids such as cysteine, histidine, and methionine are also prone to photo-oxidation. By serving as a photosensitizing agent, riboflavin appears to facilitate the photo-oxidation process.[115] ILEs are also negatively impacted by exposure to ambient light. Phototherapy might cause significant peroxidation to ILE, resulting in the formation of cytotoxic triglyceride hydroperoxides.[119] Lipid hydroperoxides have been linked with pulmonary vasoconstriction via interference with endogenous prostaglandin synthesis.[119]

Recently, ASPEN issued recommendations for the use of photoprotection of PN and ILE particularly in infants but recognized that

the limited product availability to ensure complete photoprotection is still a major hindrance.[120]

Home PN Therapy

Many pediatric patients on long-term PN support, particularly those with SBS or intestinal failure, will eventually require home PN therapy. Patients should receive cyclic PN before being considered for home PN discharge. Overnight cyclic PN allows patients time away from infusion pumps during the day to attend school and participate in typical children's activities. The process of discharge on home PN is complex and requires collaboration of the patient and caregivers and the interprofessional treatment care teams from both the discharging institution and the accepting home care company. Institutions should develop discharge policies and procedures for sending patients home on PN support to ensure a smooth and safe transition. The following procedures should be incorporated:

- Initial and follow-up care conferences.
- Home assessment.
- Home PN orders and supplies(eg, include review/verification of home PN order/label).
- Patient and caregiver education/training (eg, PN preparation/additives, CVAD care, infusion pump technology, ethanol lock, monitoring for adverse events, emergency care plans).
- Follow-up after discharge.[121–123]

The ASPEN PN Safety Consensus Recommendations include specific guidance for home PN support.[39] In addition, ASPEN standards have been published for the provision of nutrition support in home care.[123] Home PN patients should ideally be followed in the outpatient setting by an interprofessional team (eg, physician, pharmacist, dietitian, nurse) that will review laboratory results and make changes to PN and other nutrition orders as needed based on clinical status. Long-term monitoring and assessment for PN complications and micronutrient deficiency and toxicity is critical in these patients. For a more detailed discussion, refer to the monitoring recommendations for long-term PN patients reviewed earlier in this chapter

as well as Chapter 34, "Evaluation and Monitoring of Pediatric Patients Receiving Specialized Nutrition Support."

Conclusion

PN remains a therapy in evolution. New technology to help better assess caloric needs has been designed, and nutritional support standards for hospitalized pediatric patients and those on home PN continue to be revised. New products, such as alternative lipid emulsions have addressed the limitations associated with older products and when used properly, can improve patient outcomes. Special populations such as intestinal failure and prematurity are complex. Nutritional support for these children should be achieved by balancing both parenteral and enteral routes while maintaining adequate growth and development. Attempts must be made to deliver a balanced PN solution, avoid catheter-related infections, and prevent the development of hepatic complications. Additional research is needed to improve the composition of pediatric macronutrients and micronutrients.

Test Your Knowledge Questions

1. A 30-week gestation preterm neonate without a risk factor for refeeding syndrome is admitted to the neonatal intensive care unit after delivery. A starter PN solution is ordered to infuse until an individual PN solution can be prescribed and compounded. When considering bone mineralization needs, which of the following represents the optimal ratio of calcium to phosphorus (mg:mg) to provide to this patient?
   A. 1:1
   B. 1.3:1
   C. 1.7:1
   D. 2:1
2. A 3-month-old preterm infant (former 26 weeks gestation) has SBS resulting from NEC. The patient's remaining intestines include an intact duodenum, 50-cm jejunum, and 15-cm proximal ileum in continuity with the colon. The patient has had 2 CLABSIs and enteral feedings are currently only providing 20 kcal/kg/d. The patient also has

evidence of IFALD. A care conference is scheduled to discuss the long-term management of this patient and the potential for discharge home on PN support. Which of the following recommendations would be best to address this patient's recurrent CLABSIs?

A. Ethanol lock therapy
B. Cyclic oral antibiotic therapy
C. Permanent removal of central access
D. Addition of heparin 1 unit per mL PN

3. The nutrition support team is revising its PN ordering procedures to prepare for the implementation of computerized order entry and electronic medical records at their institution. Which of the following is the best way to order nutrients for pediatric PN patients?

A. Amount per day
B. Amount per kg per day
C. Amount per liter
D. Percent concentration

References

1. Corkins MR, Griggs KC, Groh-Wargo S, et al; Task Force on Standards for Nutrition Support: Pediatric Hospitalized Patients; American Society for Parenteral and Enteral Nutrition Board of Directors; American Society for Parenteral and Enteral Nutrition. Standards for nutrition support: pediatric hospitalized patients. *Nutr Clin Pract*. 2013;28:263–276. https://doi.org/10.1177/0884533613475822
2. Hay WW Jr. Strategies for feeding the preterm infant. *Neonatology*. 2008;94:245–254. https://doi.org/10.1159/000151643
3. Ehrenkranz RA. Early, aggressive nutritional management for very low birth weight infants: what is the evidence? *Semin Perinatol*. 2007;31:48–55. https://doi.org/10.1053/j.semperi.2007.02.001
4. Commare CE, Tappenden KA. Development of the infant intestine: implications for nutrition support. *Nutr Clin Pract*. 2007;22:159–173. https://doi.org/10.1177/0115426507022002159

5. Moyses HE, Johnson MJ, Leaf AA, Cornelius VR. Early parenteral nutrition and growth outcomes in preterm infants: a systematic review and meta-analysis. *Am J Clin Nutr*. 2013;97:816–826. https://doi.org/10.3945/ajcn.112.042028
6. Berseth CL. Gastrointestinal motility in the neonate. *Clin Perinatol*. 1996;23:179–190.
7. American Academy of Pediatrics Committee on Nutrition. Nutritional needs of the preterm infant. In: Kleinman RE, ed. *Pediatric Nutrition Handbook*. 6th ed. American Academy of Pediatrics; 2009:79–112.
8. Marin T, Josephson CD, Kosmetatos N, Higgins M, Moore JE. Feeding preterm infants during red blood cell transfusion is associated with a decline in postprandial mesenteric oxygenation. *J Pediatr*. 2014;165:464–471. https://doi.org/10.1016/j.jpeds.2014.05.009
9. Fallon EM, Nehra D, Potemkin AK, et al; American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. A.S.P.E.N. clinical guidelines: nutrition support of neonatal patients at risk for necrotizing enterocolitis. *JPEN J Parenter Enteral Nutr*. 2012;36:506–523. https://doi.org/10.1177/0148607112449651
10. Peterson J, Kerner JA. New advances in the management of children with intestinal failure. *JPEN J Parenter Enteral Nutr*. 2012;36(suppl):36S–42S. https://doi.org/10.1177/0148607111422069
11. Tappenden KA. Intestinal adaptation following resection. *JPEN J Parenter Enteral Nutr*. 2014;38(suppl):23S–31S. https://doi.org/10.1177/0148607114525210
12. Modi BP, Galloway DP, Gura K, et al. ASPEN definitions in pediatric intestinal failure. *JPEN J Parenter Enteral Nutr*. 2022;46(1):42–59. https://doi.org/10.1002/jpen.2232
13. Mehta NM, Compher C; A.S.P.E.N. Board of Directors. A.S.P.E.N. clinical guidelines: nutrition support of the critically ill child. *JPEN J Parenter Enteral Nutr*. 2009;33:260–276. https://doi.org/10.1177/0148607109333114
14. Tutor JD. Chylothorax in infants and children. *Pediatrics*. 2014;133:722–733. https://doi.org/10.1542/peds.2013-2072
15. Pettignano R, Heard M, Hart M, Davis R. Total enteral nutrition versus total parenteral nutrition during pediatric extracorporeal

membrane oxygenation. *Crit Care Med.* 1998;26(2):358–363. https://doi.org/10.1097/00003246-199802000-00041
16. Jaksic T, Hull MA, Modi BP, et al; American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. A.S.P.E.N. clinical guidelines: nutrition support of neonates supported with extracorporeal membrane oxygenation. *JPEN J Parenter Enteral Nutr*. 2010;34:247–253. https://doi.org/10.1177/0148607110369225
17. A.S.P.E.N. Board of Directors and the Clinical Guidelines Taskforce. Administration of specialized nutrition support—issues unique to pediatrics. *JPEN J Parenter Enteral Nutr*. 2002;26:97SA-110SA.
18. A.S.P.E.N. Board of Directors and the Clinical Guidelines Taskforce. Specific guidelines for disease—pediatrics. *JPEN J Parenter Enteral Nutr*. 2002;26:111SA–138SA.
19. A.S.P.E.N. Board of Directors and the Clinical Guidelines Taskforce. Psychiatric disorders: eating disorders. *JPEN J Parenter Enteral Nutr*. 2002;26:94SA–95SA.
20. Mirtallo J, Canada T, Johnson D, et al; Task Force for the Revision of Safe Practices for Parenteral Nutrition. Safe practices for parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2004;28:S39–S70. Published correction appears in *JPEN J Parenter Enteral Nutr*. 2006;30:177. https://doi.org/10.1177/0148607104028006s39
21. American Academy of Pediatrics Committee on Nutrition. Parenteral nutrition. In: Kleinman RE, ed. *Pediatric Nutrition Handbook*. 6th ed. American Academy of Pediatrics; 2009:519–540.
22. A.S.P.E.N. Board of Directors and the Clinical Guidelines Taskforce. Normal requirements—pediatrics. *JPEN J Parenter Enteral Nutr*. 2002;26:25SA–32SA.
23. Bresson JL, Narcy P, Putet G, Ricour C, Sachs C, Rey J. Energy substrate utilization in infants receiving total parenteral nutrition with different glucose to fat ratios. *Pediatr Res*. 1989;25:645–648. https://doi.org/10.1203/00006450-198906000-00018
24. Wright K, Ernst KD, Gaylord MS, Dawson JP, Burnette TM. Increased incidence of parenteral nutrition-associated cholestasis with Aminosyn PF compared to Trophamine. *J Perinatol*. 2003;23(6):444–450. https://doi.org/10.1038/sj.jp.7210965

25. Shulman RJ, Phillips S. Parenteral nutrition in infants and children. *J Pediatr Gastroenterol Nutr*. 2003;36:587–607. https://doi.org/10.1097/00005176-200305000-00002
26. Cole CR, Kocoshis SA. Management of infants with short bowel syndrome and intestinal failure. *Nutr Clin Pract*. 2013;28:421–428. https://doi.org/10.1177/0884533613491787
27. Vanek VW, Seidner DL, Allen P, et al; Novel Nutrient Task Force, Intravenous Fat Emulsions Workgroup and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. A.S.P.E.N. position paper: clinical role for alternative intravenous fat emulsions. *Nutr Clin Pract*. 2012;27:150–192. https://doi.org/10.1177/0884533612439896
28. Intralipid [package insert]. Fresenius Kabi (manufactured for Baxter Healthcare Corporation); 2012.
29. Cober MP, Gura KM, Mirtallo JM, et al. ASPEN lipid injectable emulsion safety recommendations part 2: neonate and pediatric considerations. *Nutr Clin Pract*. 2021;36(6):1106–1125. https://doi.org/10.1002/ncp.10778
30. Kerner JA, Poole RL. The use of IV fat in neonates. *Nutr Clin Pract*. 2006;21:374–380. https://doi.org/10.1177/0115426506021004374
31. Crill CM, Hak EB, Robinson LA, Helms RA. Evaluation of microbial contamination associated with different preparation methods for neonatal intravenous fat emulsion infusion. *Am J Health Syst Pharm*. 2010;67(11):914–918. https://doi.org/10.2146/ajhp090199
32. Chuo J, Lambert G, Hicks RW. Intralipid medication errors in the neonatal intensive care unit. *Jt Comm J Qual Patient Saf*. 2007;33:104–111. https://doi.org/10.1016/s1553-7250(07)33012-2
33. Hicks RW, Becker SC, Chuo J. A summary of NICU fat emulsion medication errors and nursing services. Data from MEDMARX. *Adv Neonatal Care*. 2007;7:299–310. https://doi.org/10.1097/01.anc.0000304969.23837.95
34. McKee KT Jr, Melly MA, Greene HL, Schaffner W. Gram-negative bacillary sepsis associated with use of lipid emulsion in parenteral nutrition. *Am J Dis Child*. 1979;133:649–650. https://doi.org/10.1001/archpedi.1979.02130060089023

35. Jarvis WR, Highsmith AK, Allen JR, Haley RW. Polymicrobial bacteremia associated with lipid emulsion in a neonatal intensive care unit. *Pediatr Infect Dis*. 1983;2:203–208. https://doi.org/10.1097/00006454-198305000-00006
36. de Beaufort AJ, Bernards AT, Dijkshoorn L, van Boven CPA. *Acinetobacter junii* causes life-threatening sepsis in preterm infants. *Acta Paediatr*. 1999;88:772–775. https://doi.org/10.1080/08035259950169080
37. Reiter PD. Sterility of intravenous fat emulsion in plastic syringes. *Am J Health Syst Pharm*. 2002;598:1857–1859. https://doi.org/10.1093/ajhp/59.19.1857
38. Boullata JI, Gilbert K, Sacks G, et al; American Society for Parenteral and Enteral Nutrition. A.S.P.E.N. clinical guidelines: parenteral nutrition ordering, order review, compounding, labeling, and dispensing. *JPEN J Parenter Enteral Nutr*. 2014;38:334–377. https://doi.org/10.1177/0148607114521833
39. Ayers P, Adams S, Boullata J, et al; American Society for Parenteral and Enteral Nutrition. A.S.P.E.N. parenteral nutrition safety consensus recommendations. *JPEN J Parenter Enteral Nutr*. 2014;38:296–333. https://doi.org/10.1177/0148607113511992
40. Chessman KH, Kumpf VJ. Assessment of nutrition status and nutrition requirements. In: Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy. A Pathophysiologic Approach*. 9th ed. McGraw-Hill; 2014:2385–2404.
41. Pelegano JF, Rowe JC, Carey DE, et al. Effect of calcium/phosphorus ratio on mineral retention in parenterally fed premature infants. *J Pediatr Gastroenterol Nutr*. 1991;12:351–355. https://doi.org/10.1097/00005176-199104000-00011
42. Bradford CV, Cober MP, Miller JL. Refeeding syndrome in the neonatal intensive care unit. *J Pediatr Pharmacol Ther*. 2021;26(8):771–782. https://doi.org/10.5863/1551-6776-26.8.771
43. Worthington P, Gura KM, Kraft MD, et al. Update on the use of filters for parenteral nutrition: an ASPEN position paper. *Nutr Clin Pract*. 2021;36(1):29–39. https://doi.org/10.1002/ncp.10587
44. Greene HL, Hambidge M, Schanler R, Tsang R. Guidelines for the use of vitamins, trace elements, calcium, magnesium, and phosphorus in

infant and children receiving total parenteral nutrition: report of the Subcommittee on Pediatric Parenteral Nutrient Requirements from the Committee on Clinical Practice Issues of the American Society for Clinical Nutrition. *Am J Clin Nutr*. 1988:48:1324–1342. https://doi.org/10.1093/ajcn/48.5.1324

45. Infuvite Pediatric [package insert]. Sandoz Canada (distributed by Baxter Healthcare Corporation); 2007.
46. MVI-Pediatric [package insert]. Hospira, Inc.; 2007.
47. Vanek VW, Borum P, Buchman A, et al; Novel Nutrient Task Force, Parenteral Multi-Vitamin and Multi–Trace Element Working Group; American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. A.S.P.E.N. position paper: recommendations for changes in commercially available parenteral multivitamin and multi-trace element products. *Nutr Clin Pract*. 2012;27:440–491. https://doi.org/10.1177/0884533612446706
48. Moukarzel A. Chromium in parenteral nutrition: too little or too much? *Gastroenterology*. 2009;137(suppl 5):S18–S28. https://doi.org/10.1053/j.gastro.2009.08.048
49. Hardy G. Manganese in parenteral nutrition: who, when, and why should we supplement? *Gastroenterology*. 2009;137(suppl 5):S29–S35. https://doi.org/10.1053/j.gastro.2009.08.011
50. Srikrishnaraj A, Chambers K, South C, et al. Trace elements' contamination of pediatric parenteral nutrition solutions in Canada: a cause for concern. *JPEN J Parenter Enteral Nutr*. 2021;45(2):347–356. https://doi.org/10.1002/jpen.1836
51. Solomons NW. Chromium. In: Baumgartner TG, ed. *Clinical Guide to Parenteral Micronutrition*. 3rd ed. Fujisawa, USA, Inc; 1997:327–339.
52. Solomons NW. Manganese. In: Baumgartner TG, ed. *Clinical Guide to Parenteral Micronutrition*. 3rd ed. Fujisawa, USA, Inc.; 1997:341–350.
53. Buchman AL, Howard LJ, Guenter P, et al. Micronutrients in parenteral nutrition: too little or too much? The past, present, and recommendations for the future. *Gastroenterology*. 2009;137(suppl 5):S1–S6. https://doi.org/10.1053/j.gastro.2009.09.001

54. Shike M. Copper in parenteral nutrition. *Gastroenterology*. 2009;137(suppl 5):S13–S17. https://doi.org/10.1053/j.gastro.2009.08.017
55. Shenkin A. Selenium in intravenous nutrition. *Gastroenterology*. 2009;137(suppl 5):S61–S69. https://doi.org/10.1053/j.gastro.2009.07.071
56. Jeejeebhoy K. Zinc: an essential trace element for parenteral nutrition. *Gastroenterology*. 2009;137(suppl 5);S7–S12. https://doi.org/10.1053/j.gastro.2009.08.014
57. Hurwitz M, Garcia MG, Poole RL, Kerner JA. Copper deficiency during parenteral nutrition: a report of four pediatric cases. *Nutr Clin Pract*. 2004;19:305–308. https://doi.org/10.1177/0115426504019003305
58. Pramyothin P, Kim DW, Young LS, et al. Anemia and leucopenia in a long-term parenteral nutrition patient during a shortage of parenteral trace element products in the United States. *JPEN J Parenter Enteral Nutr*. 2013;37(3):425–429. https://doi.org/10.1177/0148607112463942
59. Oguri T, Hattori M, Yamawaki T, et al. Neurological deficits in a patient with selenium deficiency due to long-term total parenteral nutrition. *J Neurol*. 2012;259:1734–1735. https://doi.org/10.1007/s00415-012-6427-4
60. Centers for Disease Control and Prevention. Notes from the field: zinc deficiency dermatitis in cholestatic extremely premature infants after a nationwide shortage of injectable zinc—Washington, DC, December 2012. *MMWR Morb Mortal Wkly Rep*. 2013;62:136–137.
61. Solomons NW. Copper. In: Baumgartner TG, ed. *Clinical Guide to Parenteral Micronutrition*. 3rd ed. Fujisawa, USA, Inc; 1997:311–322.
62. Corkins MR, Martin VA, Szeszycki. Copper levels in cholestatic infants on parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2013;37:92–96. https://doi.org/10.1177/0148607112443069
63. Nichoalds GE. Selenium. In: Baumgartner TG, ed. *Clinical Guide to Parenteral Micronutrition*. 3rd ed. Fujisawa, USA, Inc.; 1997:387–400.

64. Solomons NW. Zinc. In: Baumgartner TG, ed. *Clinical Guide to Parenteral Micronutrition*. 3rd ed. Fujisawa, USA, Inc.; 1997:293–307.
65. American Regent. Our Products. Multrys. Accessed September 2, 2022. https://americanregent.com/our-products/
66. American Society for Parenteral and Enteral Nutrition. Parenteral Nutrition Trace Element Product Shortage Considerations. Accessed September 2, 2022. https://www.nutritioncare.org/News/General_News/Parenteral_Nutrition_Trace_Element_Product_Shortage_Considerations/
67. Zimmermann MB, Crill CM. Iodine in enteral and parenteral nutrition. *Best Pract Res Clin Endocrinol Metab*. 2010;24:143–158. https://doi.org/10.1016/j.beem.2009.09.003
68. Kerner JA Jr, Garcia-Careaga MG, Fisher AA, Poole RL. Treatment of catheter occlusion in pediatric patients. *JPEN J Parenter Enteral Nutr*. 2006;30:S73–S81. https://doi.org/10.1177/01486071060300s1s73
69. Institute for Safe Medication Practices. Action needed to prevent dangerous heparin–insulin confusion. ISMP Medication Safety Alert. Institute for Safe Medication Practices. May 3, 2007. https://www.ismp.org/resources/action-needed-prevent-dangerous-heparin-insulin-confusion
70. Johnson OL, Washington C, Davis SS, Schaupp K. The destabilization of parenteral feeding emulsions by heparin. *Int J Pharm*. 1989;53:237–240. https://doi.org/10.1016/0378-5173(89)90317-7
71. Crill CM, Helms RA. The use of carnitine in pediatric nutrition. *Nutr Clin Pract*. 2007;22:204–213. https://doi.org/10.1177/0115426507022002204
72. Crill CM, Storm MC, Christensen ML, Hankins CT, Jenkins MB, Helms RA. Carnitine supplementation in premature neonates: effect on plasma and red blood cell total carnitine concentrations, nutrition parameters and morbidity. *Clin Nutr*. 2006;25:886–896. https://doi.org/10.1016/j.clnu.2006.05.002
73. Helms RA, Chesney RW, Storm MC. Sulfur amino acid metabolism in infants on parenteral nutrition. *Clin Nutr*. 1995;14:381–387. https://doi.org/10.1016/s0261-5614(95)80056-5

74. American Society for Parenteral and Enteral Nutrition. Parenteral nutrition cysteine product shortage considerations, September 2011. Accessed September 2, 2022. https://www.nutritioncare.org/News/General_News/A_S_P_E_N__Releases_New_Parenteral_Nutrition_L-Cysteine_Product_Shortage_Considerations/
75. Riedijk MA, van Beek RHT, Voortman G, de Bie HMA, Dassel ACM, van Goudoever JB. Cysteine: a conditionally essential amino acid in low-birth-weight preterm infants? *Am J Clin Nutr*. 2007;86:1120–1125. https://doi.org/10.1093/ajcn/86.4.1120
76. Nehra D, Carlson SJ, Fallon EM, et al; American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. A.S.P.E.N. clinical guidelines: nutrition support of neonatal patients at risk for metabolic bone disease. *JPEN J Parenter Enteral Nutr*. 2013;37:570–598. https://doi.org/10.1177/0148607113487216
77. Pereira-da-Silva L, Costa A, Pereira L, et al. Early high calcium and phosphorus intake by parenteral nutrition prevents short-term bone strength decline in preterm infants. *J Pediatr Gastroenterol Nutr*. 2011;52(2):203–209. https://doi.org/10.1097/mpg.0b013e3181f8b295
78. Oliveira C, Nasr A, Brindle M, Wales PW. Ethanol locks to prevent catheter-related bloodstream infections in parenteral nutrition: a meta-analysis. *Pediatrics*. 2012;129:318–329. https://doi.org/10.1542/peds.2011-1602
79. Wales PW, Allen N, Worthington P, et al; American Society for Parenteral and Enteral Nutrition. A.S.P.E.N. clinical guidelines: support of pediatric patients with intestinal failure at risk of parenteral nutrition-associated liver disease. *JPEN J Parenter Enteral Nutr*. 2014;38(5):538–557. https://doi.org/10.1177/0148607114527772
80. Poole RL, Pieroni KP, Gaskari S, et al. Aluminum exposure in neonatal patients using the least contaminated parenteral nutrition solution products. *Nutrients*. 2012;4:1566–1574. https://doi.org/10.3390/nu4111566
81. Poole RL, Pieroni KP, Gaskari S, et al. Aluminum in pediatric parenteral nutrition products: measured versus labeled content. *J Pediatr Pharmacol Ther*. 2011;16:92–97. https://doi.org/10.5863/1551-6776-16.2.92

82. Speerhas RA, Seidner DL. Measure versus estimated aluminum content of parenteral nutrient solutions. *Am J Health Syst Pharm*. 2007;64:740–746. https://doi.org/10.2146/ajhp060468
83. Driscoll DF, Newton DW, Bistrian BR. Potential hazards of precipitation associated with calcium chloride in parenteral nutrition admixtures: response to Migaki et al. *JPEN J Parenter Enteral Nutr*. 2012;36(5):497–498. https://doi.org/10.1177/0148607112455064
84. Clark S.F. Iron deficiency anemia. *Nutr Clin Pract*. 2008;23:128–141. https://doi.org/10.1177/0884533608314536
85. Muñoz M, Breymann C, García-Erce JA, et al. Efficacy and safety of intravenous iron therapy as an alternative/adjunct to allogeneic blood transfusion. *Vox Sang*. 2008;94(3):172–183. https://doi.org/10.1111/j.1423-0410.2007.01014.x
86. Crosby WH, O'Neil-Cutting MA. A small-dose iron tolerance test as an indicator of mild iron deficiency. *JAMA*. 1984;251(15):1986–1987. https://doi.org/10.1001/jama.1984.03340390040026
87. Josephs HW. Absorption of iron as a problem in human physiology; a critical review. *Blood*. 1958;13(1):1–54. https://doi.org/10.1182/blood.V13.1.1.1
88. INFeD (iron dextran) injection [package insert]. Watson Pharma, Inc.; 2009.
89. Venofer (iron sucrose) injection [package insert]. American Regent Inc.; 2008.
90. Ferrlecit (sodium ferric gluconate) injection [package insert]. Sanofi-Aventis US LLC; 2014.
91. Feraheme (ferumoxytol) injection [package insert]. AMAG Pharmaceuticals; 2009.
92. Ohls RK, Ehrenkranz RA, Wright LL, et al. Effects of early erythropoietin therapy on the transfusion requirements of preterm infants below 1250 grams birth weight: a multicenter, randomized, controlled trial. *Pediatrics*. 2001;108(4):934–942. https://doi.org/10.1542/peds.108.4.934
93. Mamula P, Piccoli DA, Peck SN, et al. Total dose intravenous infusion of iron dextran for iron-deficiency anemia in children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*.

2002;34:286–290. https://doi.org/10.1097/00005176-200203000-00011
94. Auerbach M, Witt D, Toler W, et al. Clinical use of the total dose intravenous infusion of iron dextran. *J Lab Clin Med*. 1988;111:566–570.
95. Halpin TC Jr, Bertino JS, Rothstein FC, et al. Iron-deficiency anemia in childhood inflammatory bowel disease: treatment with intravenous iron-dextran. *JPEN J Parenter Enteral Nutr*. 1982;6:9–11. https://doi.org/10.1177/0148607182006001096. Fishbane S, Kowalski EA. The comparative safety of intravenous iron dextran, iron saccharate, and sodium ferric gluconate. *Semin Dialysis*. 2000;13:381–384. https://doi.org/10.1046/j.1525-139x.2000.00104.x
97. Monaghan MS, Glasco G, St John G, Bradsher RW, Olsen KM. Safe administration of iron dextran to a patient who reacted to the test dose. *South Med J*. 1994;87:1010–1012. https://doi.org/10.1097/00007611-199410000-00011
98. Novey HS, Pahl M, Haydik I, Vaziri ND. Immunologic studies of anaphylaxis to iron dextran in patients on renal dialysis. *Ann Allergy*. 1994;72:224–228.
99. Bailie GR. Comparison of rates of reported adverse events associated with IV iron products in the United States. *Am J Health Syst Pharm*. 2012;69:310–320. https://doi.org/10.2146/ajhp110262
100. Wysowski DK, Swartz LB, Borders-Hemphill BV, et al. Use of parenteral iron products and serious anaphylactic-type reactions. *Am J Hematol*. 2010;85:650–654. https://doi.org/10.1002/ajh.21794
101. Auerbach M, Kane RC. Caution in making inferences from FDA's adverse event reporting system. *Am J Health Syst Pharm*. 2012;69:922–923. https://doi.org/10.2146/ajhp120138
102. Coyne DW, Adkinson NF, Nissenson AR, et al. Sodium ferric gluconate complex in hemodialysis patients. II. Adverse reactions in iron dextran-sensitive and dextran-tolerant patients. *Kidney Int*. 2003;63:217–224. https://doi.org/10.1046/j.1523-1755.2003.00703.x
103. Van Wyck DB, Danielson BG, Aronoff GR. Safety and efficacy of iron sucrose in patients sensitive to iron dextran: North American clinical trial. *Am J Kidney Dis*. 2000;36:88–97. https://doi.org/10.1053/ajkd.2000.8276

104. Silverstein SB, Rodgers GM. Parenteral iron therapy options. *Am J Hematol*. 2004;76:74–78. https://doi.org/10.1002/ajh.20056
105. Balakrishnan VS, Rao M, Kausz AT, et al. Physicochemical properties of ferumoxytol, a new intravenous iron preparation. *Eur J Clin Invest*. 2009;39(6):489–496. https://doi.org/10.1111/j.1365-2362.2009.02130.x
106. Mayhew SL, Quick MW. Compatibility of iron dextran with neonatal parenteral nutrient solutions. *Am J Health Syst Pharm*. 1997;54:570–571. https://doi.org/10.1093/ajhp/54.5.570
107. MacKay M, Rusho W, Jackson D, McMillin G, Winther B. Physical and chemical stability of iron sucrose in parenteral nutrition. *Nutr Clin Pract*. 2009;24:733–737. https://doi.org/10.1177/0884533609351528
108. Zoller H, Schaefer B, Glodny B. Iron-induced hypophosphatemia: an emerging complication. *Curr Opin Nephrol Hypertens*. 2017;26(4):266–275. https://doi.org/10.1097/mnh.0000000000000329
109. Parkkinen J, von Bonsdorff L, Peltonen S, et al. Catalytically active iron and bacterial growth in serum of haemodialysis patients after i.v. iron-saccharate administration. *Nephrol Dial Transplant*. 2000;15:1827–1834. https://doi.org/10.1093/ndt/15.11.1827
110. Barry DM, Reeve AW. Increased incidence of gram-negative neonatal sepsis with intramuscular iron administration. *Pediatrics*. 1977;60(6):908–912. https://doi.org/10.1542/peds.60.6.908
111. Hoen B, Paul-Dauphin A, Kessler M. Intravenous iron administration does not significantly increase the risk of bacteremia in chronic hemodialysis patients. *Clin Nephrol*. 2002;57:457–461. https://doi.org/10.5414/cnp57457
112. Holcombe B. Parenteral nutrition product shortages: impact on safety. *JPEN J Parenter Enteral Nutr*. 2012;36(2 suppl):44S–47S. https://doi.org/10.1177/0148607111434777
113. Ayers P, Adams S, Boullata J, et al. A.S.P.E.N. parenteral nutrition safety consensus recommendations: translation into practice. *Nutr Clin Pract*. 2014;29(3):277–282. https://doi.org/10.1177/0884533614531294
114. American Society for Parenteral and Enteral Nutrition. Parenteral nutrition resources. Accessed September 2, 2022.

http://www.nutritioncare.org/Guidelines_and_Clinical_Resources/Parenteral_Nutrition_Resources/
115. Laborie S, Lavoie JC, Chessex P. Paradoxical role of ascorbic acid and riboflavin in solutions of total parenteral nutrition: implication in photoinduced peroxide generation. *Pediatr Res.* 1998;43(5):601–606. https://doi.org/10.1203/00006450-199805000-00007
116. Lavoie JC, Bélanger S, Spalinger M, Chessex P. Admixture of a multivitamin preparation to parenteral nutrition: the major contributor to in vitro generation of peroxides. *Pediatrics.* 1997;99(3):E6. https://doi.org/10.1542/peds.99.3.e6
117. Shattuck KE, Bhatia J, Grinnell C, Rassin DK. The effects of light exposure on the in vitro hepatic response to an amino acid-vitamin solution. *JPEN J Parenter Enteral Nutr*. 1995;19(5):398–402. https://doi.org/10.1177/0148607195019005398
119. ???Bhatia J, Moslen MT, Kaphalia L, Rassin DK. Glutathione and tissue amino acid responses to light-exposed parenteral nutrients. *Toxicol Lett*. 1992;63(1):79–89. https://doi.org/10.1016/0378-4274(92)90110-6.
119. Neuzil J, Darlow BA, Inder TE, et al. Oxidation of parenteral lipid emulsion by ambient and phototherapy lights: potential toxicity of routine parenteral feeding. *J Pediatr.* 1995;126(5 Pt 1):785–790. https://doi.org/10.1016/s0022-3476(95)70412-4
120. Robinson DT, Ayers P, Fleming B, et al. Recommendations for photoprotection of parenteral nutrition for premature infants: An ASPEN position paper. *Nutr Clin Pract.* 2021;36(5):927–941. https://doi.org/10.1002/ncp.10747
121. Norman JL, Crill CM. Optimizing the transition to home parenteral nutrition in pediatric patients. *Nutr Clin Pract*. 2011;26:273–285. https://doi.org/10.1177/0884533611405797
122. Kumpf VJ, Tillman EM. Home parenteral nutrition: safe transition from hospital to home. *Nutr Clin Pract.* 2012;27:749–757. https://doi.org/10.1177/0884533612464888
123. Durfee SM, Adams SC, Arthur E, et al; Home and Alternate Care Standards Task Force; American Society for Parenteral and Enteral Nutrition. A.S.P.E.N. standards for nutrition support: home and alternate site care [published online ahead of print June 25, 2014].

Nutr Clin Pract. 2014;29(4):542–555.
https://doi.org/10.1177/0884533614539017

Test Your Knowledge Answers

1. The correct answer is **C**. The provision of adequate calcium and phosphorus in an optimal ratio is important for bone mineralization in neonates and infants, particularly those born preterm since maximum calcium and phosphorus accretion rates occur over the last 6 weeks of gestation. Providing calcium and phosphorus in a ratio of 1.7 mg calcium to 1 mg phosphorus optimizes bone accretion of both minerals and minimizes urinary losses.
2. The correct answer is **A**. Ethanol lock therapy is effective in the prevention of catheter-related infections in PN patients. ASPEN guidelines suggest using ethanol lock in pediatric intestinal failure patients to prevent CLABSIs and reduce catheter replacements. Cyclic oral antibiotics may be appropriate for patients with bacterial overgrowth. While catheters must be removed occasionally because of infection, the goal in patients with SBS is catheter retention to preserve long-term access sites. While heparin has been added to PN solutions to reduce CLABSIs, recent ASPEN clinical guidelines and ISMP recommendations do not support indication.
3. The correct answer is **B**. According to the ASPEN PN Safety Consensus Recommendations, PN ingredients for pediatric and neonatal patients shall be ordered in amount per kilogram per day. In adult patients, PN ingredients shall be ordered as amount per day. It is not recommended to order ingredients as amount per liter, percent concentration, or volume.

The authors of this chapter wish to thank Liesje Nieman Carney, RD, CNSD, LDN; Andrea Nepa, MS, RD, CSP, LDN; Sherri Shubin Cohen, MD, MPH; Amy Dean, MPH, RD, LDN; Colleen Yanni, MS, RD, LDN; and Goldie Markowitz, MSN, CRNP, for their contributions to previous editions of this text.

34

Evaluation and Monitoring of Pediatric Patients Receiving Specialized Nutrition Support

Elaina Szeszycki, PharmD, CNSC; Wendy Cruse, MMSc, RDN, CSPCC; and Clare McLaughlin, RDN, CSPCC

Learning Objectives

1. Select patient-specific objective and subjective criteria to develop and reassess nutritional goals.
2. Demonstrate gastrointestinal tolerance of enteral nutrition based on defined monitored parameters.
3. Demonstrate tolerance to parenteral nutrition based on defined monitored parameters.
4. Discriminate the appropriateness of parenteral nutrition solutions related to final solubility and stability.
5. Choose the laboratory monitoring required for patients receiving specialized nutrition support.

Introduction

Nutrition therapy is a component of medical treatment that includes oral, enteral, and parenteral nutrition. Management of pediatric patients receiving nutrition support is complex and requires continuous monitoring of tolerance and the efficacy of the nutrition interventions. The nutrition care plan must consist of both short-term and long-term nutrition goals. Monitoring parameters are established based on the patient's timely nutrition screens and assessment of initial nutrition status and route of nutrition therapy.[1,2] The monitoring is a continuous assessment of the results of the nutrition plan. These parameters are then used to determine if the patient-specific goals are being met and whether the goals and nutrition care plan need to be reformulated.

Nutrition Monitoring and Evaluation

Complications associated with the delivery of enteral nutrition (EN) and parenteral nutrition (PN) may be prevented or reduced with monitoring and timely formula adjustments based on the patient's growth and tolerance to nutrition therapy. The development of enteral and parenteral monitoring guidelines is critical to ensure all parameters are being assessed and should be included in each individualized nutrition care plan.[1–4] Institutions should follow individualized monitoring guidelines for inpatients and outpatients based on their respective patient populations. The nutrition care plan is determined based on the patient's baseline nutrition status, need for correction of nutritional deficiencies, and achievement of optimal growth.[1–4] See Chapter 30, "Assessment of Nutrition Status by Age and Determining Nutrient Needs" for nutrition assessment guidelines. Monitoring parameters are also based on nutrition goals set in the nutrition care plan, specific disease processes, clinical status, and patient tolerance.[1–4]

Nutrition monitoring includes the patient's growth, fluid status, physical assessment, clinical status, tolerance to EN and PN, medication changes, and laboratory values. The frequency of monitoring depends on the age, severity of illness, tolerance of specialized nutrition support (SNS), comorbid diseases, and degree of malnutrition.[1] Preterm neonates, infants,

patients who are critically ill, and children who are severely malnourished at risk for refeeding syndrome and during transition periods between PN, EN, and oral diet, may require more frequent monitoring as discussed later in the chapter. Indirect calorimetry may be used to more precisely determine a patient's calorie needs, especially in critically ill patients.[2,5,6]

Children's baseline and serial anthropometric measurements are monitored closely. Weight-for-age, length-for-age, and head circumference-for-age should be plotted on a preterm growth chart for preterm infants.[7] Weight-for-age, length-for-age, weight-for-length, and head circumference-for-age should be plotted on the World Health Organization Birth to 24 Months Growth Chart for term infants and preterm infants correcting to >40 weeks postmenstrual age. Weight-for-age, height-for-age, and body mass index-for-age (BMI) should be plotted on the Centers for Disease Control and Prevention (CDC) 2 to 20 Years Growth Charts.[1,6,8]

Mid-upper arm circumference-for-age *z* score (MUAC) can be used to diagnose malnutrition as a single data point for children ages 2 months to 18 years.[8,9] Baseline and serial skinfold thickness and MUAC may be used to assess a patient's lean body mass and fat mass, especially in patients with edema or ascites.[6] In addition to growth curve percentiles, *z* scores should also be used because they are more sensitive and provide a more exact identification of growth deviation, especially when growth parameters plot >97th percentile and <3rd percentile. Both are used to determine nutritional status, adequacy of nutrition support, and nutrition goals.[6] See Chapter 30, "Assessment of Nutrition Status by Age and Determining Nutrient Needs" for details regarding growth assessment and monitoring.

Refeeding Syndrome

When any form of nutrition support is initiated in a child who is malnourished, careful monitoring must occur to avoid refeeding syndrome (RS).[10–14] RS is covered in depth in Chapter 17, "Eating Disorders."

Monitoring Adequacy of Calorie and Protein Delivery

It is essential to avoid providing excess or suboptimal energy and protein to children receiving EN and/or PN because they are not utilizing hunger and satiety cues and cannot adjust intakes as their growth and nutrition needs change.[7,8] Monitoring calorie and protein delivery and comparing it with age-appropriate recommended goals should be the standard of care.[7,8] It is important to utilize growth charts to monitor *z* score changes, complete a focused physical exam to identify nutritional deficiencies or changes in subcutaneous fat/muscle mass, and calculate growth velocity over various time intervals.[17–19] In a hospital setting, growth velocity may be calculated every 3 to 7 days, and in an outpatient setting, weekly, monthly, or yearly assessment is beneficial. Laboratory values for assessing and monitoring adequacy are based on the individual patient's disease state and medical status.

Indications of Enteral and Parenteral Nutrition

Adequacy and appropriateness of the route for specialized nutrition support must be reevaluated frequently. EN is the preferred route when nutritional needs cannot be met orally. EN preserves gastrointestinal (GI) function, is less costly, and is associated with less risk compared with PN. PN should be used when the GI tract is not functional or if inadequate absorption is apparent and thus adequate nutrition support is not possible via the enteral route.[1] PN should be promptly initiated in very low birth weight infants (<1500 g).[2,20,21] PN should be considered for neonates in the critical care setting, regardless of diagnosis, when EN does not meet their estimated energy needs to support growth.[20]

In a jointly published guideline, the Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition (ASPEN) suggest initiating EN in all children with critical illness unless it is contraindicated.[2] The authors suggest early initiation of EN within the first

24 to 48 hours after admission into the pediatric intensive care unit (PICU). PN supplementation is recommended for children who are unable to receive any EN during the first week in the PICU. For patients with severe malnutrition or who are at risk of nutrition deterioration, PN may be supplemented in the first week if they are unable to advance past low volumes of EN.[2] The timing of PN initiation should be individualized.

Sunderman et al report that the provision of continuous postpyloric EN is integral to meeting the nutritional needs of pediatric patients with extensive thermal injuries.[22] PN should be considered during the preoperative and postoperative stages for neonates and children who are malnourished and unable to tolerate oral and enteral nutrition.[20] See Chapter 31, "Nutrition Access" for guidelines on determining the best feeding route.

Enteral Nutrition

Monitoring

Many parameters may be used to monitor patients receiving EN. During EN initiation and advancement, monitoring will initially be more frequent and then become less frequent as the child becomes more stable. Table 34-1 provides a proposed monitoring protocol for infants and children receiving EN in the hospital and at home.[14,23,24]

TABLE 34-1. Suggested Monitoring for Infants and Children Receiving Specialized Nutrition Support

Parameter	Initial Week	Inpatient	Outpatient
Growth parameters			
Weight NICU Infants Children Length NICU Infants Children Height (>24 mo)	Daily Daily Daily Baseline Baseline Baseline Baseline	Daily Daily Daily to twice weekly Weekly Monthly Monthly Monthly	Weekly to monthly Weekly to monthly Weekly or clinic visit Monthly or clinic visit
Head circumference (<24 mo) Weight gain Linear/OFC gain NICU Infants	Baseline Daily to weekly Weekly Weekly	Weekly to monthly Daily to weekly Weekly Weekly to monthly	Monthly or clinic visit Weekly to monthly Monthly
Intake parameters			
Intake Calories Protein Vitamins Minerals Fluid balance	Daily	Weekly	Monthly
GI tolerance			
Abdominal girth Emesis Stool (volume, frequency, consistency, color) Ostomy (volume, consistency)	As indicated As reported Daily as reported	As indicated As reported Daily as reported	As indicated As reported Change in stool pattern
Physical			
Temperature Tube placement Tube/vascular access site care	Per nursing policy Before each feeding	Per nursing policy Before each feeding	Report when >101°F (38.5°C) Before each feeding

Parameter	Initial Week	Inpatient	Outpatient
	Daily	Daily	Daily

Abbreviations: GI, gastrointestinal; NICU, neonatal intensive care unit; OFC, occipital frontal circumference.

Evaluation of Growth and Nutrition Adequacy

Monitoring serial anthropometric data, with corresponding percentiles and *z* scores, as well as growth velocity allows clinicians to determine the appropriateness of the nutrition therapy to support optimal growth. Calculating calorie, protein, vitamin, mineral, and fluid delivery is initially done to determine if the nutrition plan meets the child's nutritional needs and whether additional free water, vitamin, or mineral supplements are needed. Periodic reevaluation of nutrient delivery compared to age-based guidelines is essential to determine if the nutrition care plan continues to be adequate. Fluid status may be assessed by balancing total fluid intake/delivery with fluid output including urine, stool, or ostomy output, emesis, wound losses, and tube drainage.

Evaluation of Enteral Nutrition Tolerance

Assessing EN tolerance consists of monitoring GI symptoms[14] including nausea, vomiting, diarrhea, constipation, and abdominal pain or distention. Identification of other causes of these symptoms such as infection, bacterial overgrowth, or medications should be considered before strategies are taken to alter the type of EN or feeding delivery.[14] Care should be taken in the preparation, storage, and delivery of EN and human milk to prevent bacterial contamination. Slowing the rate of formula administration or selecting a lower calorie concentration formula are options to improve EN tolerance.

Stool frequency, consistency, color, and presence of blood or fat should be noted. If a patient has an ostomy, it is essential to record the volume of ostomy output daily. The ostomy volume goal may be $\leq$ 40 mL/kg/d with stable electrolyte and fluid status.[25] Color and consistency may also provide additional insight when evaluating ostomy output. Large amounts of stool or ostomy output may indicate the need to reduce or avoid the advancement of EN volume or caloric concentration. Large stool volume or ostomy

output or excessive vomiting may require transitioning to an elemental formula that will allow for more passive digestion and absorption. If feeding tolerance cannot be achieved by these strategies and excessive diarrhea, ostomy, or vomiting continues, intravenous (IV) fluids or PN may be required to avoid dehydration or nutritional deficiencies.

Various stool studies can also assist in identifying the causes of enteral therapy intolerance. Fecal fat is used to measure the amount of fat present in the stool to identify fat malabsorption. The presence of reducing substances and acidic stools indicates carbohydrate malabsorption. The presence of α-1 antitrypsin is a marker for a protein-losing enteropathy or an indicator of enteral protein loss. Stool osmolarity with electrolytes may help distinguish between osmotic or secretory diarrhea. Stool elastase can aid in the diagnosis of exocrine pancreatic insufficiency and the potential need for pancreatic enzyme replacement.[26] Macronutrient malabsorption prompts changing the patient's EN to improve tolerance. The presence of blood in the stool may indicate cow's milk–protein allergy.[27] A formula-fed infant may require changing to an extensively hydrolyzed protein-based formula, or in extreme cases, an amino acid–based (elemental) formula. When a cow's milk–protein allergy is suspected, an elimination diet is indicated for breastfeeding mothers. Therefore, evaluating the cause of the GI symptoms will determine therapy.

Gastric residuals have been monitored in PICU patients because of the risk of ventilator-associated pneumonia related to aspiration and in the neonatal intensive care unit (NICU) population due to the risk of developing necrotizing enterocolitis while receiving EN. However, recent literature does not support this practice.[14] Consider providing continuous enteral feeding instead of intermittent or postpyloric feedings for feeding intolerance. Changing formulas based on qualities such as osmolality and total content and type of fat, carbohydrate, protein, and fiber should be considered for feeding intolerance. Feeding intolerance may require consultation with a pediatric GI or surgical physician to evaluate conditions such as an intestinal inflammatory process, necrotizing enterocolitis, small bowel bacterial overgrowth, bowel obstruction, or intestinal strictures. Responding to gastric residual volumes leads to increased clogging of

enteral access devices, interrupting the advancement and provision of EN, thus resulting in the patient not receiving their nutritional needs.[14]

Monitoring Laboratory Values

Routine monitoring of laboratory values is not indicated for medically stable pediatric patients receiving EN at advised levels and achieving adequate growth.[1,23] Serum zinc and fat-soluble vitamins are monitored in the presence of fat malabsorption, and additional laboratory monitoring may be necessary based on concurrent disease states. Patients with chronic conditions may be at increased risk for nutrient-related deficiencies, including vitamins and trace metals.[28] A position paper from the European Society for Paediatric Gastroenterology Hepatology, and Nutrition Committee on Nutrition recommends a multimodal approach to assessment using dietary assessment, clinical examination, and laboratory biomarkers. There are pros and cons to all of these, but all can be useful in the right setting.[29] Physical assessment including clinical signs of nutrient excess or deficiency must be assessed periodically and may prompt further testing. See Chapter 30, "Assessment of Nutrition Status by Age and Determining Nutrient Needs" for details of physical findings and related nutrition concerns.

Oral Feeding

Introduction to oral feeding is critical in all infants receiving EN. Allowing the infant to take a minimal volume of formula orally may reduce the tendency toward oral aversion that is common among these children.[30] When an infant is unable to feed orally, holding the infant during feeding and allowing them to experience nonnutritive sucking at the breast or on a pacifier is important for development and promotes the feeling of satiety.

It is also critical for older children receiving tube feeding to be allowed to eat and drink once safety has been established either via observation or oximetry-swallow study. Speech-language pathologists work to reduce the occurrence of oral aversion or poor development of oral-motor skills that are common in infants and children receiving EN. This allows the EN to be transitioned to an oral diet should the child be able to tolerate and safely consume an oral diet.

Revision of the Enteral Care Plan

Revision of the EN care plan is based on the patient's tolerance of the EN regimen and achievement of goals. If goals are not being met, the nutrition care plan must be adjusted according to the patient's tolerance. As a child ages, the EN type and volume will need to be adjusted based on the child's needs, recommended daily allowance (RDA), and dietary reference intake. Vitamin and mineral supplementation may allow for the feeding plan to be nutritionally adequate. Continue to assess if the feeding plan meets estimated fluid needs. If a patient consistently consumes >80% of nutritional needs orally and maintains adequate growth, consider discontinuing EN.[14] Once a patient demonstrates adequate growth solely on an oral diet, consider removal of the feeding device.

Special care is needed for children requiring extremely low energy needs. Additional evaluation for the nutritional adequacy of the plan as well as monitoring the nutritional status of any suboptimal nutrient is warranted. If the EN plan is not supporting appropriate growth and adjusting the EN plan does not support the nutrition goals, then supplementation with PN or a transition to all PN may be required.

Parenteral Nutrition

Once the decision has been made to initiate PN, vascular access is evaluated. If deemed appropriate based on nutrition goals, a PN solution is formulated accordingly. IV access is continuously monitored for mechanical complications along with metabolic and infectious complications related to PN as discussed in the following text. As with EN, patient allergy information or any history of infusion-related incidents should be evaluated before the initiation of PN.

Evaluation of Growth and Nutrition Adequacy

Evaluation and monitoring of growth and nutrition in PN-dependent patients is similar to those receiving EN with regards to *z* scores, anthropometrics, and growth velocity. The difference lies in the provision of calories and protein, as patients will require 5% to 10% less due to

circumventing any digestion or absorption issues with direct administration of the solution into the venous system.

Evaluation of Vascular Access

Monitor for Mechanical Complications

The decision to order peripheral parenteral nutrition (PPN) versus central parenteral nutrition (CPN) is based on nutrition needs, anticipated length of therapy, and patency of peripheral veins. PPN is limited based on osmolarity because of the vesicant properties of PN ingredients. A retrospective study done at a single pediatric institution did not see any difference in catheter-related complications for PPN solutions greater than or <900 mOsm/L. However, most institutions set osmolarity limits for neonatal PPN at 900 to 1200 mOsm/L and pediatric PPN at 600 to 900 mOsm/L.[31,32] This results from concern regarding the development of thrombophlebitis and ensuing complications.

The maximum dextrose concentration for pediatric and neonatal PPN is 12.5%. However, the osmolarity of the solution ultimately dictates the amount of nutrients, electrolytes, and minerals that can be ordered. Lower concentrations of dextrose may be necessary in children with poor peripheral access, or PPN may need to be avoided completely depending on the fragility of their veins, as seen in chronically ill children. Amino acids, dextrose, calcium, sodium, and potassium are the main determinants of osmolarity. If PPN is utilized, the IV site needs to be monitored closely (every 3−4 h) for early signs of infiltration which include erythema, swelling, pain, and streaking. It is difficult to provide 100% of the nutrition goals with a peripheral solution but may be effective for a short time. While a patient is on PPN and EN is not a viable option within 5 to 7 days, serious consideration should be given to the placement of a central venous access device (CVAD).[33]

If central access is obtained, it is helpful to note the date of insertion, the location, the type of CVAD, and the number of lumens. This data will be useful when monitoring for CVAD mechanical complications such as line breaks, catheter occlusions, mechanical obstruction, precipitate, and thrombotic occlusions. A multidisciplinary team that has established a relationship with the patient and caregivers can monitor these complications

over time and provide guidance regarding repairs, any pharmacologic therapy, or lastly, CVAD replacement. A position paper from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) Intestinal Rehabilitation Special Interest Group suggests that CVAD repair and salvage be promoted for mechanical and infectious complications to avoid loss of venous access for stable patients if able.[34]

This same group recommends prophylactic anticoagulant administration as low molecular weight heparin only after treatment of a catheter-related thrombus if the thrombus persists.[34] Venous access guidelines from multiple European nutrition societies are consistent with NASPGHAN recommendations to not routinely administer prophylactic anticoagulation in new home PN patients until sufficient evidence is available otherwise.[3]

Further research is needed to identify patients who would benefit from prophylactic anticoagulation and those who are at risk for clinically significant bleeding complications. Low-flow volumes, smaller catheters, and frequent interruptions of PN solutions may play a role in the increased incidence of catheter clotting in pediatric patients compared to adults.[36] Data suggest that a heparin concentration of 0.5 units/mL in neonatal PN solutions may be as effective for maintaining catheter patency as 1 unit/mL.[37] Please see Chapter 31, "Nutrition Access" for additional information.

Precipitates from incompatible intravenous solutions, medications, blood products, and PN solutions can cause CVAD occlusion. Multiple factors can affect chemical compatibility, including solution and medication concentrations, temperature, pH, pKa, and light. Both pH and pKa are utilized to determine the amount of acidity in a system and the strength of acidity for a respective medication. Hospital and infusion pharmacists can use this information to determine what treatments might be best to dissolve precipitates and restore patency to the CVAD. The development of CVAD restoration protocols allows for the timely ordering and administration of treatments in hopes of restoring patency and avoiding delays in therapy for patients. Hydrochloric acid was used for dissolving precipitates from acidic medications but is generally unavailable due to updated regulations for compounding high-risk sterile medications and solutions. Cysteine hydrochloride has been investigated as an alternative since it is

commercially available, has a pH like hydrochloric acid, and has already been added to neonatal PN. Authors Pai and Plogsted concluded that cysteine hydrochloride is a reasonable alternative treatment for line restoration when the precipitate is due to acidic medications.[38]

Monitor for Infectious Complications

Central line–associated bloodstream infections (CLABSIs) are a well-known complication of CVADs in patients receiving PN and a significant contributor to morbidity and mortality for these patients.[34] These infections have been reported to cost approximately $30,000 per event in addition to extended hospital stays.[39] Hospital-acquired CLABSI rates range from 0.3 to 1.9 per 1000 catheter days based on reports from various sources. Health systems utilize multiple interventions to decrease this rate and improve the quality of life for patients who are dependent on PN.

Empowering patients, caregivers, and staff with data and knowledge of how to care for these access devices can decrease CVAD infection rates.[40] The most recent CDC guidelines for CVAD maintenance were published in 2011.[41] Removal of CVAD for the treatment of CLABSIs had been a routine recommendation, but continual replacement of the CVAD can lead to the loss of venous access sites. Once a patient starts to lose venous access sites, a transplant evaluation may be indicated. More recently, strategies to salvage the central line are attempted unless patient status declines or infection can't be cleared from the bloodstream.[34]

One strategy used to prevent CLABSIs has been the use of agents to sterilize the CVAD lumen. The first of these is antimicrobial lock therapy (ALT) which involves using a variety of concentrated antibiotic solutions and dwelling the solution for a minimum of 2 hours each day. Merikhi and colleagues compared ALT to ethanol 70% in 25 children undergoing hemodialysis. ALT was instilled for the first 6 months and then ethanol for the next 6 months. The authors concluded that both regimens decreased CVAD site infections, but ethanol was more effective and resulted in fewer catheter replacements. Concerns associated with ALT are the development of antibiotic resistance with long-term use, lack of documented stability, and expense.[42]

Ethanol alone is another approach that has shown to reduce CLABSI. Rahhal and colleagues performed a systemic review and meta-analysis of the utilization of ethanol locks in pediatric patients with intestinal failure. Nine studies met the criteria for review and favored ethanol over heparin for decreasing the risk of CLABSI by an average of approximately 60%. A lower CVAD replacement rate was also favored by ethanol, but there appeared to be an increase in CVAD repair for the ethanol groups.[43] Opilla et al specifically studied the use of ethanol for the home PN patient and showed a statistically significant reduction in CLABSIs and CVAD exchanges.[44] The use of ethanol lock therapy (ELT) is safe for pediatric patients.[43–45] Factors that must be considered when choosing to utilize an ethanol lock include CVAD material, CVAD age, and compliance.[48] Another review evaluating the evidence for prophylaxis of CLABSI with ELT suggests that this therapy does decrease the incidence of infections and CVAD removal and may be efficacious in combination with systemic antimicrobial agents for the treatment of CLABSI. The regimens utilized still varied among institutions regarding volume of lock, flush versus withdraw, CVAD type, frequency, and dwell time.[49]

Disruption in ethanol usage because of significant price increases after orphan drug designation has, anecdotally, resulted in increased CLABSI episodes, which is not surprising, as this was demonstrated previously during a national shortage.[50] There are no commercially available alternatives for the prevention of CVAD infections other than ALT in the United States. Taurolidine is available outside of the United States and has been found to provide similar effectiveness as ethanol with fewer mechanical CVAD complications.[51] Additional solutions that are being actively investigated are 30% ethanol-2.8% sodium citrate and sodium bicarbonate.[34]

Intestinal rehabilitation clinicians at Children's Memorial Hermann Hospital retrospectively evaluated 4 patients with intestinal failure who had been transitioned from 70% ELT to 8.4% sodium bicarbonate lock therapy (SBLT) with a minimum 4-hour dwell time for a minimum duration of 6 months. The number of CLABSI, hospitalizations, and emergency room visits was less in the sodium bicarbonate group while the CVAD-related complications were similar. There were no adverse effects reported so this

preliminary research may represent a viable alternative to ethanol for the prevention of CLABSI in patients with intestinal failure.[52]

Small intestinal bacterial overgrowth (SIBO) can be a complication in patients with intestinal failure and/or bowel dysmotility. Bowel stasis and poor gastrointestinal motility are commonly associated with short bowel or significant intestinal resection. Abdominal discomfort, bloating, cramps, gas, and changes in stool color, consistency, and odor are common signs and symptoms. When the preceding signs and symptoms are identified, the patient should be treated, as these symptoms can limit EN advancement and PN weaning.

Because of the difficulty of diagnosing SIBO, treatment centers around symptomatic improvement with cyclical antimicrobial agents covering enteric aerobic and anaerobic bacteria or probiotics.[53] Commonly prescribed antibiotics include metronidazole, amoxicillin, amoxicillin-clavulanate, gentamicin oral solution, and rifaximin. Cyclic regimens vary but may consist of alternating 7 days on and 7 days off or administered 1 week every month if SIBO recurs frequently.[54] If a fever is also present, the patient should be evaluated for bacteremia resulting from possible translocation from the GI tract.

Evaluation of PN Solution Tolerance

Monitor PN Volume

Generally, PN volume is based on a patient's maintenance volume requirement (refer to Chapter 9, "Fluids and Electrolytes"). Fluid volume may be restricted or increased depending on disease processes and clinical conditions. Evaluation of multiple subjective and objective factors can determine if the PN volume or total fluid intake is appropriate. Weight, intake from all sources, output from all sources, laboratory results, vital signs, and physical assessment should be evaluated daily when PN is started (Table 34-2).

TABLE 34-2. Parameters to Evaluate Adequacy of Parenteral Nutrition Volume

Parameter	Dehydration	Fluid Overload
Weight change: real vs fluid	Rapid ↓ weight	Rapid ↑ weight
Intake: IV fluids, PN, blood products, medications, EN	Total intake < total output	Total intake > total output
Output: urine, gastric, stool, bile, chest tube, wound, skin	Decreased urine output, dark urine	Increased urine output in patients with normal renal and liver function
Laboratory	↑ Blood urea nitrogen, ↑ sodium, ↑ serum osmolality, ↑ urine specific gravity, ↑ albumin or Hgb	↓ Sodium, ↓ serum osmolality, ↓ urine specific gravity, ↓ albumin or Hgb
Vitals	↑ Heart rate, ↑ losses with fever	↑ Respiratory rate
Medications	Addition of diuretic or change in frequency	Fluid retention with steroids or excessive sodium intake
Physical examination	Thirst, dry lips, dry mucous membranes, dry skin, headache, dizziness	Peripheral, facial, and orbital edema, ↑ abdominal girth, shortness of breath

Abbreviations: EN, enteral nutrition; Hgb, hemoglobin; IV, intravenous; PN, parenteral nutrition.

The frequency of routine weights and laboratory results can be decreased as the patient stabilizes. If a patient is going home on PN or has limited access, the total fluid requirement may be incorporated into the PN solution as stability and solubility allow. In a patient with fluid restriction or during PN weaning, pharmacists can provide information regarding PN ingredient stock solutions so that the minimal volume required can be calculated to ensure that all ordered ingredients fit in the desired total daily volume.

Monitor for Metabolic Complications of Macronutrients

Blood urea nitrogen (BUN) is used as a monitoring tool for hydration status, and it may also indicate excessive amino acid administration.[55] An

elevated BUN in the neonate more likely reflects immature renal function rather than excessive amino acid intake.[56] If an elevated BUN cannot be explained by changes in renal function, medications (eg, high-dose steroids, amphotericin, aminoglycosides, diuretics), bleeding, or dehydration, then the nonprotein calorie to nitrogen (NPC:N) ratio should be evaluated. The ideal NPC:N ratio in stable patients is 150–250:1; the ratio may be less in patients who are critically ill or higher in patients in renal failure. If the ratio is low and BUN is elevated, it may be necessary to decrease the amino acid and adjust PN accordingly to maintain adequate caloric intake. Conversely, a low BUN level may indicate suboptimal amino acid administration. Ammonia levels and mental status are monitored in liver disease patients (see Chapter 24, "Hepatic Disease").

Dextrose is best monitored by venous blood glucose and capillary glucose. The frequency of venous or capillary glucose monitoring depends on a history of glucose intolerance, the presence of diabetes, or the use of concurrent medications affecting blood glucose control. The frequency may vary from every 2 hours to every 24 hours depending on the factors listed previously. Capillary glucose monitoring is useful for frequent monitoring so that the central line does not have to be accessed numerous times during the day or when verifying an abnormal glucose level from a venous sample. The frequency of monitoring can be modified to 1 or 2 times weekly once the patient has established good blood glucose control on the goal PN formula.

Unexplained hyperglycemia should prompt the calculation of the glucose infusion rate (GIR) from the PN solution and other dextrose-containing solutions to reassess PN GIR and increase the frequency of monitoring. In the NICU setting, the maximum tolerated serum glucose level may be as high as 180 mg/dL to achieve adequate nutrition and higher levels may require a decrease in GIR.[56,57]

Pediatric patients receiving PN for >2 weeks on a stable regimen may be cycled 12 to 22 hours per day to ease daily activities and decrease hepatic complications related to PN.[58] The cycle can be tapered up over 1 to 2 hours at one-fourth to one-half of the max infusion rate respectively, and tapered down similarly at the end of the infusion to avoid rapid glucose changes and rebound hypoglycemia. Initially, blood glucose levels should

be obtained during the high rate of cyclic PN infusion and 1 to 2 hours after cycle completion to evaluate for hyperglycemia and hypoglycemia. Levels >150 mg/dL will require a decrease in dextrose amount or lengthening of cyclic infusion to decrease the GIR. Levels <60 mg/dL or any symptoms of hypoglycemia will require a longer taper period at the end of cyclic PN. Close monitoring during cyclic PN changes, tapering at the beginning and end of PN cycle, and avoidance of interruptions are strategies to avoid hypoglycemia that can be seen with abrupt discontinuation or interruption of PN as demonstrated in pediatric hematopoietic stem cell transplant patients on PN therapy. The incidence of hypoglycemia was greater with higher PN GIR.[59]

Triglyceride levels are monitored daily as lipid injectable emulsion (ILE) intake is increased and then weekly once the dose is stable and levels are adequate. In patients with sepsis, more frequent monitoring and dose adjustments may be indicated. The maximal ILE for adults is 0.11 g/kg/h.[60] Maximum infusion of soybean oil−based (SO); medium-chain triglyceride (MCT) oil−based, olive oil−based (OO), and fish oil−based (FO) ILEs for infants, children, and adolescents is 0.15 g/kg/h.[61–63] The maximum infusion of OO,SO,SMOF-ILE for infants, children, and adolescents is 0.1 g/kg/h.[64] Longer infusion rates, from 12 to 24 hours, improve tolerance to ILE infusions.[65] It is recommended to consider reducing current ILE when triglyceride levels are >265 mg/dL in infants and >400 mg/dL in children.[66] Reducing the dose of SO-ILEs, and therefore decreasing phytosterol intake may reduce the cholestasis commonly noted in pediatric patients receiving long-term PN if alternative ILEs are not readily available or limited CVAD prohibits use.[61,67]

Patients with a true hypersensitivity to egg, fish, soy, or peanut protein may require a test dose of a particular ILE to better evaluate for any allergic reaction that may result in anaphylaxis, hives, rash, or itching.[62] The emulsifier in currently marketed long-chain triglyceride ILEs contains egg phospholipid. Even though reactions to PN components are rare, some case reports suggest that multivitamins, ILEs, iron dextran, or preservatives may be causative agents.

A systemic review of publications related to PN hypersensitivity resulted in 33 hypersensitivities from 28 reports. The reactions were divided evenly

between adults and children. The most common reactions were cutaneous (81.8%) followed by anaphylaxis (45.4%), respiratory (42.4%), hemodynamic instability (21.2%), tachycardia (18.1%), back pain (9%), diarrhea (6%), and a variety of gastrointestinal symptoms. Most of the reactions (~61%) occurred during the first day of PN initiation while the remainder occurred in the next 1 to 21 days.[68] If a reaction does occur and PN is suspected, eliminating one agent at a time helps to determine the causative ingredient. If PN is required for more than a week with no EN, then alternate routes may need to be identified to provide the potential causative agent. Vitamins may be administered orally or via a feeding tube or topical safflower oil in the case of ILE hypersensitivity.[69]

Monitoring Integrity of Parenteral Nutrition Solutions

Several factors influence the solubility of minerals such as calcium and phosphorus, the compatibility of PN solutions, and the integrity of total nutrient admixtures (TNA). Factors that influence calcium and phosphorus solubility are listed in Exhibit 34-1. The pH of the amino acid solution drives the pH of the PN solution. The ideal pH for calcium and phosphorus solubility is ~5–6.[70] Solubility will decrease as the pH becomes more alkaline. Higher concentrations of amino acids allow for higher calcium and phosphorus doses to be added to a 2-in-1 or TNAs. Some clinicians believe that the amount of ILEs can influence how much calcium and phosphorus can be included in PN solutions, but the concentration of ILEs is not a variable evaluated in calcium/phosphorus solubility curves.

EXHIBIT 34-1. Factors Negatively Affecting Calcium and Phosphorus PN Solubility

- Increased temperature
- Increased concentrations of calcium and phosphorus
- Type of amino acid product and decreased concentration
- Decreased dextrose concentration
- pH of final solution <5 and >7
- Omission of cysteine
- Bright lighting

- Order of mixing without significant separation of phosphorus and calcium

---

Solubility curves in Trissel's and King's reference texts have been a primary source for determining the maximum calcium and phosphorus amounts that can be ordered in various PN solutions.[71] Boullata's article provides a comprehensive review of the knowledge and attention to detail necessary to adequately assess for safe PN compatibility and stability.[70]

Practitioners were tragically reminded how important mixing order is when compounding PN admixtures. At least 2 deaths have been associated with calcium-phosphorus precipitation in PN admixtures.[72] Temperature and lighting also play a role and need to be investigated when precipitation occurs, PN admixtures look abnormal or become discolored, PN filters occlude, or when the admixtures otherwise meet all solubility and stability limits. Neonatal PN admixtures are particularly at risk for stability issues because of bilirubin lights, heat from the extensive amount of equipment utilized in these units, and frequent co-infusion of medications because of limited IV access.

TNAs are complex admixtures that require additional scrutiny and compounding limits because of their opaque nature. Factors involved in ensuring the integrity of the emulsion are listed in Table 34-3. Minimum concentrations of the macronutrients should be determined to maintain the integrity of the emulsion.[70,73] A minimum amount of ILE is required to provide adequate emulsifier for a TNA.[74] It has yet to be determined how current ILE product packaging will affect the integrity of TNA.[75]

TABLE 34-3. Factors Affecting Total Nutrient Admixture Stability

Factor	Effect
Final pH (5–6)	Optimal pH for stability
Divalent cation concentration (calcium, magnesium, zinc)	Maximum concentration limits required
Trivalent cations (iron dextran)	Not stable in TNA
Type of amino acid and concentration	Higher concentration improves stability
Dextrose concentration	Lower concentrations will limit stability
Anionic emulsifier	Protects emulsion integrity
Multivitamin products	Protects emulsion integrity
Temperature	Avoid administration in warm areas
Order of mixing	Critical to avoid precipitation and instability
Product packaging	ILEs in plastic vs glass: effect on stability?

Abbreviations: ILE, injectable lipid emulsion; TNA, total nutrient admixtures.

Comparison of Total Nutrient Admixtures and 2-in-1 Admixtures

When PN is compounded with amino acids and dextrose it is referred to as 2-in-1. TNA, or 3-in-1, refers to PN admixtures compounded with amino acids, dextrose, and ILEs. The opaque nature of a TNA or 3-in-1 is considered a disadvantage because of the inability to see obvious precipitates. Calcium and phosphorus intakes are felt to be less with TNA, but again ILE is not a limiting factor in the solubility of these 2 minerals. Divalent cations such as calcium, magnesium, and zinc may be somewhat limited in TNA due to the anionic nature of the ILEs.[70]

As with calcium and phosphorus solubility, higher concentrations of amino acids and dextrose provide a protective effect on the emulsion. The amino acids form a protective layer around the lipid globules, while the hypertonicity of the dextrose prohibits excessive movement and possible coalescence of globules.[70] The most problematic TNAs are the initial neonatal formulations for extremely low birth weight infants with low

dextrose and ILE concentrations. Centers that compound TNAs must invest in automated compounding systems that interface with advanced order-entry software containing multiple manufacturer and institutional limits. These dosing and stability limits will aid in identifying admixtures potentially unsafe for patient administration. It is of the utmost importance that all clinicians involved in the prescribing, ordering, compounding, labeling, and dispensing of PN review their work with a critical eye due to the complexity of these solutions.[32]

Although TNAs require rigorous review, they do allow for all nutrients to be in 1 bag, therefore only requiring 1 infusion pump. Nursing time is less compared with the time needed when ILEs are administered separately in syringes every 12 hours and co-infused with a 2-in-1 admixture. Some institutions infuse ILE in syringes over 24 hours, but the CDC recommendation states that ILEs should not be infused longer than 12 hours to avoid microbial growth.[76]

ILE infusion time may vary from 12 to 24 hours depending on the dispensing and administration techniques. ILE may be transferred from the original container into a syringe, drawdown from the original container, or infused directly from the manufacturer container.[77,78] Concern exists for an increase in lipid peroxidation once ILEs are transferred from their original container. The clinical consequence is not known yet, and it is unclear whether peroxidation occurs at a quicker rate in TNA or syringe-administered ILE.

There is increasing evidence of peroxide formation when PN solutions and ILEs undergo photo-oxidation when exposed to ambient light and phototherapy. Neonates are at increased risk of complications associated with oxidative stress such as bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, and intestinal failure-associated liver disease (IFALD).

After a review of available literature, an ASPEN working group recommended photoprotection of all neonatal PN and ILE infusions from the compounding stage to infusion. This also includes administration tubing. While it is inferred that older children and adults may experience similar oxidative stress from photo-oxidation, there is minimal-to-no corroborating evidence to support photoprotection of pediatric/adult PN

admixtures. Barriers to full photoprotection include supply issues of the appropriate coverage materials and the ability to ensure coverage at each step of the PN compounding, delivery, and administration process. Partial photoprotection was still associated with decreased oxidative stress.[79]

Another advantage of TNA is the 24-hour infusion of ILE and decreased risk of microbial growth compared to ILE alone.[76] Each institution needs to determine which mode of PN-ordering works best for its patient populations.

Metabolic Bone Disease

Metabolic bone disease (MBD) is a complication that may result from long-term PN. It may present as osteomalacia, osteopenia, or osteoporosis. Several factors may increase the incidence of MBD including medications, calcium and vitamin D malabsorption, metabolic acidosis, high aluminum concentrations in PN, and other nutrient deficiencies. In addition to bone pain or nontraumatic fracture, the following laboratory tests may indicate suspected MBD:

- Low-to-normal parathyroid hormone (PTH) with elevated vitamin D levels.
- Elevated alkaline phosphatase.
- Elevated PTH with suboptimal vitamin D levels.
- Changes in serum calcium levels.
- Hypercalciuria.[81,82]

Therefore, monitoring a yearly PTH along with vitamin D (25-hydroxy) and bone-density measurements may be indicated in long-term PN patients.[83]

Preterm neonates are already at an increased risk of MBD for various reasons listed previously, in addition to missing out on mineral accretion during the third trimester and other prenatal risk factors. Exhibit 34-2 lists factors that will predispose neonates to the development of MBD.[84] It is recommended to maximize calcium and phosphorus intake in neonatal PN solutions with an optimal calcium-to-phosphorus ratio based on gestational age, chronological age, serum mineral levels, and other MBD monitoring parameters while providing parenteral vitamin D (included in parenteral

multivitamin products).[85] Enteral and parenteral dose suggestions for optimization of calcium and phosphorus intake are listed in Table 34-4.[84]

EXHIBIT 34-2. Factors Associated With Increased Risk for Metabolic Bone Disease in Neonates

- Prematurity
- Medical history
- Surgical history
- High-risk medications (diuretics, corticosteroids, caffeine, aluminum, phenobarbital)
- Long-term PN or EN
- Type of EN (+/- fortification)
- Vitamin deficiencies
- Liver disease
- Renal disease

Abbreviations: EN, enteral nutrition; PN, parenteral nutrition.

TABLE 34-4. Doses of Calcium and Phosphorus Dosing for Prevention/Treatment of Metabolic Bone Disease

	Starting Dose	Maximum Dose	Ratio (Ca:P)
Enteral Ca (elemental)	20 mg/kg	70−80 mg/kg	1.5−2 mg: 1 mg
Enteral P (elemental)	10−20 mg/kg	40−50 mg/kg	—
Parenteral Ca	1.6−2 mEq/kg	2−4 mEq/kg	2−2.6 mEq: 1 mMol
Parenteral P	1 mMol/kg	1−2 mMol/kg	—

Abbreviations: Ca, calcium; P, phosphorus.

Monitoring Nutrition Laboratory Values in Children Receiving EN and PN

The goals for monitoring patients receiving SNS include ensuring the efficacy of the regimen and identifying and preventing potential

complications. The nutrition support team (eg, physician, nurse, pharmacist, and dietitian) must establish goals for patients before initiating SNS. The monitoring of patients requiring EN and/or PN must include both clinical data and laboratory testing.[86] Sample patient nutrition monitoring forms are included in Appendices 34-1 through 34-3. Appendix 34-1 may be utilized for patients started on PN or a combination of PN/EN. Appendix 34-2 can be utilized in addition to Appendix 34-1 for those patients receiving PN for >3 months. Appendix 34-3 can be used for pediatric patients weighing >40 kg with PN units listed as grams, milliequivalents, or millimoles per day. Every patient must have documented baseline data for appropriate evaluation and monitoring to occur.

It is impossible to create a "one size fits all" set of monitoring guidelines. Each patient's monitoring regimen must be created based on the specific disease state and individualized long-term goals. New patients will require the most frequent monitoring, while stable long-term SNS patients may require less intense monitoring. EN-only patients will require less laboratory monitoring, while those receiving PN will require regular laboratory testing. The following information should be used as a general guideline and can be customized to the specific patient's needs. Please refer to disease-specific chapters in this book for additional monitoring that may be required. Tables 34-5 and 34-6 provide examples of suggested monitoring for short-term and long-term laboratory testing.

TABLE 34-5. Frequency of Short-Term and Long-Term Metabolic Monitoring

Parameter	Initial	Follow–Up
BMP	Daily	Included in CMP
CMP	Weekly	Every 1–4 wk
Magnesium	Daily to weekly	Every 1–4 wk
Phosphorous	Daily to weekly	Every 1–4 wk
Prealbumin	Weekly	Monthly
Triglycerides	Daily to weekly	Monthly
PT/INR	Weekly	Monthly
CBC differential/platelets	Weekly	Every 1–4 wk
GGTP	Baseline if indicated	Monthly

Abbreviations: BMP, basic metabolic panel; CBC, complete blood count; CMP, comprehensive metabolic panel; GGTP, γ-glutamyl transpeptidase; INR, international normalized ratio; PT, prothrombin time.

TABLE 34-6. Frequency of Long-Term Nutrition-Related Monitoring

Parameter	Initial	Follow–Up
Iron studies	3 mo	Every 3–6 mo
Zinc	3 mo	Every 3–6 mo
Selenium	3 mo	Every 3–6 mo
Manganese	3 mo	Every 3–6 mo
Copper	3 mo	Every 3–6 mo
Chromium	3 mo	Every 3–6 mo
25-hyroxy-vitamin D	3–6 mo	Every 12 mo
Vitamins A and E	6 mo	Every 12 mo
Vitamin B12 and folate	6 mo	Every 12 mo
Carnitine	3 mo	Every 3–12 mo
Thyrotropin	Baseline if indicated	Every 12 mo

Physical Data

Objective physical data can be collected to aid in evaluating adequacy and tolerance to SNS. Developing standards of practice, order sets, policies, and procedures in all institutions caring for patients requiring SNS can assist those individuals responsible for monitoring these complex patients. Critically evaluating the type and amount of body fluid loss through vomiting, diarrhea, drain loss, and others can aid in anticipating the type and dose of electrolytes and minerals needed.[87] Table 34-1 delineates some general guidelines, but specific monitoring parameters and frequency should be dictated by individual patient needs and the clinical situation.

Chemistry Profile Monitoring

Monitoring electrolytes, minerals, renal function, glucose, and acid-base balance is essential in PN. When initiating a patient on PN, a baseline basic metabolic panel (BMP), magnesium, phosphorous, and triglyceride levels should be ordered and monitored daily until the patient has reached the caloric goal established at the initial assessment. The frequency may be decreased to twice weekly with 1 day including the comprehensive metabolic panel (CMP), which encompasses the hepatic function along with the BMP. As the patient stabilizes, laboratory tests may be decreased to weekly. Finally, these tests may be reduced to every 2 to 4 weeks when the PN formula is stable and if appropriate goals are being met for the current condition and growth needs.[83,88,89]

Nutrition-Related Laboratory Tests

Prealbumin can be used to monitor protein status because of its shorter half-life of 2 to 3 days compared to albumin.[90] However, other factors can influence prealbumin levels such as inflammatory states, end-stage liver disease, untreated thyroid disease, renal disease, and zinc deficiency. These limitations should be considered when interpreting a patient's prealbumin level.[91,92] Monitoring prealbumin and albumin levels in long-term stable patients may help identify the resolution of acute illness or readiness for surgery.[93]

Changes in triglyceride levels can be influenced by a variety of factors including disease state, organ function, medications, nutrition status, and

current nutrient intake. They should be monitored daily when SNS is initiated, followed by weekly, and then decreased to monthly.[88,94]

When a patient is not receiving EN or a deficiency has been documented, adding carnitine to the PN solution should be carefully considered. A patient who has a deficiency may present with hypertriglyceridemia, hypoglycemia, hyperbilirubinemia, muscle weakness, or decreased weight gain along with a multitude of other clinical symptoms. While there is not a consensus regarding the optimal carnitine dose for pediatric PN, generally 10 to 20 mg/kg/d is recommended for IV or oral supplementation and should be initiated in any patient receiving PN for >7 days.[95] Data supports dosages as little as 2 to 5 mg/kg/d for neonates when started in PN from day 1 of therapy to prevent deficiency.[96]

Carnitine facilitates the transport of free fatty acids into the mitochondria so in theory, hypertriglyceridemia related to inadequate carnitine supplementation or carnitine deficiency in PN patients could be reversed with carnitine treatment. Olid and colleagues reviewed studies evaluating the effect of prophylactic carnitine in neonatal PN and although they saw an increase in carnitine levels, there was minimal to no effect on clinical outcomes such as improvement in lipid profile, weight gain, apnea, or hospital stay.

More research is needed to determine the optimal dose in long-term PN that will provide clinical benefit.[97] Although most EN formulas contain adequate dietary carnitine, supplementation can be considered in EN patients with malabsorption or bowel resection if deficiency is suspected or confirmed by laboratory testing. A carnitine profile, including ester/free ratio, should be monitored every 3 to 6 months if the patient is being supplemented. A yearly carnitine profile is sufficient for patients not receiving the RDA.

Linoleic and α-linolenic acids, known as essential fatty acids (EFAs), must be obtained orally, enterally, or parenterally in all patients because the body cannot synthesize them. If inadequate amounts are provided, an essential fatty acid deficiency (EFAD) may eventually occur. If reduced or ILE-free PN is provided for a significant amount of time or a clinical manifestation of an EFAD occurs, ordering an EFA profile is recommended. The resulting triene-to-tetraene ratio can determine if an EFAD exists.[98–100]

Other levels such as mead acid, alpha-linolenic acid, linoleic acid, and arachidonic acid are also considered.[100] The increased utilization of alternative ILEs containing less soy or long-chain triglycerides, and therefore less essential fatty acid intake, makes it imperative to monitor closely for EFAD. This is especially true for the smallest patients who have increased ILE requirements for brain and retinal development. Balancing the need for essential fatty acids and avoiding adverse consequences related to plant-based ILEs can be challenging.[100]

Liver Enzymes and Bilirubin

Hepatic and biliary complications are a well-documented adverse effect of PN in children.[65] It is necessary to monitor liver enzymes, which include alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase weekly when initiating PN. A total bilirubin should also be followed. If prolonged PN is anticipated or if the patient becomes jaundiced, a direct or conjugated bilirubin level is helpful to monitor for cholestasis.[88] A direct bilirubin >2 mg/dL may prompt earlier monitoring of copper and manganese trace elements given that the biliary tract is the primary excretory pathway for copper and manganese.[101] Monitoring is key, however, as Corkins et al found contrary evidence indicating that the degree of cholestasis did not correlate with serum copper levels, and the majority of long-term PN patients with cholestasis required a standard dose of copper or more to maintain normal serum copper levels.[102] Liver enzymes and total bilirubin are included when ordering the CMP as previously discussed. Once stabilized these laboratory tests can be monitored every 2 to 4 weeks.

The liver enzyme γ-Glutamyl transpeptidase (GGTP) is more specific for liver and biliary tract problems. GGTP is the most sensitive liver enzyme for detecting biliary obstruction, cholangitis, or cholecystitis. It can be ordered for further diagnosis when the traditional liver enzymes are elevated or as a regularly monitored monthly test if the patient is at risk for biliary complications.[103]

If a patient on long-term PN has a significantly increased alkaline phosphatase level, requesting an alkaline phosphatase isoenzyme test may

be advisable. This test will provide a breakdown of the source of the alkaline phosphatase, which can be liver, bone, or intestinal. This is clinically useful if liver dysfunction or metabolic bone disease resulting from PN therapy is suspected.[104]

The prothrombin time (PT) and international normalized ratio (INR) can be utilized in long-term monitoring of PN. The PT can be elevated in a patient who is developing hepatocellular disease, obstructive biliary disease, or more rarely, vitamin K deficiency.[105] Vitamin K or phytonadione content in injectable adult and pediatric multivitamins should provide the recommended daily amount parenterally, but patients with malabsorption and liver disease may require additional supplementation via PN. These same patients on EN may also require additional supplementation enterally. A baseline and then monthly check of the PT/INR is adequate.

Trace Elements

A patient's initial PN usually contains a trace element package that has a manufacturer-determined dose of zinc, copper, manganese, chromium, and selenium (see Chapter 33, "Parenteral Nutrition Support").[106] In preterm neonates, trace elements may need to be prescribed separately to reduce the risk of providing too much or too little when utilizing a commercial multi-nutrient product. Clinicians must consider the addition of certain trace elements, such as chromium and manganese, because of their contamination within other PN components.[107] When a patient has been receiving PN for several months or has developed cholestasis, it is important to assess the status of those trace elements.

After 3 consecutive months on PN (unless clinically indicated earlier), a patient should be assessed for zinc, selenium, manganese, copper, and chromium.[24,28] Long-term use of standard multi-trace products can result in both excessive and deficient concentrations, especially in patients who have GI tract abnormalities. Although measuring blood concentrations of these trace elements is not the most accurate because of the body's ability to store these elements, it is the easiest and most cost-effective monitoring method. These elements should not be checked during acute inflammatory conditions because the body sequestrates certain elements during this time. Levels may be falsely decreased in these situations.[28,29]

Assessment of these elements should occur every 3 to 12 months while receiving PN.[88] Increased frequency may be considered in pediatric malnourished patients, infants, and children receiving long-term (>4 wk) PN, and during times of shortages.[28] If a patient has an elevated level of any standard element, the multi-trace element of the PN can be omitted and individual elements can be added.[28] Additionally, if any element is found to be deficient, it can be added in addition to the standard multi-trace. Being familiar with the content of both pediatric and adult trace mineral solutions is important for adjusting supplementation accordingly when switching to individual trace minerals. There are limits to PN trace element concentrations that must be considered,[70] thus, oral supplementation may be an option (see Table 34-7). After altering the dosage of any element, it should be rechecked in approximately 1 to 3 months. If a patient's condition has completely stabilized, it is reasonable to monitor only once per year depending on age (see Tables 34-5 and 34-6).

TABLE 34-7. Enteral Dosing Options for Trace Metals[a]

Trace Metal	Preterm[1]	Term <6 mo	Pediatric			
			7 mo–3 y	4–8 y	9–13 y	14–18 y, Adults
Zinc	1000–3000 mcg/kg/d	2000 mcg/d[b]	3000 mcg/d[c]	5000 mcg/d[c]	8000 mcg/d[c]	Male: 11,000 mcg/d[c] Female: 9000 mcg/d[c]
Copper	120–150 mcg/kg/d	200 mcg/d[b]	7 mo–1 y: 220 mcg/d[b] 1−3 y: 340 mcg/d[c]	440 mcg/d[c]	700 mcg/d[c]	890 mcg/d
Selenium	1.3–4.5 mcg/kg/d	15 mcg/d[b]	20 mcg/d[b,c]	30 mcg/d[c]	40 mcg/d[c]	55 mcg/d[c]

[a] Doses listed as elemental.

[b] Adequate intake.

[c] Recommended dietary allowance.

Aluminum, considered an ultra-trace element, is a known contaminant of PN products. Monitoring is important because of the patient's continued exposure and risk for toxicity, especially for high-risk populations such as preterm neonates, infants receiving long-term PN, and hemodialysis patients on PN. It is reasonable to check aluminum levels each year during PN therapy. If the aluminum is elevated, the PN pharmacist can look at the current PN components and adjust if possible given that aluminum contamination varies between different PN product manufacturers.[106,108] One example would be to omit cysteine from a neonatal PN order if the infant is >3 months of age and PN-dependent.

Iodine is an element not supplied by standard multi-trace products in PN or individual injectable solutions in the United States. While it is uncommon for a patient to develop iodine deficiency, it should still be

monitored since iodine plays a role in thyroid function.[103,106] This can be assessed with a yearly thyrotropin and triiodothyronine test or urine iodine concentration. If a patient is found to be hypothyroid then thyroid replacement will be prescribed. In a case report of a PN-dependent pediatric patient, the use of iodized salt is discussed as a supplement for iodine deficiency.[110]

Table 34-7 lists suggested enteral doses[111] for trace mineral supplementation if parenteral options are not available or a patient is on EN. Compounding of liquid preparations may be required for suitable concentration and administration via feeding tubes. Consult your multivitamin formulary because some of these preparations may contain the desired minerals.

Iron Studies and Anemia

When patients are dependent on EN and/or PN, the potential exists for them to become anemic. The 4 nutrients that are most likely to be the reason for anemia are (1) iron, (2) copper, (3) vitamin B12, and (4) folic acid. Standard PN contains 3 of the previous nutrients except for iron because of its incompatibility with ILE.[70] Enterally fed patients are typically provided with all 4 nutrients. However, the standard quantities provided may not always be adequate for the specific disease process that is being treated. For example, a patient who has a shortened bowel length will generally have less nutrient absorption from EN and may become deficient over time.

Iron deficiency can be recognized by abnormalities in the complete blood count (CBC). In general, a decrease in hemoglobin and mean corpuscular volume (MCV) are present. It may take some time for the deficiency to occur, so a routine CBC (at least monthly) is recommended to monitor for these changes.[112] When these abnormalities are present, an iron panel can be ordered to confirm the deficiency. An iron panel should include serum iron, ferritin, transferrin saturation, and iron-binding capacity. In a patient who is deficient, the serum iron and ferritin may be reduced, and the binding capacity elevated. It is best to draw this panel in the absence of acute infectious or inflammatory processes because they can lower serum iron, as iron can be bound to proteins and elevate ferritin, an acute phase reactant, as listed in Table 34-8.[112] After confirming the

deficiency, the iron may be supplemented orally. If the patient does not respond to oral iron, iron sucrose or ferric carboxymaltose may be used as a separate infusion.[113,114] The only parenteral iron that may be used in PN is iron dextran (refer to Chapter 33, "Parenteral Nutrition Support"), and it can only be added in the absence of lipids in the formulation for stability reasons.[115,116] Monitoring of iron status should occur every 3 to 6 months in a deficient patient or a patient receiving supplementation.

TABLE 34-8. Effect of Disease and Clinical Status on Iron Studies

Iron Panel	Increased Levels	Decreased Levels
Iron	More than adequate iron	Infection, inflammation, iron deficiency
TIBC	Iron deficiency	Infection, inflammation
Ferritin	Infection, inflammation	Iron deficiency
% transferrin saturation	More than adequate iron	Iron deficiency

Abbreviations: TIBC, total iron binding capacity.

Copper deficiency can also present with anemia and neutropenia.[117,118] This can result from decreased absorption or increased losses from the intestinal tract. Copper deficiency can also occur from high zinc, vitamin C, or iron supplementation or the use of gastric acid-suppressing medications.[119] Iatrogenic copper deficiency may occur with inadequate amounts in PN because of concern for accumulation in patients with cholestasis. Measuring serum copper or serum ceruloplasmin levels can assess the patient's copper status.[28] This test can be performed with the other trace elements levels as previously discussed.

Both vitamin B12 and folic acid deficiencies present as macrocytic anemia with an elevated MCV. Because these 2 nutrients have an intertwined relationship in the body, it is recommended to assess the status of both whenever either is measured. Patients without an ileocecal valve are particularly at risk for the development of vitamin B12 deficiency since this is a site for absorption. The body can maintain serum vitamin B12 levels

even though storage has been depleted. Therefore, it can also be beneficial to check methylmalonic acid and homocysteine levels when vitamin B12 deficiency is truly suspected. These 2 tests will be elevated in most patients even with a minimal vitamin B12 deficiency. However, homocysteine levels may also be elevated in the presence of folic acid and vitamin B6 deficiency, therefore it is not a specific indicator of vitamin B12 deficiency.[120] An annual measurement of these vitamins is normally sufficient unless deficiency is suspected or in follow-up after an increase in supplementation.[24] See also Chapter 6, "Minerals" and Chapter 8, "Fat-Soluble Vitamins."

Vitamins

Fat-soluble vitamins A, D, E, and K are standard components of most parenteral multivitamin products and EN products. Patients can accumulate excessive amounts because of the body's storage of these vitamins, but deficiency can also occur with certain disease states. Monitoring vitamins A, D, and E once yearly is recommended unless otherwise clinically indicated.[24] Obtaining vitamin D levels every 3 to 6 months may be necessary in patients malnourished before initiation of SNS, patients with malabsorption, and patients with reduced sun exposure.[121] Vitamin K status is more commonly assessed by the PT or INR as previously discussed.

The water-soluble vitamins including B1, B2, B6, B12, niacin, folic acid, pantothenic acid, biotin, and vitamin C are also components of parenteral multivitamins and EN. Routine monitoring of these vitamins is not indicated (except for B12 and folic acid as previously discussed) unless a clinical reason exists to believe that a deficiency or toxicity is occurring; for example, when a patient receives loop diuretic therapy, which has been associated with thiamin deficiency.[28,122] See also Chapter 7, "Water-Soluble Vitamins" and Chapter 8, "Fat-Soluble Vitamins."

Pharmacotherapy Issues Related to Evaluation and Monitoring

Medication and PN Ingredient Shortage

Chronic medication and PN shortages have made it challenging to ensure adequate therapy for patients receiving SNS. Shortages have forced many practitioners to be creative with the available supply, even utilizing very

small amounts of adult trace element solution in neonates so that selenium can be provided. Increased utilization of enteral supplementation and increased laboratory draws for monitoring have also resulted from the PN ingredient shortages. This is not ideal and raises the question of individual risk versus benefit for each patient. ASPEN provides several documents to assist practitioners in making decisions regarding managing available supply.[123]

It is crucial for inventory specialists, buyers, managers, operation supervisors, and nutrition support experts to meet regularly to discuss current shortages, anticipated shortages, and restriction criteria in the event of critical shortages. Dissemination of information and education regarding the shortages is crucial as well. For the most current information and recommendations regarding managing PN ingredient shortages, refer to the following websites:

- ASPEN: https://www.nutritioncare.org/Guidelines_and_Clinical_Resources/Clinical_Practice_Library/Product_Shortage_Recommendations/
- American Society for Health-System Pharmacists: https://www.ashp.org/drug-shortages
- U.S. Food and Drug Administration Drug Shortages: https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages

Drug and Nutrient Interactions

The process of evaluating drug-nutrient interactions begins with the patient medication profile and nutrition regimen. Several excellent published resources and pharmacy computer databases can be utilized to identify drug-nutrient interactions.[124,125] Pharmacy order entry systems can provide alerts for known drug-nutrient interactions (eg, fluoroquinolones and phenytoin) when patients are receiving enteral feedings. Once an interaction is identified, the severity along with the source of the interaction must be evaluated closely to determine a course of action. Some interactions may be avoided by administering the drug and the interacting nutrient, vitamin, or mineral at separate times during the day. If EN ingredients interfere with drug absorption, consultation with a pharmacist and dietitian can aid in

developing a revised enteral regimen for the patient to allow for improved drug absorption.

Certain medications may induce a variety of electrolyte and mineral wasting or retention. Oral, enteral, or parenteral electrolyte and mineral supplementation may be required while a patient is receiving these offending agents. PN is not meant to be a vehicle for acute electrolyte and mineral replacement but can aid in supplementing patients with chronic electrolyte and mineral abnormalities. Electrolyte and mineral supplementation should not be added directly to enteral formulas because of potential instability resulting in clogging, rather each medication should be diluted and given orally or flushed via a feeding tube.[14] Table 34-9 lists some common drug-induced metabolic adverse effects.[126] Patients on these medications require at least weekly laboratory monitoring. The frequency of monitoring is dependent on renal and hepatic function as well.

TABLE 34-9. Drug-Induced Metabolic Adverse Effects

Medication	Adverse Effects
Loop diuretics	Hyponatremia, hypokalemia, hypocalcemia, metabolic alkalosis
Histamine 2 antagonists	Hyponatremia
Corticosteroids	Hypokalemia, hypocalcemia, hypophosphatemia, metabolic alkalosis
Amphotericin B	Hypokalemia, hypomagnesemia, metabolic acidosis
Cyclosporine, Tacrolimus	Hypomagnesemia, hyperkalemia, hypertriglyceridemia
Aminoglycosides	Metabolic acidosis
Citrate	Hypocalcemia

Compatibility of Medications

Nutrition support practitioners rely on a critical review of available PN stability literature, parenteral product manufacturer studies, and in-house stability studies to determine maximum concentrations for micronutrients and compatible medications that can be safely added to PN solutions.

Certain medications may be co-infused with PN or TNA if no other access is available. Published compatibility charts exist, but it is good practice to compare your own institution's PN solutions against published charts and studies.[70,116,127] A range of PN admixtures and TNA have been tested, but it is impossible to test the stability of each solution that may be prescribed in clinical practice. Because of the limited data available, it is best to avoid admixing or co-administering medications with PN and EN unless necessary and after consultation with a pharmacist. Conducting periodic literature reviews for new research related to the stability and compatibility of PN solutions and lipid emulsions is good practice to ensure the currency of computer limits and resources for clinicians.[128]

Conclusion

In summary, subjective and objective patient data must be evaluated to determine the efficacy, tolerance, or any complications of the SNS. The frequency of evaluating and monitoring the data is dependent on the type of SNS provided, the patient's stability, any concurrent medical diagnoses, and progression to nutrition goals. This is a constant process throughout the growth and development of pediatric patients.

Test Your Knowledge Questions

1. You are following a former 28-week gestation female child who is now 2 years old and receives bolus G-tube feedings because of a history of malnutrition and severe oral-motor feeding aversion. Appropriate growth parameters have been achieved on the current feeding plan. She has a recent history of aspiration pneumonia and received antibiotics. She is admitted with acute onset of diarrhea. Which of the following options should not be considered?
   A. Screen for bacterial overgrowth
   B. Review current medications with a pharmacist to identify any that could cause diarrhea
   C. Transition to an elemental formula
   D. Rule out infectious causes of diarrhea such as *Clostridium difficile*

2. A previously stable patient on cyclic PN is now experiencing hyperglycemia. Which of the following is NOT an acceptable response?
   A. Decrease GIR
   B. Increase duration of PN cycle time
   C. Consider work-up for infection
   D. Start subcutaneous long-acting insulin
3. Which of the following nutritional components cannot be added to a TNA?
   A. ILEs containing essential fatty acids
   B. Iron
   C. Vitamin K
   D. Carnitine
4. A child is admitted to the pediatric intensive critical care unit with respiratory distress, fever, and history of poor growth. The admitting physician wanted to check nutrition labs because of poor growth. Which lab should be delayed until the patient is more stable?
   A. Zinc
   B. Electrolytes
   C. Phosphorus
   D. Blood glucose

References

1. Corkins MR, Griggs KC, Groh-Wargo S, et al. Task Force on Standards for Nutrition Support: Pediatric Hospitalized Patients; American Society for Parenteral and Enteral Nutrition Board of Directors; American Society for Parenteral and Enteral Nutrition. Standards for nutrition support: pediatric hospitalized patients. *Nutr Clin Pract.* 2013;28(2):263–276. https://doi.org/10.1177/0884533613475822
2. Mehta NM, Skillman H, Irving S, et al. Guidelines for the provision and assessment of nutrition support therapy in the pediatric critically ill patient: Society of Critical Care Medicine and American Society of

Parenteral and Enteral Nutrition. *JPEN J Parenter Enteral Nutr*. 2017;41(5):706–742. https://doi.org/10.1177/0148607117711387

3. Green Corkins K, Teague E. Pediatric nutrition assessment: anthropometrics to zinc. *Nutr Clin Pract*. 2017;32(1):40–51. https://doi.org/10.1177/0884533616679639
4. Green Corkins K. Nutrition-focused physical examination in pediatric patients. *Nutr Clin Pract*. 2015;30(2):203–209. https://doi.org/10.1177/0884533615572654
5. Mehta NM, Smallwood CD, Graham RJ. Current applications of metabolic monitoring in the pediatric intensive care unit. *Nutr Clin Pract.* 2014;29:338–347. https://doi.org/10.1177/0884533614526259
6. Mehta NM, Corkins MR, Lyman B, et al. American Society for Parenteral and Enteral Nutrition Board of Directors. Defining pediatric malnutrition: a paradigm shift toward etiology-related definitions. *JPEN J Parenter Enteral Nutr*. 2013;37(4):460–481. https://doi.org/10.1177/0148607113479972
7. Goldberg D, Becker P, Brigham K, et al. Identifying malnutrition in preterm and neonatal populations: recommended indicators. *JAND J Acad Nutr Diet*. 2018;118(9):1571–1582. https://doi.org/10.1016/j.jand.2017.10.006
8. Becker P, Nieman Carney L, Corkins M, et al. Consensus statement of the Academy of Nutrition and Dietetics/American Society of Parenteral and Enteral Nutrition: indicators recommended for the identification and documentation of pediatric malnutrition (undernutrition). *Nutr Clin Pract*. 2015:30(1)147–161. https://doi.org/10.1177/0884533614557642
9. Abdel-Rahman S, Bi C, Thaete K. Construction of lambda-mu, sigma values for determining mid-upper arm circumference *z* scores in U.S. children aged 2 months through 18 years. *Nutr Clin Pract*. 2017:32(1):68–76. https://doi.org/10.1177/0884533616676597
10. da Silva J, Seres D, Sabino K, et al. ASPEN consensus recommendations for refeeding syndrome. *Nutr Clin Pract*. 2020;35(2):178–195. https://doi.org/10.1002/ncp.10474
11. Blanc S, Vasileva T, Tume L, et al. Incidence of refeeding syndrome in critically ill children with nutritional support. *Frontiers in Pediatrics*. 2022;10:1–10. https://doi.org/10.3389/fped.2022.932290

12. Marino L, Jotterand Chaparro C, Moullet C. Refeeding syndrome and other related issues in the paediatric intensive care unit. *Pediatric Med*. 2020;3:15–26. https://pm.amegroups.org/article/view/5618/html
13. Santanan e Meneses JF, Leite HP, de Carvalho WB, Lopes E Jr. Hypophosphatemia in critically ill children: prevalence and associated risk factors. *Pediatr Crit Care Med.* 2009;10:234–238. https://doi.org/10.1097/pcc.0b013e3181937042
14. Boullata J, Carrera A, Harvey L, et al. ASPEN safe practices for enteral nutrition therapy. *JPEN J Parenter Enteral Nutr*. 2017;41(1):15–103. https://doi.org/10.1177/0148607116673053
15. Bradford CV, Cober MP, Miller JL. Refeeding syndrome in the neonatal intensive care unit. *J Pediatr Pharmacol Ther.* 2021;26(8):771–782. https://doi.org/10.5863/1551-6776-26.8.771
16. Cormack BE, Jiang Y, Harding JE, et al. Neonatal refeeding syndrome and clinical outcome in extremely low-birth-weight babies: Secondary cohort analysis from the ProVIDE trial. *J Parenter Enteral Nutr*. 2021;45(1):65–78. https://doi.org/10.1002/jpen.1934
17. Danner E, Joeckel R, Michalak S, et al. Weight velocity in infants and children. *Nutr Clin Pract*. 2009;24:76–79. https://doi.org/10.1177/0884533608329663
18. Keller J. Counting the weights: Growth velocity tables for preterm infants. *Nutr Clin Pract*. 2020;35(6):1119–1128. https://doi.org/10.1002/ncp.10550
19. Fenton T, Chan H, Madhu A, et al; Preterm infant growth velocity calculations: a systematic review. *Pediatrics.* 2017;139(3):1–10. https://doi.org/10.1542/peds.2016-2045
20. Worthington P, Balint J, Bechtold M, et al. When is parenteral nutrition appropriate? *JPEN J Parenter Enteral Nutr*. 2017;41(3):324–377. https://doi.org/10.1177/0148607117695251
21. Groh-Wargo S, Barr S. Parenteral nutrition. *Clin Perinatol*. 2022;49(2):355–379. https://doi.org/10.1016/j.clp.2022.02.002
22. Sunderman C, Gottschlich M, Allgeier C, Warden G. Safety and tolerance of intraoperative enteral nutrition support in pediatric burn patients. *Nutr Clin Pract*. 2019;34(5):728–734. https://doi.org/10.1002/ncp.10399

23. Moyer-Mileur L. Anthropometric and laboratory assessment of very low birth weight infants: the most helpful measurements and why. *Semin Perinatol.* 2007;31(2):96–103. https://doi.org/10.1053/j.semperi.2007.02.006
24. Bering J, DiBaise J. Home parenteral and enteral nutrition. *Nutrients.* 2022;14(13):2558–2576. https://doi.org/10.3390/nu14132558
25. Wessel JJ, Kocoshis SA. Nutritional management of infants with short bowel syndrome. *Semin Perinatol.* 2007;31(2):104–111. https://doi.org/10.1053/j.semperi.2007.02.009
26. Zella GC, Israel EJ. Chronic diarrhea in children. *Pediatr Rev.* 2012;33(5):207–218. https://doi.org/10.1542/pir.33-5-207
27. Heine R. Food allergy prevention and treatment by targeted nutrition. *Ann Nutr Metab*. 2018;72(suppl 3):33–45. https://doi.org/10.1159/000487380
28. Gerasimidis K, Bronsky J, Catchpole A, et al. ESPGHAN Committee on Nutrition. Assessment and interpretation of vitamin and trace element status in sick children: a position paper from the European Society for Paediatric Gastroenterology Hepatology, and Nutrition Committee on Nutrition. *J Pediatr Gastroenterol Nutr*. 2020;70(6):873–881. https://doi.org/10.1097/mpg.0000000000002688
29. Berger MM, Talwar D, Shenkin A. Pitfalls in the interpretation of blood tests used to assess and monitor micronutrient nutrition status. *Nutr Clin Pract.* 2023;38(1):56–69. https://doi.org/10.1002/ncp.10924
30. Edwards S, Davis A, Bruce A, et al. Caring for tube-fed children: a review of management, tube weaning, and emotional considerations. *JPEN J Parenter Enteral Nutr.* 2016;40(5):616–622. https://doi.org/10.1177/0148607115577449
31. Cies JJ, Moore II WS. Neonatal and pediatric peripheral parenteral nutrition: What is a safe osmolarity? *Nutr Clin Pract.* 2014;29(1):118–124. https://doi.org/10.1177/0884533613510947
32. Boullata JI, Gilbert K, Sacks G, et al. A.S.P.E.N. Clinical Guidelines: Parenteral nutrition ordering, order review, compounding, labeling, and dispensing. *JPEN J Parenter Enteral Nutr.* 2014;38(3):334–377. https://doi.org/10.1177/0148607114521833
33. Gura KM. Is there still a role for peripheral parenteral nutrition? *Nutr Clin Pract.* 2009;24(6):709–717.

https://doi.org/10.1177/0884533609351318
34. Wendel D, Mezoff EA, Raghu VK, et al. Management of central venous access in children with intestinal failure: A position paper from the NASPGHAN intestinal rehab special interest group. *J Pediatr Gastroenterol Nutr.* 2021;72(3):474–486. https://doi.org/10.1097/mpg.0000000000003036
35. Kolaček S, Punis J, and Hosjak I. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Venous access. *Clinical Nutrition.* 2018;37(6):2379–2391. https://doi.org/10.1016/j.clnu.2018.06.952
36. Kakzanov V, Monagle P, Chan A. Thromboembolism in infants and children with gastrointestinal failure receiving long-term parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2008;32(1):88–93. https://doi.org/10.1177/0148607108032001188
37. Szeszycki E, Kastner A, Mobley L, Gervasio J. A comparison of the efficacy of 0.5 unit/mL versus 1 unit/mL of heparin in neonatal parenteral nutrition. A.S.P.E.N. 2009, Nutrition Practice Poster Presentation.
38. Pai VB, Plogsted S. Efficacy and safety of using L-cysteine as a catheter-clearing agent for nonthrombotic occlusions of central venous catheters in children. *Nutr Clin Pract.* 2014;29(5):636–638. https://doi.org/10.1177/0884533614539177
39. Talathi S, Mezoff E, Galloway D, et al. Anticipated impact of recent ethanol lock shortage and price increase on practice among pediatric intestinal rehabilitation programs across the United States. *JPEN J Parenter Enteral Nutr.* 2022;46(2):319–323. https://doi.org/10.1002/jpen.2128
40. Mezoff EA, Roberts E, Ernst D, et al. Elimination of hospital-acquired central line-associated bloodstream infection on a mixed-service pediatric unit. *JPEN J Parenter Enteral Nutr.* 2022;46(3):608–617. https://doi.org/10.1002/jpen.2195
41. O'Grady NP, Alexander M, Burns LA, et al; the Healthcare Infection Control Practices Advisory Committee (HICPAC). *Guidelines for the Prevention of Intravascular Catheter-Related Infections*. Centers for Disease Control and Prevention; 2011:1–83.

42. Merikhi A, Gheysari A, Madahi Y, et al. Comparison of the effect of antibiotic-lock and ethanol-lock methods on infection rate in children with hemodialysis catheter. *Am J Clin Exp Urol*. 2019;7(6):384–390. https://e-century.us/files/ajceu/7/6/ajceu0103911.pdf
43. Rahhal R, Abu-El-Haija MA, Fei L, et al. Systemic review and meta-analysis of the utilization of ethanol locks in pediatric patients with intestinal failure. *JPEN J Parenter Enteral Nutr.* 2018;42(4):690–701. https://doi.org/10.1177/0148607117722753
44. Opilla MT, Kirby DF, Edmond MB. Use of ethanol lock therapy to reduce the incidence of catheter-related bloodstream infections in home parenteral nutrition patients. *JPEN J Parenter Enteral Nutr*. 2007;31(4):302–305. https://doi.org/10.1177/0148607107031004302
45. Mouw E, Chessman K, Lesher A, Tagge E. Use of an ethanol lock to prevent catheter-related infections in children with short bowel syndrome. *J Pediatr Surg*. 2008;43(6):1025–1029. https://doi.org/10.1016/j.jpedsurg.2008.02.026
46. Onland W, Shin CE, Fustar S, et al. Ethanol-lock technique for persistent bacteremia of long-term intravascular devices in pediatric patients. *Arch Pediatr Adolesc Med*. 2006;160(10):1049–1053. https://doi.org/10.1001/archpedi.160.10.1049
47. Dannenberg C, Bierbach U, Rothe A, et al. Ethanol-lock technique in the treatment of bloodstream infections in pediatric oncology patients with broviac catheter. *J Pediatr Hematol Oncol*. 2003;25(8):616–621. https://doi.org/10.1097/00043426-200308000-00006
48. Crnich CJ, Halfmann JA, Crone WC, Maki DG. The effects of prolonged ethanol exposure on the mechanical properties of polyurethane and silicone catheters used for intravascular access. *Infect Control Hosp Epidemiol*. 2005;26(8):708–714. https://doi.org/10.1086/502607
49. Tan M, Lau J, Guglielmo BJ. Ethanol locks in the prevention and treatment of catheter-related bloodstream infections. *Ann Pharmacother.* 2014;48(5):607–615. https://doi.org/10.1177/1060028014524049
50. Ralls MW, Blackwood RA, Arnold MA, et al. Drug shortage-associated increase in catheter-related blood stream infection in

children. *Pediatrics.* 2012;130(5):e1369–e1373. https://doi.org/10.1542/peds.2011-3894
51. Strauss J, Boctor DL, Silverman JA, et al. Mechanical complications in central lines using taurolidine versus ethanol lock therapy in children with intestinal failure. *JPGN Pediatr Gastroenterol Nutr*. 2022;74(6):776–781. https://doi.org/10.1097/mpg.0000000000003434
52. Josyabhatla R, Naik M, Liu Y, et al. Sodium bicarbonate locks may be a safe and effective alternative in pediatric intestinal failure–a pilot study. *JPGN Pediatr Gastroenterol Nutr.* 2022;75(3):304–307. https://doi.org/10.1097/MPG.0000000000003506
53. Grace E, Shaw C, Whelan K, Andreyev HJ. Review article: small intestinal bacterial overgrowth—prevalence, clinical features, current and developing diagnostic tests, and treatment. *Aliment Pharmacol Ther.* 2013;38:674–688. https://doi.org/10.1111/apt.12456
54. Sieczkowska A, Landowski P, Kamin'ska B, et al. Small bowel bacterial overgrowth in children. *JPGN Pediatr Gastroenterol Nutr.* 2016;62(2):196–207. https://doi.org/10.1097/mpg.0000000000000920
55. Shulman RJ, Phillips S. Parenteral nutrition in infants and children. *JPGN J Pediatr Gastroenterol Nutr.* 2003;36(5):588–607. https://doi.org/10.1097/00005176-200305000-00002
56. Paolo Carnielli V, Correani A, Giretti I, et al. Practice of parenteral nutrition in preterm infants. In: Koletzko B, ed. *Nutritional Care of Preterm Infants: Scientific Basis and Practical Guidelines*. 2nd ed. Karger; 2021:198–211. https://doi.org/10.1159/000514751
57. Kumar Jain A, Nilson J. Parenteral nutrition. In: Goday P, Walia C, ed. *Pediatric Nutrition for Dietitians*. CRC Press; 2002:111–125.
58. Jensen AR, Goldin AB, Koopmeiners JS, et al. The association of cyclic parenteral nutrition and decreased incidence of cholestatic liver disease in patients with gastroschisis. *J Pediatr Surg.* 2009;44(1):183–189. https://doi.org/10.1016/j.jpedsurg.2008.10.033
59. Yanagisawa R, Takeuchi K, Komori K, et al. Hypoglycemia during the temporary interruption of parenteral nutrition infusion in pediatric hematopoietic stem cell transplantation. *JPGN Pediatr Gastroenterol Nutr*. 2017;41(8):1414–1418. https://doi.org/10.1177/0148607116665797

60. Mirtallo JM, Ayers P, Boullata J, et al. ASPEN lipid injectable emulsion safety recommendations, part 1: Background and adult considerations. *Nutr Clin Pract.* 2020;35(5):769–782. https://doi.org/10.1002/ncp.10496
61. Cober MP, Gura K, Mirtallo J, et al. ASPEN Parenteral Nutrition Safety Committee. ASPEN lipid injectable emulsion safety recommendations part 2: Neonate and pediatric considerations. *Nutr Clin Pract*. 2021;36(1):1106–1125. https://doi.org/10.1002/ncp.10778
62. Smoflipid 20%. Package insert. Fresenius Kabi; 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/207648s005lbl.pdf
63. Omegaven 10%. Package insert. Fresenius Kabi; 2022.
64. Clinolipid 20%. Package insert. Baxter Healthcare; 2021.
65. Mirtallo J, Canada T, Johnson D, et al; Task Force for the Revision of Safe Practices for Parenteral Nutrition. Safe practices for parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2004;28(6):S39–S70. Published correction appears in *JPEN J Parenter Enteral Nutr.* 2006;30(2):177. https://doi.org/10.1177/0148607104028006s39
66. Lapillonne A, Fidler Mis N, Goulet O, et al. ESPGHAN/ESPEN/ESPR/CSPEN Working Group on Pediatric Parenteral Nutrition. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition. *Clin Nutr*. 2018;37:2324–2336. https://doi.org/10.1016/j.clnu.2018.06.946
67. Wales PW, Allen N, Worthington P, et al. A.S.P.E.N. Clinical guidelines: Support of pediatric patients with intestinal failure at risk of parenteral nutrition-associated liver disease. *JPEN J Parenter Enteral Nutr*. 2014;38(5):538–557. https://doi.org/10.1177/0148607114527772
68. Christian VJ, Tallar M, Walia CLS, et al. Systematic review of hypersensitivity to parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2018;42:1222–1229. https://doi.org/10.1002/jpen.1169
69. Mogensen KM. Essential fatty acid deficiency. *Nutrition Issues in Gastroenterology, Series #164.* 2017; June. https://med.virginia.edu/ginutrition/wp-content/uploads/sites/199/2014/06/Parrish-June-17.pdf

70. Boullata JI, Mirtallo JM, Sacks, GS, et al. Parenteral nutrition compatibility and stability: A comprehensive review. *JPEN J Parenter Enteral Nutr.* 2022;46:273–299. https://doi.org/10.1002/jpen.2306
71. Trissel LA, ed. *Handbook on Injectable Drugs*. 11th ed. American Society of Health-System Pharmacists; 2001:195–205.4
72. Food and Drug Administration. Safety alert: hazards of precipitation associated with parenteral nutrition. *Am J Hosp Pharm.* 1994;51:1427–1428.
73. Bullock L, Fitzgerald JF, Walter WV. Emulsion stability in total nutrient admixtures containing a pediatric amino acid formulation. *JPEN J Parenter Enteral Nutr.* 1992;16:64–68. https://doi.org/10.1177/014860719201600164
74. Gervasio J. Total nutrient admixtures (3-n-1): Pros versus cons for adults. *Nutr Clin Pract.* 2015;30(3):331–335. https://doi.org/10.1177/0884533615578458
75. Driscoll DF, Ling PR, Bistrain BR. Physical stability of 20% lipid injectable emulsions via simulated syringe infusion: effects of glass vs. plastic product packaging. *JPEN J Parenter Enteral Nutr.* 2007;31(2):148–153. https://doi.org/10.1177/0148607107031002148
76. O'Grady NP, Alexander M, Dellinger EP, et al; Healthcare Infection Control Practices Advisory Committee. Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis*. 2011;52(9):e162–e193. https://doi.org/10.1093/cid/cir257
77. Crill CM, Hak EB, Robinson LA, Helms RA. Evaluation of microbial contamination associated with different preparation methods for neonatal intravenous fat emulsion infusions. *Am J Health Syst Pharm.* 2010;67(11):914–918. https://doi.org/10.2146/ajhp090199
78. DeDonato BM, Bickford LI, Gates RJ. Microbial growth in neonatal intravenous fat emulsion administered over 12 hours versus 24 hours. *J Pediatr Pharmacol Ther.* 2013;18(4):298–302. https://doi.org/10.5863/1551-6776-18.4.298
79. Robinson DT, Ayers P, Fleming B, et al. Recommendations for photoprotection of parenteral nutrition for premature infants: An ASPEN position paper. *Nutr Clin Pract.* 2021;36(5):927–941. https://doi.org/10.1002/ncp.10747

80. O'Grady NP, Alexander M, Burns LA, et al; Healthcare Infection Control Practices Advisory Committee. Guidelines for the prevention of intravascular catheter-related infections. *Infect Control Hosp Epidemiol.* 2002;23(12):759–769. https://doi.org/10.1086/502007
81. Ferrone M, Geraci M. A review of the relationship between parenteral nutrition and metabolic bone disease. *Nutr Clin Pract.* 2007;22(3):329–339. https://doi.org/10.1177/0115426507022003329
82. Namjoshi SS, Muradian S, Bechtold H, et al. Nutrition deficiencies in children with intestinal failure receiving chronic parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2018;42(2):427–435. https://doi.org/10.1177/0148607117690528
83. Dibb M, Lal S. Monitoring long-term parenteral nutrition. *Curr Opin Gastroenterol.* 2019;35(2):119–125. https://doi.org/10.1097/mog.0000000000000504
84. Lee B, Beritto TD. Metabolic bone disease of prematurity. *NeoReviews.* 2022;23(5):e311–e318. https://doi.org/10.1542/neo.23-5-e311
85. Nehra D, Carlson SJ, Fallon EM, et al; American Society for Parenteral and Enteral Nutrition. A.S.P.E.N. clinical guidelines: nutrition support of neonatal patients at risk for metabolic bone disease. *JPEN J Parenter Enteral Nutr.* 2013;37(5):570–598. https://doi.org/10.1177/0148607113487216
86. Merritt RJ, Cohran V, Raphael BP, et al. Intestinal rehabilitation programs in the management of pediatric intestinal failure and short bowel syndrome. *JPGN Pediatr Gastroenterol Nutr.* 2017;65(5):588–96. https://doi.org/10.1097/mpg.0000000000001722
87. Alexander E, Weatherhead J, Creo A, et al. Fluid management in hospitalized pediatric patients. *Nutr Clin Pract.* 2022;37(5):1033–1040. https://doi.org/10.1002/ncp.10876
88. Smith A, Feuling MB, Larson-Nath C, et al. Laboratory monitoring of children on home parenteral nutrition: A prospective study. *JPEN J Parenter Enteral Nutr.* 2018;42(1):148–155. https://doi.org/10.1177/0148607116673184
89. Norman JL, Crill CM. Optimizing the transition to home parenteral nutrition in pediatric patients. *Nutr Clin Pract.* 2011;26(3):273–285. https://doi.org/10.1177/0884533611405797

90. Marshall WJ. Nutritional assessment: its role in the provision of nutrition support. *J Clin Pathol.* 2008;61(10):1083–1088. https://doi.org/10.1136/jcp.2007.051813
91. Myron Johnson A, Merlini G, Sheldon J, Ichihara K; Scientific Division Committee on Plasma Proteins (C-PP), International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). Clinical indications for plasma protein assays: transthyretin (prealbumin) in inflammation and malnutrition. *Clin Chem Lab Med.* 2007;45(3):419–426. https://doi.org/10.1515/cclm.2007.051
92. Evans DC, Corkins MR, Malone A, et al. The use of visceral proteins as nutrition markers: An ASPEN position paper. *Nutr Clin Pract.* 2021;36(1):22–28. https://doi.org/10.1002/ncp.10588
93. Yang HT, Yim H, Cho YS, et al. Prediction of clinical outcomes for massively-burned patients via serum transthyretin levels in the early postburn period [Erratum in *J Trauma Acute Care Surg.* 2012;73(2):534]. *J Trauma Acute Care Surg.* 2012;72(4):999–1005. https://doi.org/10.1097/ta.0b013e3182413bd8
94. Crook MA. Lipid clearance and total parenteral nutrition: the importance of monitoring plasma lipids. *Nutrition.* 2000;16(9):774–775. https://doi.org/10.1016/s0899-9007(00)00381-6
95. Crill CM, Helms RA. The use of carnitine in pediatric nutrition. *Nutr Clin Pract.* 2007;22(2):204–213. https://doi.org/10.1177/0115426507022002204
96. Vanek VW, Borum P, Buchman A, et al. Novel Nutrient Task Force, Parenteral Multi-Vitamin and Multi–Trace Element Working Group; American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. ASPEN position paper: recommendations for changes in commercially available parenteral multivitamin and multi-trace element products. *Nutr Clin Pract*. 2012;27:440–491. https://doi.org/10.1177/0884533612446706
97. Olid AS, Sanchez B, Ojembarrena AA. A systematic review about prophylactic L-carnitine administration in parenteral nutrition of extremely preterm infants. *Farm Hosp.* 2018;42(4):168–173. https://doi.org/10.7399/fh.10976
98. Hamilton C, Austin T, Seidner DL. Essential fatty acid deficiency in human adults during parenteral nutrition. *Nutr Clin Pract.*

2006;21(4):387–394. https://doi.org/10.1177/0115426506021004387
99. Panel on Macronutrients, Panel on the Definition of Dietary Fiber, Subcommittee on Upper Reference Levels of Nutrients, Subcommittee on Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. *Dietary Reference Intakes for Energy, Carbohydrate, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. Washington DC: The National Academies Press; 2005:422–541.
100. Huff K, Breckler F, Cruse W, et al. Pediatric smoflipid therapy: Patient response and safety concerns. *JPEN J Parenter Enteral Nutr.* 2021;45(4):792–799. https://doi.org/10.1002/jpen.1929
101. McMillan NB, Mulroy C, MacKay MW, et al. Correlation of cholestasis with serum copper and whole-blood manganese levels in pediatric patients. *Nutr Clin Pract.* 2008;23(2):161–165. https://doi.org/10.1177/0884533608314529
102. Corkins MR, Martin VA, Szeszycki EE. Copper levels in cholestatic infants on parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2013;37(1):92–96. https://doi.org/10.1177/0148607112443069
103. Cabrera Abreu J, Anne Green. Gamma-glutamyltransferase: value of its measurement in paediatrics. *Ann Clin Biochem.* 2002;39(1):22–25. https://doi.org/10.1258/0004563021901685
104. Litmanovitz I, Eliakim A, Arnon S, et al. Enriched post-discharge formula versus term formula for bone strength in very low birth weight infants: A longitudinal pilot study. *J Perinat Med.* 2007;35(5):431–435. https://doi.org/10.1515/jpm.2007.095
105. Duerksen DR, Papineau N. The prevalence of coagulation abnormalities in hospitalized patients receiving lipid-based parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2004;28(1):30–33. https://doi.org/10.1177/014860710402800130
106. Hardy G, Wong T, Morrissey H, et al. Parenteral provision of micronutrients to pediatric patients: An international expert census paper. *JPEN J Parenter Enteral Nutr*. 2020;44(2):S5–S23. https://doi.org/10.1002/jpen.1990
107. Sauberan J, Mercier M, and Katheria A. Sources of unintentional manganese delivery in neonatal parenteral nutrition. *JPEN J Parenter*

Enteral Nutr. 2022;46(6):1283–1289. https://doi.org/10.1002/jpen.2315
108. Poole RL, Hintz SR, Mackenzie NI, et al. Aluminum exposure from pediatric parenteral nutrition: meeting the new FDA regulation. *JPEN J Parenter Enteral Nutr.* 2008;32(3):242–246. https://doi.org/10.1177/0148607108316187
109. Ibrahim M, Morreale de Escobar GM, Visser TJ, et al. Iodine deficiency associated with parenteral nutrition in extreme preterm infants. *Arch Dis Child Fetal Neonatal Ed.* 2003;88:F56–F57. https://doi.org/10.1136/fn.88.1.f56
110. Moretensen M, Williamson N, Davis C, et al. Iodine deficiency in a parenteral nutrition-dependent adolescent with intestinal pseudo-obstruction. *J Parenter Enteral Nutr.* 2016;40(5):730–733. https://doi.org/10.1177/0148607114551799
111. Otten JJ, Pitzi-Hellwig J, Meyers LD, eds. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements.* National Academies Press; 2006.
112. Northrop-Clewes CA. Interpreting indicators of iron status during an acute phase response—lessons from malaria and human immunodeficiency. *Ann Clin Biochem.* 2008;45(1):18–32. https://doi.org/10.1258/acb.2007.007167
113. Lepus CA, Samela K, Mokha JS. Efficacy and safety of intravenous iron sucrose in children younger than 2 years with intestinal failure. *Nutr Clin Pract.* 2023;38(4):899–903. https://doi.org/10.1002/ncp.10936
114. Cococcioni L, Pensabene L, El-Khouly S, et al. Ferric carboxymaltose treatment for iron deficiency anemia in children with inflammatory bowel disease: Efficacy and risk of hypophosphatemia. *Digestive and Liver Disease.* 2021;53(7):830–834. https://doi.org/10.1016/j.dld.2021.02.017
115. Hwa YL, Rashtak S, Kelly DG. Iron deficiency in long-term parenteral nutrition therapy. *JPEN J Parenter Enteral Nutr.* 2016;40(6):869–876. https://doi.org/10.1177/0148607115587329
116. Trissel LA. Compatibility of medications with 3-in-1 parenteral nutrient admixtures. *JPEN J Parenter Enteral Nutr.* 1999;23(2):67–74. https://doi.org/10.1177/014860719902300267

117. Nagano T, Toyoda T, Tanabe H, et al. Clinical features of hematological disorders caused by copper deficiency during long-term enteral nutrition. *Intern Med.* 2005;44(6):554–559. https://doi.org/10.2169/internalmedicine.44.554
118. Fuhrman MP, Herrmann V, Masidonski P, Eby C. Pancytopenia after removal of copper from total parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2000;24(6):361–366. https://doi.org/10.1177/0148607100024006361
119. Blackmer AB and Bailey E. Management of copper deficiency in cholestatic patients: Review of the literature and case series. *Nutr Clin Pract.* 2013;28(1):75–86. https://doi.org/10.1177/0884533612461531
120. Clark SF. Vitamins and trace elements. In: Gottschlich MM, DeLegge, MH, Mattox T, Mueller C, Worthington P, eds. *The A.S.P.E.N. Nutrition Support Core Curriculum: A Case-Based Approach—The Adult Patient*. *American Society for Parenteral and Enteral Nutrition; 2007:*129–159.
121. Misra M, Pacaud D, Petryk A, et al. Vitamin D deficiency in children and its management: Review of current knowledge and recommendations. *Pediatrics.* 2008;122:398–417. https://doi.org/10.1542/peds.2007-1894
122. Sica DA. Loop diuretic therapy, thiamine balance, and heart failure. *Congest Heart Fail* 2007;13(4):244–247. https://doi.org/10.1111/j.1527-5299.2007.06260.x
123. A.S.P.E.N. Clinical Practice Committee Shortage Subcommittee. A.S.P.E.N. parenteral nutrition trace element product shortage considerations. *Nutr Clin Pract.* 2014;29(2):249–251. https://doi.org/10.1177/0884533614522497
124. Nyffeler MS, Frankel E, Hayes E, et al. Drug-nutrient interactions. In: Merritt R, DeLegge MH, Holcombe B, et al., eds. *The A.S.P.E.N. Nutrition Support Practice Manual.* 2nd ed. American Society for Parenteral and Enteral Nutrition; 2005:118–136.
125. Navaneethan SD, Sankarasubbaiyan SG, Jeevanantham VM. Tacrolimus-associated hypomagnesemia in renal transplant recipients. *Transplantation Proc.* 2006;38(5):1320–1322. https://doi.org/10.1016/j.transproceed.2006.02.077

126. Brown RO. Drug-nutrient interactions. In: Cresci G, ed. *Nutrition Support for the Critically Ill Patient: A Guide to Practice.* CRC Press; 2005:341–355.
127. Robinson CA, Lee JE. Y-site compatibility of medications with parenteral nutrition. In: Phelps SJ, Hak EB, Crill CM, eds. *Teddy Bear Book: Pediatric Injectable Drugs.* 8th ed. American Society of Health-System Pharmacists; 2007:459–463.
128. Ross EL, Salina A, Petty K, et al. Compatibility of medications with intravenous lipid emulsions: Effects of simulated Y-site mixing. *AJHP Am J Health Syst Pharm.* 2020;77(23):1980–1985. https://doi.org/10.1093/ajhp/zxaa299

Test Your Knowledge Answers

1. The correct answer is **C**. Since the current tube-feeding regimen has promoted appropriate growth and has otherwise been well tolerated, it is recommended to review the other options before trialing a new formula. Considering recent antibiotic therapy, it would be possible that she has developed bacterial overgrowth, resulting in diarrhea. Therefore, it would be practical to screen and treat if indicated. It is reasonable to review the medications with the pharmacist. It is possible that the recent antibiotic therapy caused the acute diarrhea event. She could have developed *Clostridium difficile* resulting from the antibiotic therapy. It would be reasonable to test for an infectious cause of the diarrhea and treat it accordingly.
2. The correct answer is **D**. Hyperglycemia in a stable patient usually indicates an acute issue with a high likelihood of infection, so a work-up may be warranted depending on other clinical parameters. Initially decreasing the GIR or extending the PN cycle are the easiest and safest interventions while the etiology of hyperglycemia is being determined. It is recommended to hold off on any insulin therapy until the etiology of acute hyperglycemia can be elucidated. If insulin is started, then hypoglycemia may result after the etiology of the hyperglycemia has resolved.

3. The correct answer is **B**. Iron products cannot be added to PN that contains ILEs because of incompatibility. Essential fatty acids are contained in the lipid emulsions so are therefore provided in a TNA. Vitamin K is a component of injectable multivitamin products and can also be added separately if indicated. Carnitine is compatible with PN and can be ordered if needed.
4. The correct answer is **A**. Zinc is protein-bound and will appear falsely low in patients who are acutely ill with infection or inflammation from the sequestration and decreased synthesis of visceral proteins. Electrolytes, phosphorus, and blood glucose require close monitoring because of potential harm if these are not at least reasonable serum levels and based on clinical need.

APPENDIX 34-1. Neonatal and Pediatric Nutrition Monitoring Form

Name:_____ MRN:_____ Admit Date:_____ MD:_____

DOB:_____ Age:___y___m___d DX: _____

Date:_____ wt_____:___%ile WA_____

ht/lt_____:___%ile HA_____

wt/ht_____%ile BMI_____

dry wt_____ IBW_____

Goals: Calories (kcal/d):_____ kcal/kg:_____

Protein (g/d):_____ g/kg:_____

Fluid (mL/d):_____ mL/kg:_____

LABS								
Date								
Weight (kg)								
Sodium/Potassium	/	/	/	/	/	/	/	/
Chloride/Carbon Dioxide	/	/	/	/	/	/	/	/
BUN/Creatine	/	/	/	/	/	/	/	/
Glucose/Calcium	/	/	/	/	/	/	/	/
Phosphorous/Magnesium	/	/	/	/	/	/	/	/
Total/conj. Bilirubin	/	/	/	/	/	/	/	/
Cholesterol/Triglyceride	/	/	/	/	/	/	/	/
AST/ALT	/	/	/	/	/	/	/	/
AlkPhos/GGT	/	/	/	/	/	/	/	/
Hgb/Hct	/	/	/	/	/	/	/	/
WBC/platelets	/	/	/	/	/	/	/	/
INR								
Zinc								
Albumin/Prealbumin	/	/	/	/	/	/	/	/
PN SCRIPT								
AA/Dex/lipid (gm/kg/d)	/ /	/ /	/ /	/ /	/ /	/ /	/ /	/ /
Na (mEq/kg)								
K (mEq/kg)								
Cl (mEq/kg)								
Anions (A,C)								
Ca (mEq/kg)								
P (mmol/kg)								
Mg (mEq/kg)								
Heparin								
MVI:Peds/Adult								
TMS:Peds/Adult								
Zinc (mcg/kg)								
Copper (mcg/kg)								
Manganese (mcg/kg)								
Chromium (mcg/kg)								
Selenium (mcg/kg)								
Carnitine (mg/kg)								
Rate/Cycle								
Total Volume/d								
Total Calories/d								
Kcal/kg								
GIR								
NPC:N								
Wt used for script								
kcal/mL								
ENTERAL								
Formula								
Rate/Cycle	/	/	/	/	/	/	/	/
Route								
TOTALS								
mL PN/EN	/	/	/	/	/	/	/	/
kcal								
kcal/kg								
Protein (g)								
Protein (g/kg)								
OUTPUT								
UOP mL/kg/h	/	/	/	/	/	/	/	/
Emesis								
Stool								
Ostomy mL/d/mL/kg	/	/	/	/	/	/	/	/
Total mL								

APPENDIX 34-2. Long-Term Lab Tracking Sheet

Patient: D.O.B.				**Physician:**					**Diagnosis:**							
Medical Record Number:				**Fax:** Phone:					**Home Health Care:**							
PN start date:				**Pager:**					**Lab Location/Phone:**							
Enteral Formula:				**Other Contact:**					**Family Contact:**							
Lab Location:																
Date:																
Every Month																
Pre-Albumin																
Triglyceride																
GGT																
MCV																
Every 3 Months																
Selenium																
Manganese																
Copper																
Chromium																
Zinc																
Ferritin																
Iron Serum																
TIBC																
Transferrin Saturation																
Carnitine Total																
Carnitine Free																
Carnitine Ratio																
Every 12 Months																
Vitamin A																
Vitamin D																
Vitamin E																
Vitamin B-12																
RBC Folate																
TSH																
Free T4																
Aluminum																
Recorded By:																
Reviewed By:																
Date Faxed to Physician:																

APPENDIX 34-3. Example Pediatric Patient >40 kg Nutrition Monitoring Form

Pediatric Patient Nutrition Monitoring Form (Patients > 40 kg)							
Name: MRN: DOB: Age: y m d Admit Date:							
Allergies: Dx:							
Actual Body Wt: IBW: Adjusted Body Wt: Wt for Calc: BMI:							
				Goals			
LABS							
Date							
Daily weight (kg)							
Sodium Potassium Chloride Bicarbonate BUN/SCr Glucose							
Calcium							
Phosphorus							
Magnesium							
Total/Conj. Bilirubin	/	/	/	/	/	/	/
Cholesterol/ Triglyceride	/	/	/	/	/	/	/
AST/ALT	/	/	/	/	/	/	/
AlkPhos/GGT	/	/	/	/	/	/	/
Hgb/Hct	/	/	/	/	/	/	/
WBC/Platelets	/	/	/	/	/	/	/
INR							
Zinc							
Albumin							
Prealbumin							
PN ORDER							
AA/Dextrose/ILE (g/d)	/ /	/ /	/ /	/ /	/ /	/ /	/ /
NaCl (mEq/d)							
Na Acetate (mEq/d)							
Na Phos (mmol/d)							
KCl (mEq/d)							
K Acetate (mEq/d)							
K Phos (mmol/d)							
Mg Sulfate (mEq/d)							
Ca Gluconate (mEq/d)							
Reg Insulin (units/d)							
Heparin (units/d)							
Multivitamin	Y N	Y N	Y N	Y N	Y N	Y N	Y N
Trace Minerals	Y N	Y N	Y N	Y N	Y N	Y N	Y N
Selenium (mcg/d)							
Zinc (mg/d)							
Copper (mg/d)							
Thiamine (mg/d)							
Folic Acid (mg/d)							
Rate or Cycle (mL/time)							
TOTAL Volume (daily)							
TOTAL Calories (daily)							
kcal/kg | kcal/mL	|	|	|	|	|	|	|
GIR (mg/kg/min)							
NPC:Nitrogen (150-250:1)							
Wt. Used for Order							

DAILY I/O							
INPUT							
IVF (mL)							
TPN (mL)							
IV/EN Liquid Meds (mL)							
EN Formula / Liquids							
EN Route(s)							
Total EN Fluid Volume							
TOTAL INPUT (mL)							
OUTPUT							
Urine (mL □mL/kg/h □#)	□ □	□ □	□ □	□ □	□ □	□ □	□ □
Mixed Urine/Stool □mL	Y N □	Y N □	Y N □	Y N □	Y N □	Y N □	Y N □
Stool (mL □#)	□	□	□	□	□	□	□
Emesis (mL □#)	□	□	□	□	□	□	□
Drains/G Tube/Misc (mL)							
Ostomy (mL/d)							
TOTAL OUTPUT (mL)							
I/O Difference (± mL)							
Home Diet:							
Home Medications/Supplements:							
Procedures:							
Scope Results							
Endoscopy:							
Colonoscopy:							
Progress Notes:							

Periodic Lab Monitoring of Trace Elements										
Date:										
Copper										
Manganese										
Chromium										
Selenium										
Carnitine										
Aluminum										
Zinc										

35

Ethical Issues in Providing Nutrition

Kelly Cronin Komatz, MD, MPH, FAAP, FAAHPM

Learning Objectives

1. Define “natural” vs “medical” provision of nutrition.
2. Identify the importance of joint determination of goals of treatment with the family.
3. Utilize the American Academy of Pediatrics Clinical Report on Forgoing Artificial Hydration and Nutrition to direct end-of-life care.
4. Discuss the ethical principles in decision-making and how they direct the eventual patient care plan.

Introduction

This entire curriculum has focused on nutrition support in pediatric patients. This last chapter focuses on some very important questions about the ethics of providing nutrition support. Just because we can, does not always mean we should or are obligated to provide nutrition support in every pediatric patient. This area gets very little focus in our educational process and day-to-day clinical practices. Nonetheless, sooner or later most practitioners eventually find themselves in a situation where they are faced with important ethical considerations.

“Natural” Versus “Medical” Provision of Nutrition

It is important when discussing ethical issues that the terms and phrases being used are understood by all parties involved in the patient’s care. An important difference exists between the “natural” provision of nutrition and the “medical” provision of nutrients. These terms can be used in various manners, but for this chapter, the definition by Porta and Frader[1] is helpful because they describe their typical usage in clinical and bioethical literature. The natural provision of nutrition refers to all feedings that do not require medical intervention—specifically breast, bottle, cup, and other oral feedings. Medical provision of nutrition refers to nutrition that requires a special physician order; for example, the use of a nasogastric or orogastric tube, central intravenous (IV) catheter, or the placement of a gastrostomy or jejunostomy feeding tube.

Determining the Goals of Nutrition

When ethical questions arise in healthcare decision-making, using a framework of goals for treatment is important when discussing the use or disuse of a particular medical intervention. For example, a child who is placed on a ventilator after a sudden acute event affecting their ability to breathe has normal oxygenation and ventilation as the goal. Another example is a child who has undergone cardiac surgery to correct a congenital heart defect. That child is likely to be maintained on a ventilator and to receive infusions of blood pressure-sustaining medications, as well as nutrition provided through a central IV catheter during the immediate postoperative period. Therefore, the goal in both cases is sustaining the child until the time their healing begins.[2]

However, when discussing the ethics of providing nutrition, it is important to expand the discussion related to the overall goals of treatment. The basic goal of providing pediatric patients with nutrition is to provide them with the calories, protein, vitamins, and minerals needed to meet basic metabolic demands for appropriate growth and development. It is important to recognize that goals of treatment can change with time and often do. For

example, providing parental nutrition through a central IV catheter to a child awaiting an organ transplant can change if the patient experiences severe complications that preclude receipt of a transplant. The discussion related to continuing the parenteral nutrition might change to new goals related to improved quality of life and allow for "de-medicalization" of the child and their nutrition.[2]

Is There a Tendency To View Medically Provided Nutrition Differently Than Other Medical Interventions?

The provision of nutrition to a pediatric patient often has values assigned to it that make medically provided nutrition unique from other forms of life-sustaining medical interventions. Rarely is the removal of a ventilator described as "suffocating the patient to death." However, when the decision is made to withhold or withdraw medically provided nutrition, it is often described as "starving the patient to death." The tendency to use this language demonstrates that a certain value is associated with the provision of medical "feedings" that is inherently related to the value of providing a patient nutrition.[3]

An example of this perspective of value assigned to feeding and nutrition is demonstrated in a survey with pediatric healthcare providers. The Pediatric Section of the Society of Critical Care Medicine found that 98% of physicians were likely to withhold cardiopulmonary resuscitation, 86% withdrew ventilators, but only 42% withdrew tube feedings.[4] Often the main reason given for continuing medically provided nutrition and hydration is concern about the child's suffering. However, in a recent survey completed by Lazzara and Boss of 195 clinicians who collectively have medically managed over 900 infants/children during the process of withholding/discontinuing medically provided nutrition and hydration, results indicated that the patients were comfortable, peaceful, and had decreased work of breathing and secretions.[5]

Why Is Unique Value Assigned to Feeding Versus Nutrition?

Ethical issues involving the provision of withholding or withdrawing nutrition often occur in a unique and complex social dynamic and are charged with emotions. What is it about feeding that makes it more likely to have additional value ascribed to it as opposed to other medical interventions? Language and terminology are always important in conversations, but especially when discussing end-of-life decisions. The term "food" elicits images of eating, chewing, tasting, and swallowing along with the pleasures and social connotations that accompany those actions. Failing to distinguish between "food" and the medical process of delivering hydration and nutrition will make discussions surrounding end-of-life decisions more difficult.

The Clinical Report on Forgoing Artificial Hydration and Nutrition from the American Academy of Pediatrics outlines several general principles when considering withholding or withdrawing medically provided hydration and nutrition[6]:

- Medically provided fluids and nutrition constitute a medical intervention that may be withheld or withdrawn for the same types of reasons that justify the medical withholding or withdrawal of other medical treatments.
- Decisions about whether medical interventions should be provided to a child, including medically provided fluids and nutrition, should be based on whether the intervention provides a net benefit to the child.
- Medically provided fluids and nutrition can be withdrawn when such measures only prolong and add morbidity to the process of dying.
- Parents or guardians should be fully involved in shared decision-making with the physician and healthcare team and should support the decision to withhold or withdraw medically provided fluids and nutrition.
- Parents or guardians should be reassured that their child will be kept comfortable and should be informed about the likely course of events, including broad estimates of when the child's death is anticipated.

Ethical Principles in Decision Making

Ethical theories are broad-based and reflect a philosophical commitment to moral reasoning and decision-making that may apply to many situations throughout all types of human interactions, not just medically based issues. Bioethics reflects the adaptation of ethical considerations with an emphasis on how best to support quality of life with changing advances in medicine and biological sciences. The basic bioethical principles include the following:

1. Autonomy—Respect the ability of individuals to make informed decisions affecting health. Parents/guardians are the decision-makers for infants and children who cannot make their own decisions and therefore are understood to be surrogate decision-makers.
2. Nonmaleficence—Avoid doing harm.
3. Beneficence—Do good.
4. Justice—Distribute goods and resources fairly.

Decision-making in pediatrics is unique because in most situations the parents or legal guardians are the decision-makers. It is understood that they are the "surrogate decision-makers." In adult medicine, competent adults can make their own decisions, thereby exercising their autonomy. Medical decision-making in children has centered on the best-interest standard focusing on the interests of the pediatric patient rather than the interests of the parents or caregivers. There might be cases where adolescents are involved in the decision-making, assenting or refusing to a medical decision being made on their behalf. These situations are found typically in adolescents who are living with a chronic medical disease.

The principles of avoiding harm (nonmaleficence) and doing good (beneficence) are more heavily weighted when making decisions related to medically provided hydration and nutrition. How can it be harmful to provide nutrition and hydration to a child? Is it not good when a child is fed and thriving? Professionals are obligated to report to child protection agencies when a child is "malnourished" due to lack of adequate nutrition. So how can it be okay to withhold adequate nutrition in a child?[7]

Palliative Care

Ethical challenges in nutrition management for pediatric patients always need to be evaluated in the context of goals and values, which warrants open communication and a collaborative approach within the medical team. Most major hospitals, including pediatric hospitals, have dedicated palliative care teams. These teams are crucial in assisting the medical team and parents/guardians when making difficult medical decisions. When a decision is made to move from life-sustaining or life-prolonging treatment to comfort measures, the palliative care team is invaluable to the patient, the family, and the medical team caring for the patient during the dying process.[2]

Hellmann et al[8] surveyed parents who decided to withdraw medically provided hydration and nutrition while their infant was in the neonatal intensive care unit. Their study concentrated on only the parents who decided to withdraw medical hydration and nutrition independent of withdrawing mechanical ventilator support. The study identified 3 themes regarding the decision to withdraw medical hydration and nutrition: communication, decision-making, and the dying experience. The authors further identified subthemes within these categories.

In the communication category, parents' responses consistently identified subthemes of the virtues of good communication, the importance of relationship building, admitting the uncertainty of prognoses, and ways of sharing information.

The decision-making domain encompassed subthemes of the parents as decision-makers, their reluctance to have to make the decision, the actual decision itself, and the process of getting to that decision. As expected, parents struggled the most with the domain of decision-making.

In the dying experience, subthemes included the myriad of parent emotions, achieving the best in a bad situation, receiving encouragement and support, and making a life after the death of their infant. In this study, the median time between the actual withdrawal of medical hydration/ nutrition and the child's death was 16 days.

After the decision has been made to withhold or withdraw medically provided hydration and nutrition, the medical team needs to continue to support the parents/caregivers in their decision. Medical and ancillary staff

caring for the patient and family also require continuous support, especially when the patient starts to linger. The palliative care team is essential in providing these services to all involved. The physical changes can be "normalized" by the palliative care medical team. Continued reflection and making meaning of the situation is important for all and palliative care teams are uniquely positioned to provide this support.

> Dr. Frader states in his perspective piece in the Hastings Center Report[9]: I believe candor, acknowledgement of uncertainty about the child's experience, and a solemn promise to respond quickly and unhesitatingly to signs of distress or discomfort make a difference. I believe clinicians need to spend all available time at the bedside during the child's dying because we clinicians need to stay connected to the reality of death.

Case Study

Mary is a 12-year-old girl who was diagnosed soon after birth with congenital toxoplasmosis. Mary has been cared for by her parents and younger brother in her home with the assistance of nurses throughout her life. She is unable to walk or care for herself, but she is interactive with her family through vocalizations, smiles, grimaces, and laughs.

The family has made several difficult decisions over Mary's 12 years of life, including not having surgery for her scoliosis or tendon releases for her hip contractures and not having a tracheostomy placed when she was admitted for aspiration pneumonia last year. The family has always known that Mary's life expectancy was limited and has made medical decisions for Mary based on her quality of life and comfort.

Mary is now demonstrating signs and symptoms of not being able to tolerate her gastrostomy tube feedings. The palliative care team has been making home visits to assess Mary and has prescribed different treatment options to try to keep Mary comfortable. These treatments have included medications, changes in her enteral nutrition, attempts at changing the rate of her feedings, and eventually attempting clear fluids only. However, each time Mary's feedings approach the goal for volume and/or calories, she demonstrates pain within an hour of starting the feeding.

The family sees that the enteral feedings are causing Mary pain and distress. The father is struggling with withdrawing her medically provided enteral nutrition and "starving Mary to death." The father also expresses concern that if they do choose to withhold her nutrition, the local news channel will be on their front lawn because they are "starving" their daughter.

This family's struggle to withdraw medically provided nutrition is commonplace for any caregiver whose loved one is nearing the end of life, whether from a lifelong medical condition or an acute illness.

Conclusion

The provision of medically provided hydration and nutrition has become readily accepted within the practice of medicine and is often overlooked as being a "medical" therapy that is essentially life-prolonging. This includes enteral feedings through oro/nasal or gastrostomy/jejunostomy tubes, as well as parenteral nutrition. Ethical challenges present themselves when families are facing the decision to forgo these medical treatment options, and the challenge is best met with open dialogue, respectful listening, and clarity of communication and sensitivity between the patient, family, and medical team. Palliative care and bioethicists are available to parents/guardians and team members when making these decisions.

Test Your Knowledge Questions

1. Withholding or withdrawing medically provided hydration and nutrition is no different from an ethical perspective than the removal of ventilator support when the goal of treatment is for comfort at the end of life. True or False?
2. Which of the following actions is *not* recommended to help reach an ethical decision regarding the provision of nutrition?
   A. Make sure everyone on the team is using the same definition for commonly used medical and ethical terms.
   B. Avoid talking to the family or the patient until a decision is made so that the team does not appear uncertain.

C. Define the long-term goal of providing nutrition to the patient.
D. Discuss with the family their views and beliefs regarding feeding and/or the provision of nutrition.

References

1. Porta N, Frader J. Withholding hydration and nutrition in newborns. *Theor Med Bioeth*. 2007;28:443–451. https://doi.org/10.1007/s11017-007-9049-6
2. Jones PM, Carter B. Ethical issues in the provision of nutrition. In: Corkins M, Balint J, eds. *A.S.P.E.N. Pediatric Nutrition Support Core Curriculum.* American Society for Parenteral and Enteral Nutrition; 2010:477–486.
3. Carter BS, Leuthner SR. The ethics of withholding/withdrawing nutrition in the newborn. *Semin Perinatol.* 2003;27(6):480–487. https://doi.org/10.1053/j.semperi.2003.10.007
4. Society of Critical Care Medicine, Task Force on Ethics. Consensus report on the ethics of forgoing life-sustaining treatments in the critically ill. *Crit Care Med*. 1990;18(12);1435–1439. https://doi.org/10.1097/00003246-199012000-00026
5. Lazzara A, Boss RD. Observation of child experience during discontinuing of medically provided nutrition and hydration. *J Pain Symptom Manage*. 2022;65(3):155–161. https://doi.org/10.1016/j.jpainsymman.2022.12.008
6. Diekema DS, Botkin JR. Forgoing medically provided nutrition and hydration in children. *Pediatrics*. 2009;124(2):813–822. https://doi.org/10.1542/peds.2009-1299
7. Truog RD. Withholding and withdrawing life-sustaining treatments. In: Quill TE, Miller FG, eds. *Palliative Care and Ethics.* Oxford University Press; 2014:187–198.
8. Hellmann J, Williams C, Ives-Baine, L, Shah PS. Withdrawal of artificial nutrition and hydration in the neonatal intensive care unit: parental perspectives. *Arch Dis Child Fetal Neonatal Ed.* 2013;98(1):F21–F25. https://doi.org/10.1136/fetalneonatal-2012-301658

9. Frader JE. Discontinuing artificial fluids and nutrition: discussions with children's families. *Hastings Cent Rep.* 2007;37(1):49.
10. Schwartz DB, Barrocas A, Annetta MG et al. Ethical aspects of artificially administered nutrition and hydration: an ASPEN Position Paper. *Nutr Clinical Pract.* 2021;36(2):254–267. https://doi.org/10.1002/ncp.10633

Test Your Knowledge Answers

1. The correct answer is **True**. Medically provided fluids and nutrition is a medical intervention akin to other medical treatments, for example, a ventilator.
2. The correct answer is **B**. Parents and caregivers appreciate open and honest communication even if the information is difficult to share.

The author of this chapter wishes to thank Patrick Jones, MD, MA, and Brian Carter, MD, for their contributions to previous editions of this text.

Contributors

Suzanna L. Attia, MD, MScPH
Assistant Professor of Pediatrics
University of Kentucky College of Medicine
Lexington, KY

Jane Balint, MD
Emeritus Physician, Center for Intestinal Rehabilitation and Nutrition Support
Pediatric Gastroenterology, Hepatology and Nutrition, Nationwide Children's Hospital
Emeritus Associate Professor of Clinical Pediatrics, The Ohio State University College of Medicine
Columbus, Ohio

Elizabeth Bobo, MS, RD, LDN, CNSC, FAND
Senior Clinical Dietitian
Division of Gastroenterology and Nutrition
Nemours Children's Health
Jacksonville, FL

Julie Bonn, MD
Assistant Professor of Pediatrics

University of Cincinnati College of Medicine Attending Physician
Division of Gastroenterology, Hepatology & Nutrition
Cincinnati Children's Hospital Medical Center
Cincinnati, OH

Peggy R. Borum, PhD
Professor of Human Nutrition
Institute of Food and Agricultural Sciences
University of Florida
Gainesville, FL

Sandy van Calcar, PhD, RD, LD
Associate Professor
Department of Molecular and Medical Genetics
Graduate Programs in Human Nutrition
Oregon Health and Science University
Portland, OR

Danielle H. Campbell, MS, RDN, LDN, CLC
Pediatric Clinical Dietitian
Children's Hospital of Philadelphia
Philadelphia, PA

Esther Castanys-Muñoz, PhD
University Site Manager
Abbott Nutrition R&D, University Science Park
Granada, Spain

Judith Christie, RN, MSN
Nutrition Support Nurse
Children's Hospital of Michigan

Detroit, MI

Kelly Green Corkins, MS, RD, LDN, CNSC, FAND, FASPEN
Clinical Dietitian III
Le Bonheur Children's Hospital
Memphis, TN

Mark R. Corkins, MD, FAAP, FASPEN, CNSC
Division Chief of Pediatric Gastroenterology
University of Tennessee Health Science Center/Le Bonheur Children's Hospital
Memphis, TN

Catherine M. Crill, PharmD, FCCP, BCNSP
Associate Professor, Department of Clinical Pharmacy & Translational Science and Pediatrics
The University of Tennessee Health Science Center
Clinical Pharmacy Specialist, Parenteral Nutrition Service
Le Bonheur Children's Hospital
Memphis, TN

Wendy Cruse, MMSc, RDN, CSPCC
Pediatric Clinical Dietitian Specialist
Riley Hospital for Children at Indiana University Health
Indianapolis, IN

Molly Dienhart, MD
Medical Director
Center for Intestinal Rehabilitation and Nutrition Support
Nationwide Children's Hospital

Associate Professor of Clinical Pediatrics
The Ohio State University College of Medicine
Columbus, Ohio

Jill Dorsey, MD, MS
Pediatric Gastroenterologist
Division of Gastroenterology and Nutrition
Nemours Children's Health
Jacksonville, FL

Mary Beth Feuling, MS, RD, CD
Advanced Practice Dietitian
Research and Technology
Children's Wisconsin
Milwaukee, WI

David Freestone, DO
Pediatric Gastroenterology
Children's Nebraska
University of Nebraska Medical Center
Omaha, NE

Amy Gates, PhD, RDN, LD
Associate Medical Director
Evidence Generation and Clinical Research
Reckitt Mead Johnson Nutrition
Clarks Hill, SC

Donald George, MD
Chief (Retired)
Division of Gastroenterology and Nutrition

Nemours Children's Health
Jacksonville, FL

James Gherardi, BS, DTR
Dietetic Technician
The Children's Hospital of Philadelphia
Philadelphia, PA

Leslie M. Gimenez, MD
Associate Professor
Division of Allergy and Clinical Immunology
Medical College of Wisconsin
Milwaukee, WI

Praveen S. Goday, MBBS, FAAP
Director of Nutrition and Feeding Programs Nationwide Children's Hospital
Professor of Clinical Pediatrics
The Ohio State University
Columbus, OH

Memorie M. Gosa, PhD, CCC-SLP, BCS-S
Associate Professor/Chair
Department of Communicative Disorders
The University of Alabama
Tuscaloosa, AL

Kathleen M. Gura, PharmD, FASHP, FPPA, FASPEN, FMSHP, BCNSP
Pharmacy Clinical Research Program Manager Boston Children's Hospital

Assistant Professor, Pediatrics
Harvard Medical School
Boston, MA

Richard A. Helms, PharmD, FPPAG, FASPEN
Emeritus Professor and Past Chair
Department of Clinical Pharmacy and Translational Science
University of Tennessee Health Science Center

Oscar R. Herrera, PharmD, BCNSP
Assistant Professor
Department of Clinical Pharmacy and Translational Science
University of Tennessee Health Science Center
Memphis, TN

Kishore R. Iyer, MBBS, FRCS(Eng), FACS
Director
Adult and Pediatric Intestine Rehab & Transplant Program
Mount Sinai Hospital
Professor of Surgery, Pediatrics and Global Health
Transplant Surgery Fellowship Program Director
Icahn School of Medicine at Mount Sinai
New York, NY

Marisa Juarez-Calderon, MPH, RD, LD
Manager
Renal Allied Health
Texas Children's Hospital
Houston, TX

Samuel A. Kocoshis, MD

Professor of Pediatrics
University of Cincinnati College of Medicine
Medical Director, Intestinal Transplantation and Medical Director Emeritus
Intestinal Rehabilitation
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Rachel Kofsky, MA, RD, CSP, LDN, CLC
Clinical Dietitian
Children's Hospital of Philadelphia
Philadelphia, PA

Kelly Cronin Komatz, MD, MPH, FAAP, FAAHPM
Medical Director
Bower Lyman Center for Medically Complex Children
Program Director
UFCOM Jacksonville Pediatric Hospice and Palliative Medicine Fellowship
Jacksonville, FL

Winston Koo, MBBS, FACN, CNS
Professor
Department of Nutrition and Food Science
Wayne State University
Detroit, MI

Arlet G. Kurkchubasche, MD
Professor
Emeritus of Surgery and Pediatrics

Alpert School of Medicine
Brown University
Providence, Rhode Island

Lindsey Lee, MS, RD, LDN, CSP
Clinical Dietitian III
St. Jude Children's Research Hospital
Memphis, TN

José M. López-Pedrosa, PhD
Volwiler Senior Associate Research Fellow
Research Section Manager
Abbott Nutrition R&D
Granada, Spain

Yen-Ling Low, PhD
Senior Director
International Nutrition Science and Global Platforms Innovation and Research
Abbott Nutrition R&D
Singapore

Mirjana Lulic-Botica, PharmD, BCPS
Neonatal Clinical Pharmacy Specialist
Hutzel Women's Hospital
Detroit Medical Center
Assistant Professor
College of Nursing
Wayne State University
Adjunct Assistant Professor

College of Pharmacy
Wayne State University
Detroit, MI

Nicole M. Martin, RD, CSP, CD
Clinical Dietitian Lead
Children's Wisconsin
Milwaukee, WI

Maria Mascarenhas, MBBS
Medical Director
Department of Clinical Nutrition
Nutrition Section Chief
Division of Gastroenterology, Hepatology, and Nutrition
The Children's Hospital of Philadelphia
Philadelphia, PA

Carol G. McKown, DDS, MS, PC
Owner/President
Carmel Pediatric Dentist
Volunteer Faculty
Riley Hospital Pediatric Dentistry Department
Carmel, IN

Clare McLaughlin, RDN, CSPCC
Pediatric/Neonatal Clinical Dietitian Senior
Riley Hospital for Children at Indiana University Health
Indianapolis, IN

Jessica Monczka, RD, CNSC, FASPEN
Quality Assurance Manager

Option Care Health
Denver, CO

Erika May Murphy, PharmD, BCPPS
Clinical Pharmacist
Oncology and Bone Marrow Transplant
Children's Hospital of Philadelphia
Philadelphia, PA

Christina L. Nelms, MS, RD, LMNT/LD
Pediatric Renal Dietitian
Children's Mercy, Kansas City
Kansas City, MO

Laura Padula, MS, RD, LDN
Senior Clinical Dietitian
The Children's Hospital of Philadelphia
Philadelphia, PA

Vikram Raghu, MD MS
Assistant Professor of Pediatrics
University of Pittsburgh School of Medicine
UPMC Children's Hospital of Pittsburgh
Pittsburgh, PA

Katina Rahe, BSN, RN, CPN
Certified Pediatric Nurse
Children's Mercy Kansas City, Adele Hall
Kansas City, MO

Michelle Reed, MS, RD, CSP, LDN, CDCES

Diabetes Educator
Children's Hospital of Philadelphia
Philadelphia, PA

Gina Rempel, MD, FRCPC, FASPEN
Pediatric Nutrition Support and Complex Care Specialist
Children's Hospital Winnipeg, University of Manitoba Winnipeg, MB, Canada

Susan R. Rheingold, MD
Professor of Clinical Pediatrics
Division of Oncology
The Children's Hospital of Philadelphia
Philadelphia, PA

Ricardo Rueda, MD, PhD, MSc
Volwiler Senior Research Fellow
Associate Director Strategic Research
Abbott Nutrition R&D
Granada, Spain

May Saba, PharmD, BCNSP
Adjunct Associate Professor
Eugene Applebaum College of Pharmacy and Allied Health
Wayne State University
Detroit, MI

Gerald L. Schmidt, PharmD, BCNSP
Pharmacy Nutrition Specialist
UF Health Jacksonville
Jacksonville, FL

Timothy Sentongo, MD
Professor of Pediatrics
Director of Pediatric Nutrition Support;
Director of Pediatric Gastrointestinal Endoscopy
University of Chicago Medical Center
Chicago, IL

Kavisha Shah, MD
Assistant Professor
Division of Pediatric Cardiology
Faculty Member
Department of Pediatrics
Minneapolis, MN

Sarah Simental, MS, RD, CSNC, CSPCC
Clinical Dietitian III
Pediatric Intensive Care Unit
Children's Hospital Los Angeles
Los Angeles, CA

Karen Smith, MS, RD, CSO, LD/LDN
Manager of Clinical Nutrition
Texas Oncology
Dallas, TX

Paula Soriano, MSc
Nutrition Research Intern.
Abbott Nutrition R&D- University Science Park
Granada, Spain

Bethany Squillante, MS, RD, CSP, LDN

Lead Clinical Dietitian
Children's Hospital of Philadelphia
Philadelphia, PA

Elaina Szeszycki, PharmD, CNSC
Clinical Pharmacist
Nutrition Support, Intestinal Rehabilitation and Ambulatory Pediatric Gastroenterology
Riley Hospital for Children at Indiana University Health
Indianapolis, IN

Mary Pat Turon-Findley, MEd, RD, CMHIMP, LD
Registered Dietitian III
Cincinnati Children's Hospital Medical Center
Cincinnati, OH

Christina J. Valentine, MD, MS, RD, FAAP, FASPEN
Professor of Neonatology
Department of Pediatrics
University of Arizona
Tucson, AZ

Ellen Wagner, MD
Pediatric GI Fellow
University of Chicago
Chicago, IL

Bradley A. Warady, MD
Professor of Pediatrics
University of Missouri-Kansas City School of Medicine
Director of the Division of Pediatric Nephrology,

Director of Dialysis and Kidney Transplantation
Children's Mercy Kansas City
Kansas City, MO

Letitia Warren, RD, CSP
Pediatric Dietitian
Department of Clinical Nutrition
Children's Hospital of Michigan
Detroit, MI

Darielle Wilhelm, RD, LDN, CNSC
Lead Clinical Dietitian
Department of Clinical Nutrition
Children's Hospital of Philadelphia
Philadelphia, PA

Hannah Williams, RD, LDN, CSP, CSO
Lead Clinical Dietitian
Department of Clinical Nutrition
Children's Hospital of Philadelphia
Philadelphia, PA

Elizabeth L. Wright, MS, RDN, CSP, LDN, FAND, CLC
Clinical Pediatric Dietitian
Children's Hospital of Philadelphia
Philadelphia, PA

Desale Yacob, MD
Medical Director of the Motility Center
Nationwide Children's Hospital
Associate Professor of Pediatrics

The Ohio State University College of Medicine
Columbus, OH

Reviewers

Katelyn Ariagno, MPH, RD, CNSC
Senior Nutrition Specialist; Parenteral Nutrition Education Coordinator
Division of Gastroenterology, Hepatology and Nutrition
Boston Children's Hospital

M. Petrea Cober, PharmD, BCNSP, BCPPS, FASPEN
Professor of Pharmacy Practice
Northeast Ohio Medical University, College of Pharmacy

Ada Tina Lin, MD, FAAP
Pediatric Critical Care Medicine
Nationwide Children's Hospital
The Ohio State University College of Medicine

Russell J. Merritt, MD, PhD
Founding Medical Director
Intestinal Rehabilitation Program
Children's Hospital Los Angeles
Emeritus Professor of Clinical Pediatrics
Keck School of Medicine
University of Southern California

Anita Nucci, PhD, RD, LD, FASPEN
Department of Nutrition
Byrdine F. Lewis College of Nursing and Health Professions
Georgia State University

Gina Rempel, MD, FRCPC, FASPEN
Nutrition Support and Complex Care Pediatrician
Section of Rehabilitation and Complex Care
Department of Pediatrics & Child Health
Rady Faculty of Health Science, Max Rady College of Medicine
University of Manitoba

Justine Turner, MBBS, FRACP, PhD
Professor of Pediatrics
Division of Gastroenterology and Nutrition
University of Alberta

Gerald L. Schmidt, Pharm.D., BCNSP
Pharmacy Nutrition Specialist
UF Health Jacksonville
Jacksonville, FL