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Enteral Feeding Intolerance: Updates in Definitions and Pathophysiology

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Abstract

Enteral feeding intolerance (EFI) is a common feature in critically ill patients worldwide. However, there is no clear, widely agreed-upon definition available, with various studies rarely using the same definition. The term EFI is frequently used to describe vomiting or large gastric residual volumes associated with enteral feeding as a result of gastroparesis/delayed gastric emptying. However, the syndrome of EFI may represent the consequence of various pathophysiological mechanisms, and this heterogeneity may explain varying associations with outcomes. In clinical practice, a pragmatic definition may be useful. A pragmatic definition of EFI is that a clinician has decided to reduce the amount of enteral nutrition specifically because features of gastrointestinal dysfunction appeared during enteral feeding. For research purposes, a more detailed definition of EFI is required to improve knowledge and explore interventions that may improve patient-centered outcomes. The objective of this review is to summarize available evidence on existing definitions, pathophysiological mechanisms, and the clinical relevance of EFI in critically ill patients. Based on current knowledge, we propose a conceptual framework for a definition of EFI for a future consensus process. (*Nutr Clin Pract.* 2020;0:1–10)

Keywords

definition; enteral feeding intolerance; enteral nutrition; gastrointestinal dysmotility; pathophysiology

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Introduction

Enteral feeding intolerance (EFI) in critically ill patients is a common problem in intensive care units (ICUs) worldwide.[1,2] Using existing definitions, it has been estimated that EFI occurs in about one-third of critically ill patients.[3] Despite the prevalence, there is no widely agreed-upon definition of EFI. [3] A major challenge in having a unified definition is the wide spectrum of pathophysiological mechanisms that affect different parts and functions of the gastrointestinal (GI) tract, resulting in a variety of clinical symptoms and signs that are all considered manifestations of EFI. These symptoms and signs are largely nonspecific, limiting any assumptions regarding the actual severity of GI dysfunction and related outcome.[4] Moreover, there is no robust, well-validated and widely used objective methodology to measure GI dysfunction in critically ill patients. Furthermore, the clinical outcomes may be affected by EFI in several ways: the underlying GI dysfunction and the resulting underfeeding due to EFI, as well as interventions applied to manage EFI, may all affect outcome. Accordingly, the impact of EFI on clinical outcome may vary considerably between patients despite similar clinical manifestation. It is not entirely clear which pathophysiological mechanisms of EFI play a causative role in adverse outcomes and which mechanisms and manifestations in which patients should be targeted with interventions.

In this narrative review, we summarize evidence on existing definitions, pathophysiological mechanisms, and the clinical relevance of EFI in critically ill patients. Based on current knowledge, we propose a conceptual framework to reach a unified definition of EFI in a future consensus process.

Definitions in the Literature

A systematic review published in 2014 identified 43 different existing definitions of EFI and suggested that these definitions could be categorized into 3 main categories: "large" gastric residual volumes (GRVs), GI symptoms, and "inadequate" delivery of enteral nutrition (EN)[3] (Table 1). As a result of the heterogeneity of the definitions used, the prevalence of GI dysfunction leading to EFI and the strength of associations with outcomes vary over a very wide range. Accordingly, the reported prevalence has varied between 2% and 75%.[3] It has been shown that the application of different definitions of EFI in the same patient cohort results in a wide variability in prevalence and an association with mortality.[5] The definition of EFI that has been shown to have the highest predictive value for ICU mortality appeared to be based on a complex assessment of GI symptoms (including large GRVs), whereas enteral underfeeding was the definition of EFI identified as the strongest predictor of death within 90 days of admission.[5] To which extent various pathophysiological mechanisms may explain this heterogeneity in prevalence and outcomes is currently unclear, as some definitions (eg, amount of EN) do not include any information on etiopathogenesis. At the same time, the differentiation of pathophysiological mechanisms would be central in choosing the correct management strategy.

Similar to the literature on adult critically ill patients, literature on EFI in critically ill children reports various definitions of EFI, including large GRVs, vomiting, diarrhea, abdominal distention, pain/discomfort, and elevated plasma lactate.[6–9] Consistent with data from adults, these definitions are associated with wide variations in prevalence and outcomes.[10]

Table 1. Different Definitions of EFI (Numbers of Studies and Reported Prevalence of EFI Based on a Previously Published Systematic Review[3]).

Definition	Number of studies	Prevalence of EFI (range)
Large GRV, cutoff 150 mL[a]	18/63[b]	8%–67%
Large GRV, cutoff 200–250 mL	22/63	
Large GRV, cutoff 300–400 mL	4/63	
Large GRV, cutoff 500 mL	7/63	
Other cutoff (cumulative for 24 h or based on the amount of EN)	8/63	
GI symptoms (vomiting, diarrhea, and/or abdominal distension) combined with large GRV	33/72	2%–75%
GI symptoms without large GRV, only vomiting or diarrhea considered	3/72	18%–40%
Inadequate EN based on proportional (70%–90% of energy) or absolute (500 or 750 kcal/24h) amount of energy	6/72	36%–37%

EN, enteral nutrition; GI, gastrointestinal; GRV, gastric residual volume.
[a]Cutoffs presented for single measurement. One single measurement defined EFI in 48 of 63 studies.
[b]63 od 72 studies used GRV as a criterion, and in 30 of them, GRV was the only criterion.

One practical definition of EFI that is frequently used in daily practice is GI dysfunction resulting in a reduction in the delivery of enteral feeding, regardless of the underlying cause.[1,11,12] Obviously, such a pragmatic, nonprecise definition is insufficient when trying to study the prevalence, association with outcome, and effect of interventions targeting EFI for research purposes.

These inconsistencies and wide variations in definitions highlight the need for a consensus definition. We think that the ideal definition should (1) be clinically relevant; (2) be associated with a patient-centered outcome; (3) be reproducible for measurement in clinical trials; (4) be easy to implement at bedside; (5) cover different pathophysiologic mechanisms of EFI; and (6) incorporate the application of EN, signs of EN intolerance, and consequent action regarding EN.

To improve the consistency of clinical descriptions, simple definitions for single GI symptoms and their usage in complex assessment of GI dysfunction were proposed.[12] Despite this effort, the use of a single GI sign or symptom to define EFI is imprecise, and their assessment is observer dependent. Also, for diarrhea (a symptom that is obvious and per se not difficult to assess), there is no consensus regarding a uniform definition. The work performed decades ago helped to reach agreement regarding stool frequency and consistency.[13] However, some more recent evidence indicates the importance of the stool amount/weight,[14] and an inclusion of this third component in the definition of diarrhea has been repeatedly suggested.[15,16]

None of the single GI signs or symptoms have been independently associated with mortality, whereas associations with mortality in univariate analyses have been demonstrated for absent bowel sounds, abdominal/bowel distension, GI bleeding, and large GRVs.[17–19]

Given the current uncertainty regarding definitions of EFI, an iterative consensus process has been proposed.[4] Of note, EFI may occur in patients with or without primary GI pathology, whereas feeding practices in these groups may differ substantially.

It is unclear which specific patient-centered outcomes (eg, mortality) should guide the development and validation of the definition of EFI.

Pathophysiology

There are several mechanisms underlying EFI in critically ill patients (Figure 1). These include malfunctioning enteric and autonomic nervous systems, alterations in hormonal regulating pathways, smooth muscle dysfunction, multiple drugs, electrolyte and glucose abnormalities, and inflammation. Detailed reviews can be found elsewhere.[20–23]

Neurohumoral mechanisms underlying GI motility disturbances. The autonomic nervous system is of specific relevance in the pathogenesis of disordered GI motility during critical illness and can be influenced by a multitude of stressors. The topic has been reviewed elsewhere.[24–27] Besides, also disturbed integrity of the network of the interstitial cells of Cajal, located between the nerve endings and smooth muscle cells in the GI tract, may importantly affect GI motility.[28]

GI hormonal pathways regulating motility. Next to neurally mediated pathways, hormonal mechanisms are important, with hormones such as cholecystokinin, glucagon-like peptide-1, peptide YY, and amylin slowing down gastric emptying and ones like ghrelin and motilin accelerating it.[23,29–33]

Even though a motilin-agonist erythromycin is frequently administered, and also supported by recent guidelines,[34] its effect and usefulness for patient-centered outcomes is not uniformly confirmed.[35,36] Other treatment modalities targeting hormonal pathways to accelerate gastric emptying were unable to inaugurate a new, efficient, and safe drug for clinical practice.[37–39] The limited efficacy of the pharmacological approach designed to manipulate hormonal pathways highlights the complexity and time-varying pattern of EFI.

Mechanisms related to the management of critical illness. Drugs administered to critically ill patients are known to impair GI motility.[40–45] A detailed review of drug-induced effects on GI motility can be found elsewhere.[20,46]

Recently published data suggest that altered gut microbiome in patients receiving broad-spectrum antibiotics[47,48] may lead to malabsorption of nutrients and thereby contribute to EFI.[49]

Fluid overload may result in intestinal edema and thereby inhibit normal bowel motility, and negative fluid balance in these patients may improve motility.[49] On the other hand, the benefit of unselectively applied restrictive fluid balance in patients with major abdominal surgery is controversial, possibly due to the risk of hypovolemia and the impact on organs other than the GI tract.[50,51] Recent studies have tested bedside ultrasound as a tool to assess intestinal diameter, wall thickness, peristalsis, and intestinal folds.[52,53] Increased intestinal thickness and bowel-wall stratification were associated with acute GI injury, whereas the visualization of abnormal peristalsis and intestinal folds (decreased and shortened) as direct indicators of motility disturbance, and increased intestinal diameter as a sign of absorption/discharge abnormality, was achieved.[52]

Focus on gastroparesis. There has been a focus on gastric emptying when identifying EFI, with impaired gastric emptying considered as a key finding in patients with GI dysmotility. In ICU patients receiving intragastric tube feeding, large GRVs are frequent, especially in patients receiving intravenous sedation/analgesia and/or catecholamines.[17]

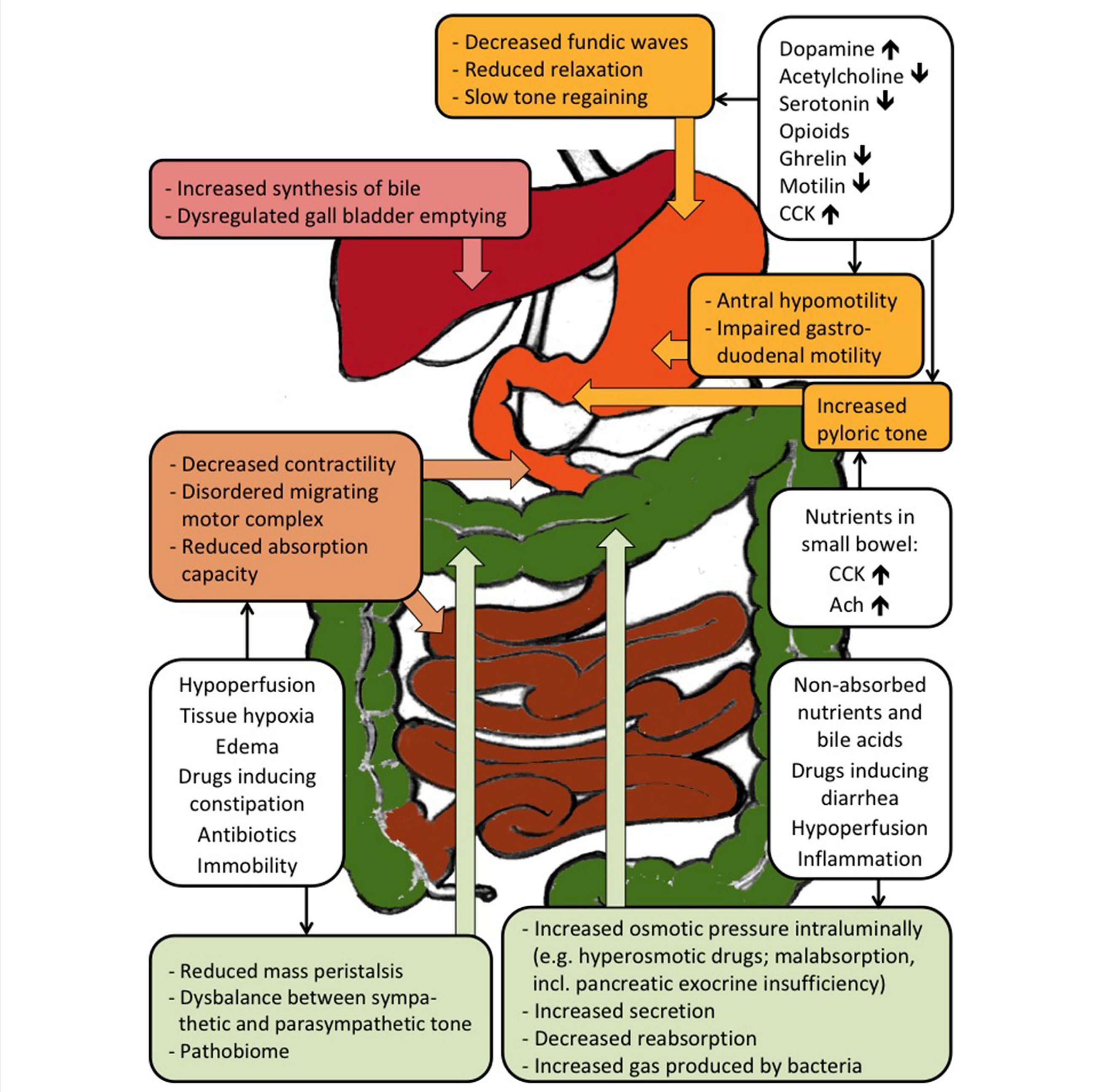

Figure 1. Overview of pathophysiological mechanisms that may lead to clinical signs of enteral feeding intolerance.[46,87–89] Ach, acetylcholine; CCK, cholecystokinin.

Prokinetic agents seem to reduce EFI and the risk to develop large GRVs.[54] Furthermore, the presence of large GRVs is dependent on provided EN, and, accordingly, a reduction in energy delivery reduces the prevalence of EFI assessed by the presence of large GRVs.[55,56] Associations with poor outcome (pneumonia, ICU stay, or mortality) have been observed in a few observational studies for GRVs of >500 mL per 1 measurement[17,18] and between 150 and 500 mL at 2 consecutive measurements.[17] Aspiration of gastric contents has been shown to occur more often with GRVs twice or more > 200 mL or once > 250 mL.[57] However, associations with adverse outcomes were not confirmed in a few randomized clinical trials investigating different cutoffs (between 200 and 500 mL) for GRV[58,59] or abandoning GRV measurements at all.[60] Moreover, omitting monitoring of GRV resulted in significantly increased provision of early EN during the ICU stay, with reduced use of prokinetic drugs and less GI complications.[61] This may question the use of GRV in guiding EN[62] and as a sign of EFI. Ultrasound has been used to evaluate gastric volume by measuring the diameter of gastric antrum,[63] but no monitoring tool has replaced GRV for the assessment of gastric filling/emptying so far.

The focus on gastric emptying when identifying EFI has, at least in part, developed because of the greater difficulty to detect GI function distally from the stomach. In critically ill patients, gastric motility and function are better understood than motility and function of the small bowel. However, the concept of EFI being limited to proximal to the pylorus should be revised, and both hypomotility and hypermotility throughout the GI tract (eg, dumping syndrome, diarrhea, bowel paralysis, and distension) should be considered. Delayed gastric emptying may be "requested" by the small bowel experiencing problems to accommodate, process, or absorb nutrients. At the same time, hypomotility distal to the pylorus is more difficult to assess and manage and, therefore, may have more potential for complications. Nevertheless, lower GI paralysis has not been universally included as a sign of EFI in available studies. The problem here is a lack of a reliable monitoring tool for lower GI paralysis.

Diarrhea as a sign of dysmotility and/or malabsorption. A feature of GI dysfunction, in addition to delayed gastric emptying, may be diarrhea. Diarrhea occurs frequently in critically ill patients.[18,64] Although there are numerous reasons for diarrhea in critically ill patients (eg, antibiotics, hypertonic medications, and pancreatic exocrine insufficiency), including EN itself,[15,16] dysregulation of neurohumoral control of GI motility may also contribute.

Indeed, instead of aiming for the GI tract to move the contents downward at a predefined rate, the appropriate absorption of macronutrients and micronutrients, together with the appropriate regulation of water and electrolyte balance, should be the aim. The problem here is the lack of a tool to assess absorption or detect malabsorption at bedside. The only symptom that has been suggested to reflect malabsorption in critically ill patients is diarrhea, whereas the direct measurement of fecal weight and determination of macronutrient contents in feces may help to assess intestinal absorption capacity in ICU patients.[14,65] In the gut, abnormal communication between gut epithelium, immune system, and microbiome may not only impair nutrient absorption but also have important systemic effects, including increased mortality.[66,67] However, exact mechanisms remain hypothetical. Factors leading to the development of pathobiome in critical illness have been reviewed recently.[68]

Taken together, many different pathophysiological mechanisms that may lead to distinctly different clinical manifestations are involved in the development of EFI in critical illness.

Clinical Relevance of EFI in Critical Illness

EFI may represent a maladaptive physiological response that affects outcomes via either a direct effect (on GI motility) or an indirect effect, with inadequate nutrition intake increasing the risk of adverse outcomes and/or delayed recovery. EFI may conceptually be harmful via a direct effect, as GI dysmotility might affect the microbiota. The resulting increases in pathogenic organisms lead to systemic effects via translocation or via regurgitation and aspiration.[68] An interesting hypothesis here is that EN may improve the (recovery of) enterocyte functional mass, as assessed by citrulline,[69] and, therefore, itself prevent EFI.[70] Whether a biomarker could help in evaluating the severity of GI dysfunction and adapting the dosage of EN remains to clarified. EFI may lead to worse outcomes via an indirect effect, as inadequate energy and protein delivery exacerbate catabolism and muscle wasting, leading to adverse patient-centered outcomes.[33]

On the other hand, EFI may represent an adaptive and protective physiological response to critical illness.[71,72] The rationale for this alternative theory is that an adaptive response is appropriate and proportionate to the event (illness or injury) and has evolved to attenuate nutrient intake. One of the underlying, proposed mechanistic pathways that EFI promotes a physiological response to reduce nutrients is the body's attempt to preserve autophagy (or 'self-eating').[73] Autophagy is an ubiquitous cellular pathway of recycled cytoplasmic material and is considered essential to facilitate adaption to a changing environment.[74,75] Although present at low levels in almost all cells, autophagy is markedly upregulated in response to stress.[74,75] However, the provision of nutrient suppresses the autophagy pathway.[75] It has, therefore, been suggested that EFI may represent an adaptive physiological response to critical illness, with evolution favoring GI dysmotility as a protective response to limit nutrient intake and preserve the autophagy pathway during a time of stress. It has also been speculated that EFI is an adaptive response during periods of shock.[76] This hypothesis is based on physiological and pathophysiological processes. In health and critical illness, small-intestinal nutrients increase blood flow through the superior mesenteric artery.[77] However, similar to shunting that occurs within the kidney during shock leading to acute kidney failure,[78] shunting within the GI tract may occur at the level of arterioles and capillaries despite increased blood flow through the larger arteries. Via this mechanism, or due to global supply-demand mismatch, increased metabolic demand of enterocytes triggered by luminal nutrients may lead to nonocclusive mesenteric ischemia.[79]

The various approaches to managing EFI are based on the underlying premises of whether is EFI is a maladaptive or an adaptive response. Based on the consideration that EFI is a maladaptive physiological response, it follows

Table 2. Pros and Cons of Different Components Used to Define EFI in the Literature.

	Pro	Con
GRV	Easily measurable Allows to avoid overdistension of the stomach	Limited correlation with gastric emptying Interruptions of EN Loss of gastric secretions when discarded
Vomiting	Does not need any special measurement/assessment	Small amounts (regurgitation) not detected in sedated patients Risk of aspiration
Diarrhea	Does not need any special measurement/assessment for detection of presence	Nonspecific for EFI (application of laxatives and other drugs) Quantification of severity (could be based on stool weight) is difficult
Combination of GI symptoms	Allows more complex assessment of different aspects and parts of the GI tract	Subjective importance of each single symptom is unclear Requires clear guidance and time for assessment
IAP added to combination of GI symptoms	Dynamics of a numerical value can be easily followed If IAP is clearly increasing with application of EN, it may suggest increasing intraluminal pressure	IAP may not directly reflect GI function IAH is multifactorial How IAP itself influences GI function in an individual patient is not clear
Amount of energy administered by EN	Possible to easily identify EFI based on a defined cutoff	Is rather a consequence of EFI as the syndrome itself Depends on feeding practices Does not differentiate etiology and is useless for management decisions

EFI, enteral feeding intolerance; EN, enteral nutrition; GI, gastrointestinal; GRV, gastric residual volume; IAH, intra-abdominal hypertension; IAP, intra-abdominal pressure.

that the pathophysiological condition should be treated to achieve success of EN and thereby improve outcomes. In contrast, if EFI is considered as an adaptive and protective physiological response theory, then EFI is as a reason to reduce nutrient intake rather than to initiate treatment. It is likely that EFI represents a spectrum of adaptive and maladaptive responses; one or the other may predominate in individual critically ill patients. Based on this consideration, not only administration of EN but also the dosage of EN in these different phases may play an important role. This hypothesis is supported by existing evidence suggesting on one hand improved outcome with early EN[80,81] and on the other hand detrimental outcomes with early full-energy EN in patients with severe shock.[79]

Observational data demonstrates strong associations between EFI and adverse outcomes.[3,82] However, such associations do not establish causality in the absence of robust data from randomized clinical trials proving that an intervention to treat EFI (either via the direct GI motility mechanism[36] or indirect nutrient provision mechanism) improves patient-centered outcomes.[83]

Conceptually, the pathophysiological responses to critical illness of other organ systems manifest as signs (eg, tachycardia) that are initially adaptive but, if left untreated or uncontrolled for extended periods, the physiological responses themselves cause harm. Intuitively, it may be that EFI is also initially adaptive, but when severe or persistent, EFI may progress to becoming a maladaptive process that requires intervention. Accordingly, it may be that EFI is better observed left untreated for short periods but treated when features persist and/or if EFI itself is leading to further complications (eg, progressing bowel distension).

Conceptual Framework for Definition

Focus of EFI on gastric emptying has caused narrowing treatment options to emptying or bypassing the stomach[54,84,85] and commonly neglected that vomiting and large GRVs may also occur when motility of the small bowel is primarily affected.[85,86] Application of small-bowel feeding in a patient with isolated gastroparesis is undoubtedly effective.[84] However, feeding into a small bowel that is paralytic and already distended may be dangerous. From the practical and safety aspect, it also needs to be considered that drainage of contents from the stomach is fairly easy, whereas "decompression" of the overfilled small bowel is challenging. However, there is no bedside test to identify or exclude small bowel dysfunction.[4] Nonetheless, a definition of EFI solely on symptoms related to the stomach is probably insufficient and may ignore important aspects of safety.

Table 3. Framework for Developing Consensus Definition of Enteral Feeding Intolerance.

Step	Task	Questions
1) Description of the problem	Describe enteral feeding intolerance as a problem (short general description)	Should this general description include different mechanisms?
2) Scope/future application of the definition	To define for which purposes should this definition be used. To define whether there should be 1 definition for research and 1 for clinical practice and whether the clinical practice and research definitions should be integrated into 1 definition?	Which criteria need to be fulfilled so that this definition could be used (1) for clinical practice and (2) for research?
3) Components of the definition	To define the essential components of the definition	What is the optimal balance between simplicity and comprehensiveness?
4) Structure of the definition	To construct the best structure considering different aspects and clinical manifestations but also simplicity and practicability	Should different anatomical parts of the gastrointestinal tract be assessed separately in the definition?
5) Final presentation	To present the definition and its parts in a clear form	Should the definition include, be based on, or be complemented with an assessment (and management) algorithm?

Furthermore, the lower GI tract should also be covered in the definition of EFI because malabsorption of nutrients in the small bowel commonly leads to diarrhea. Therefore, the consideration of diarrhea as a possible manifestation of EFI is justified. At the same time, there are multiple reasons for diarrhea other than malabsorption/EFI.[15,16] Differentiation of diarrhea based on etiology is very difficult and possibly needs to include several assessments (exclusion/confirmation of infectious diarrhea, considering applied medications, pancreatic exocrine insufficiency, bile acid malabsorption, etc as causes for diarrhea).[16] In clinical practice, lower GI paralysis is often encountered as more serious problem than diarrhea, although both may appear difficult to manage. EN may be able to stimulate bowel motility; however, increased gas production and increasing volume of contents in the large bowel may lead to distension of the bowel, with jeopardized perfusion and risk of perforation.

Taken together, EFI may arise from different parts of the GI tract, which require different complexities in assessment and management:

- gastric EFI (gastroparesis) = easy to detect and manage*
- small bowel EFI = difficult to detect, difficult to manage, possibly dangerous
- large bowel EFI (diarrhea) = easy to detect, difficult to manage

* Complexity and availability of management suggestions rather than the achievement of treatment effect.

A conceptually different approach is to define EFI based on the success of EN. Such definition could be created easily based on a cutoff of administered EN but would result in oversimplification and be useless for management decisions. Moreover, composition of nutrients (possibly a relevant factor for outcome) has been so far neglected with such approach. Pros and cons for the possible components of the definition of EFI are summarized in Table 2.

We suggest an approach to EFI that considers the following steps: (1) application of EN; (2) development or worsening of GI dysfunction in response to EN; (3) cessation or reduction of EN due to GI symptoms, and possibly (4) differentiating respective pathophysiological mechanisms behind EFI that would allow choosing a correct management approach. Considering the multiple aspects of EFI, excluding a straight-forward approach for a comprehensive definition, an iterative consensus process is required.[4] At the same time, more sensitive and reproducible characteristics of GI dysfunction need to be generated. Respective current knowledge and future goals are summarized in a recent review.[4] We propose a framework for developing a consensus definition in Table 3. Ideally, consensus should be reached for each step presented in this table.

Conclusion

A uniform definition of EFI is lacking. Despite the lack of an agreed-upon definition, EFI occurs frequently and is associated with adverse outcomes. A current pragmatic definition (reduction or cessation of EN due to clinical manifestation of GI dysfunction) can still be used for everyday clinical practice at bedside. However, to improve future knowledge, a more detailed definition is needed for studies. EFI as a consequence of various pathophysiological mechanisms is heterogeneous, and definitions focusing on only 1 mechanism are incapable to cover the whole spectrum. We propose a conceptual framework for a definition of EFI for future consensus process.

Statement of Authorship

A. Reintam Blaser, J.-C. Preiser, S. Jakob, A. Deane, and Y. Arabi equally contributed to the conception and design of the manuscript; A. Reintam Blaser, J.-C. Preiser, S. Jakob, and A. Deane drafted the manuscript. A. Reintam Blaser, J.-C. Preiser, S. Jakob, A. Deane, and Y. Arabi critically revised the manuscript, agree to be accountable for all aspects of work ensuring integrity and accuracy, and read and approved the final manuscript.

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