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Review

Definitions, predictors and outcomes of feeding intolerance in critically ill children: A systematic review

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SUMMARY

Background & aims: Clinicians and researchers often use feeding intolerance (FI) as main cause for insufficient enteral nutrition (EN). However, there is no uniform definition for FI. A uniform definition is essential for future studies focusing on predictors and outcomes of FI and enteral nutrition. A systematic review was performed to investigate the definitions, prevalence, predictors and outcomes of FI in critically ill children.

Methods: The databases Medline, Embase, Cochrane CENTRAL, Web of Science were searched. Inclusion criteria were interventional, observational or case-control studies (>10 patients) in which a definition of FI was reported in critically ill children (0–21 years).

Results: FI was defined in 31 unique studies performed in 2973 critically ill children. FI was most commonly defined as presence of gastrointestinal (GI) symptoms and/or large gastric residual volume (GRV) (n = 21), followed by discontinuation of EN due to GI symptoms (n = 7) and inadequate delivery of EN (n = 3). Median prevalence of FI was 20.0% [IQR 7.4%–33.0%]. Large GRV, abdominal distention, diarrhoea and vomiting/emesis, were the predominantly reported GI symptoms to define FI. FI was associated with severity of illness, mortality and nosocomial infections.

Conclusions: Feeding intolerance is inconsistently defined in the current literature, but appears to be a prevalent concern in critically ill children. FI is most frequently defined by the presence of GI symptoms. A standardized definition is needed for both clinical and research purpose to determine the consequences of FI in relation to short-term and long-term outcomes. The new proposed definition for FI entails the inability to achieve enteral nutrition target intakes in combination with the presence of GI symptoms indicating GI dysfunction.

Protocol registration: PROSPERO registration number: CRD42018092967. Registered on 07 June 2018.

1. Introduction

The preferred route to administer nutritional support in the paediatric intensive care unit (PICU) is through enteral nutrition (EN) and achieving adequate energy and protein target intakes via enteral nutrition is associated with improved outcome. In clinical practice nutritional targets are often not reached during critical illness [1,2]. Failure to achieve enteral target intakes in the PICU can be caused by a diversity of reasons, of which fear for poor gut function, interruptions around procedures, fluid restriction and feeding intolerance (FI) are frequently reported [2,3].

Although FI is declared a main reason for insufficient enteral intake, it is inconsistently defined among the different PICUs [3]. A standardized definition is essential from a clinical and scientific perspective, providing insight into possible causes and consequences of difficulties with enteral intake in critically ill children. Furthermore, such a definition is needed to compare interventions in studies to optimize enteral intake during critical illness.

A systematic review was performed to evaluate the definitions and to investigate the prevalence, predictors and outcomes of FI in critically ill children. Our primary aim was to evaluate all the reported definitions in research. Furthermore, the prevalence of FI,

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and associated predictors and outcomes of the different definitions were evaluated. Finally, we aimed to propose a definition for further validation.

2. Materials and methods

The study protocol and objectives were established a priori (PROSPERO protocol number: CRD42018092967) and performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [4].

2.1. Eligibility criteria

Studies were included if the following eligibility criteria were met: 1) the study had an interventional, observational cohort or case-control design; 2) study participants were admitted to a paediatric intensive care unit (PICU); 3) investigators provided a definition of 'feeding intolerance' or derivative terms (combination of the following terms: (in)tolerance, enteral, nutritional, GI, difficulties, complications). All studies reporting a definition were included, feeding intolerance was not necessarily the main topic of investigation. Studies were excluded if they: 1) were case reports or case series including <10 patients; 2) included infants <35 weeks of gestational age or included patients >21 years old.

2.2. Strategy

The search was conducted in the following databases: Medline Ovid, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and Google scholar. The search strategy was first developed by a Biomedical Information Specialist of the Medical Library of the Erasmus Medical Center in Medline and adapted for the other databases. The search was limited to English language, and data published as conference abstract, letter, note or editorial were excluded. The search was performed on 11 January 2018 and updated on 07 Sept 2018. It included a citation review of all eligible articles (Supplement file 1). All articles were independently screened on title and abstract by two reviewers and followed by full-text screening (RE, SV). When reviewers disagreed a third investigator made the final decision (KJ).

2.3. Data extraction and risk of bias assessment

Data were extracted from eligible articles by two reviewers (RE; SV). The following data were extracted: 1) study design and setting; 2) inclusion criteria; 3) population; 4) study objective; 5) interventions; 6) definition of FI; 7) incidence or prevalence of FI; 8) predictors and/or presumed causes of FI; and 9) clinical outcome measures (mortality, infection, mechanical ventilation, use of vasoactive agents, or other adverse events). Only data of unique studies were extracted to report the definitions or prevalence. However, secondary analysis of previous published populations were included in the predictors and outcomes sections of this systematic review.

The risk of bias was assessed by description of study design, feeding route, description of nutritional policy and the clearness in the definition of FI. The investigated PICU population was reported to determine the clinical heterogeneity of the studies, which potentially could result into bias. Methodological quality of non-randomized studies was evaluated using the STROBE checklist [5]. Quality of randomized trials were assessed with the Cochrane risk of bias tool [6]. This tool assesses the different types of bias for RCTs, divided into selection, performance, detection, attrition, reporting and other bias.

2.4. Statistical analysis

Descriptive statistics are reported as number (percentages), mean (standard deviation (SD)) if normally distributed or as median (interquartile range (IQR)) if not normally distributed. A random effect meta-analysis was used to calculate the pooled prevalence of FI and the 95% confidence intervals (CI) using R studio version 3.4.1 (Boston, USA). Heterogeneity was clinically and statistically assessed using Cochran's Q homogeneity and I-squared inconsistency statistics. Due to the clinical heterogeneity of the definition categories, separate analyses were performed for the different FI definitions. The Agresti-Coull (AC) binominal CI was used if only one prevalence per definition was reported.

3. Results

A total of 3572 unique studies were identified and after reviewing title and abstract 101 potentially relevant studies remained (Fig. 1). After full-text screening 39 articles met the full eligibility criteria [7–45], of which 10 were identified with possible overlapping participants [7–14,29,45]. After contact with the authors, the two primary studies with the largest population and a clear definition of FI were selected for the data pooling analyses [7,45]. Therefore, 31 unique studies, reporting definitions of FI on 2973 critically ill children, were included in the analysis. Of these studies, 9 studies were RCTs, 5 non-randomized interventional trials, 8 were prospective observational and 9 retrospective observational studies. The majority of the included studies were performed in a mixed PICU population and reported a median participant size of 60 (range 20–526). In all studies, EN was the main topic of investigation, whereas in 17 studies (54%) FI was the main objective of the study.

3.1. Risk of bias assessment

The majority of the studies included a mixed PICU population. Two studies were performed in term neonates; one with neonates receiving venoarterial extracorporeal membrane oxygenation (VA-ECMO) treatment [19] and one receiving prostaglandin medication [20]. Other studies with non-mixed population included infants with respiratory diagnosis [28,40], post-surgery for congenital heart diseases (CHD) [21,22,24], and children with a hypoplastic left heart syndrome (HLHS) [23].

In the nine RCTs, FI was either the primary or secondary objective of the study [24–28,30,43–45]. The risk of bias from the randomization process (selection bias), selective reporting or incomplete outcome data was generally low, however, in three studies there might be selection bias because of exclusion or switching of patients to the other treatment arm after the randomization process due to the inability to place a post-pyloric tube [25,43,44]. There was potential performance and detection bias in four studies due to the inability to blind the participants, clinicians and investigators [25,26,43,45] and one study did not report if investigators were blinded for outcome data (detection bias) [24].

The methodological quality varied among the observational and non-randomized interventional studies but was overall medium to poor. The highest score obtained from the STROBE checklist [5] was 12 of a maximum of 22 points. Most studies did not report the method section according to the checklist and information on selection and inclusion of participants, methods of data assessment, bias, quantitative variables and/or detailed statistical plan were missing.

EN was provided in the majority of studies via the combination of gastric, post-pyloric and oral route. Ten studies (32%) investigated exclusive gastric feeding and four (13%) post-pyloric feeding.

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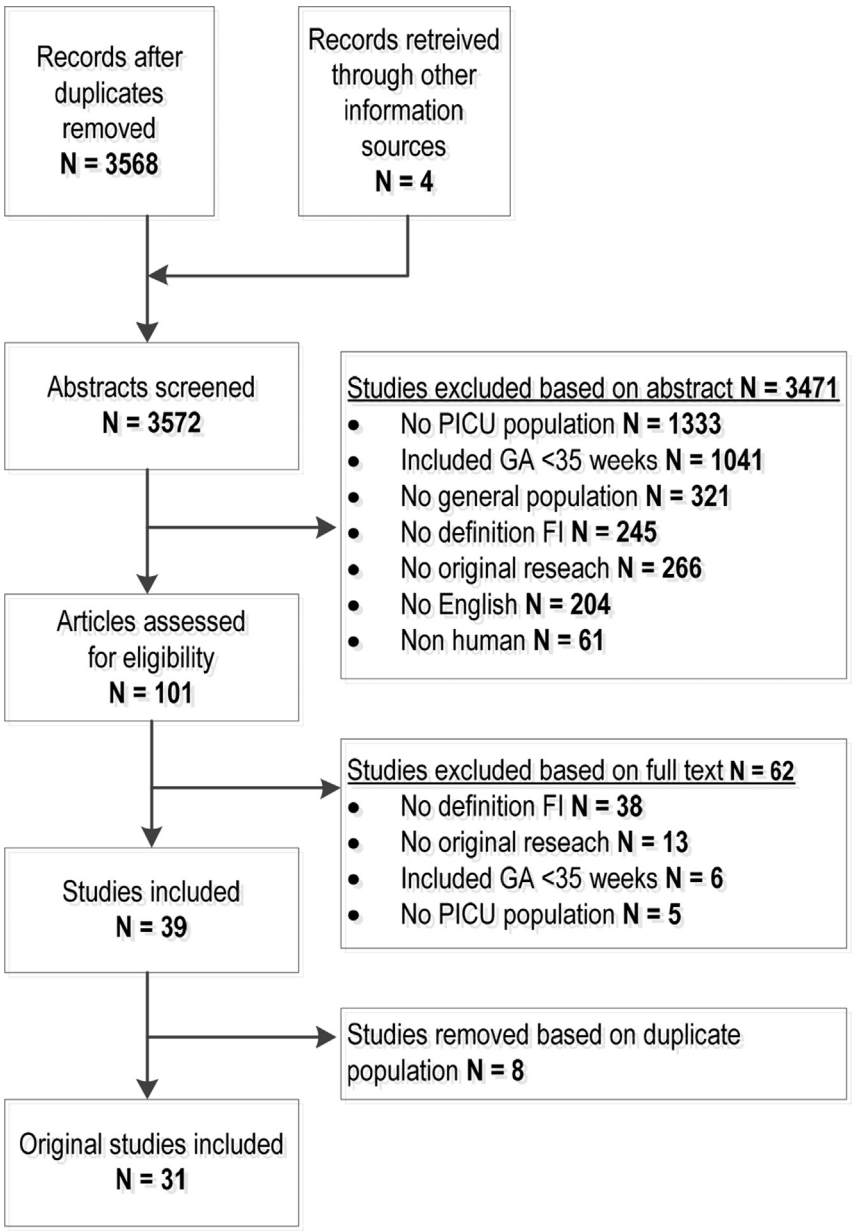

Fig. 1. Flow chart depicting search for eligible studies for inclusion in systematic review about feeding intolerance in critically ill children.

In three studies no information on feeding route was provided. Also, not all studies provided information on patient characteristics. Three studies (10%) did not report an age range in method or result section [15,18,26]. Detailed description of nutritional policy was reported in 23 studies (74%). The majority of the studies reported exclusion criteria, which were expected limited admission duration (range 12 h to 5 days), GI-disorders or surgery, congenital or genetic abnormalities, renal or liver failure. Seven studies (23%) excluded children if GI symptoms or pro-kinetic agents were present at baseline [22,24,37,39,44–46].

3.2. Definitions of feeding intolerance

There was a wide variety in definitions used to determine FI, which were classified into three main categories:

1) Discontinuations of EN due to gastrointestinal (GI) symptoms (n = 7 studies);
2) Presence of GRV and/or GI symptoms, divided in
   a. GRV and GI symptoms (n = 12 studies)
   b. Only GI symptoms (n = 6 studies)
   c. Only GRV (n = 3 studies);
3) Inability to achieve enteral target intake (n = 3 studies).

3.2.1. Gastrointestinal symptoms

Table 1 presents an overview of the reported GI symptoms used to describe FI in the studies from category 1 (discontinuations of EN due to gastrointestinal (GI) symptoms) and category 2 (Presence of GRV and/or GI symptoms), which were reported in 28 studies (90%) in total. Most reported symptoms were diarrhoea, large GRV, abdominal distention and vomiting. Twenty studies (65%) reported large GRV as a marker for feeding intolerance (category 1, 2a and 2c), but this was defined inconsistently among the studies. Four studies reported large GRV as >50% of previous 4 h of feeding [7,42,46]. All other cut-off values for large GRV were

Table 1
Number of times gastrointestinal symptoms were used to define feeding intolerance (n = 28 studies).

Definition category	Category 1	Category 2	Category 1 & 2
	Discontinuation of EN due to GI symptoms	GRV and/or GI symptoms	All GI symptoms reported
Diarrhoea	5	17	22
Large GRV	5	15	20
Vomiting/emesis	5	15	20
Abdominal distention	5	13	18
Constipation	3	2	5
Aspiration	2	3	5
GI-bleeding	1	3	4
Abdominal discomfort	–	3	3
NEC	1	1	2
Reflux	–	2	2
Hemoccult positive stool	–	1	1
Absent bowel sounds	–	1	1

EN: enteral nutrition; GI: gastrointestinal; GRV: gastric residual volume; NEC: necrotizing enterocolitis.

used only once per study, i.e. 100–150% of previous 4 h of feeding, > 300% of previous 3 h of feeding, >66% of previous feeding, >125% after 4 h feed challenge, > 2 ml/kg per 3 h, >3 ml/kg/day, >5 ml/kg per 4–5 h, >10 ml/kg per 4 h, >100 ml per 4 h or >150 ml per hour. In the remaining six studies large GRV was not specified. No values or definitions were provided in the majority of the studies regarding the other GI symptoms. Diarrhoea was specified in eight studies as having more than 3, 4 or 6 loose stools per day or exciding the amount of 2.5 L per day [15,24,25,37,40,44–46]. Four studies mentioned a threshold value for abdominal girth, which were ≥2 times increase [34,38], >3 cm increase [20] or ≥15% increase [40]. Emesis or vomiting was defined in two studies as having two or more episodes of spitting-up gastric content [34,38].

3.2.2. Enteral target intake

Inability to achieve enteral target intake was used to determine FI in the remaining three studies (10%) (category 3) and GI-symptoms were not part of the definitions. In one study FI was defined by not reaching 75% of target intake (estimated energy expenditure * 1.3) within 48 h of initiation of EN [30]. A second study defined intolerance as the inability to reach 120 ml/kg/day of continuous enteral feeds without interruption [23]. The third study defined FI as the inability to reach target caloric intake (70 kcal * kg * day) in children aged 1–3 years [27].

3.3. Prevalence of feeding intolerance

Prevalence of FI was reported in 17 studies (55%) and ranged from 0.0 to 57.1% with a median prevalence of 20.0% [IQR 7.4–33.0]. Due to the clinical heterogeneity within the category definitions, a pooled prevalence was calculated per group category (Table 2). The pooled percentage of children with feeding intolerance was 15% (95% CI 7–30%) in six studies with the FI definition EN discontinuation, 22% (95% CI 9–44%) in seven studies with the FI definition of GI symptoms including large GRV and 42% (95% CI 30–54%) in two studies defining FI with large GRV. However, the heterogeneity of the pooled prevalence was considered large in the definitions, with an I-squared of 91% in studies which used discontinuation of EN and 85% in studies using GI symptoms and GRV.

3.4. Predictors associated with feeding intolerance

Causes and predictors of FI were mentioned in 23 studies (74%) and are presented in Table 3 and Supplemental Table 1. Eight studies were randomized controlled trials (RCTs) with a primary focus on FI (Table 3), 10 studies had a prospective design and 5 studies a retrospective design (Supplemental Table 1). In the 8 RCTs that were identified, various nutritional interventions were compared in critically ill children. In one study comparing intermittent versus continuous gastric feeding a significant higher prevalence of FI was found in the intermittent group ($p = 0.02$) [43]. The other studies comparing gastric versus post-pyloric [25] and intermittent versus continuous feeding, did not find differences in FI [26,45]. Also studies comparing standard formula with formulas that were enriched with either pre- and probiotics [27], with immunomodulators [30] or with protein and energy did not report differences in FI [24,46].

3.5. Clinical outcome measures associated with feeding intolerance

There were three observational studies associating clinical outcomes with FI and no interventional trials (Table 4) [13–15]. In one study mortality was higher in children with FI (30% versus 13%); however this was not significant [13]. A retrospective study in 91 severely burned children receiving post-pyloric EN did find a

Table 2
Prevalence of FI with use of different definitions.

Definition of FI	Number of studies[a]	Number of patients	Number of FI patients	Binominal proportion (95% CI)[b]	Pooled proportion (95% CI)[b]	Heterogeneity I^2% (95% CI)
1. EN discontinued due to GI symptoms	6	1026	119	NA	0.15 (0.07–0.30)	91 (87–96)
2a. GI symptoms including large GRV	7	854	238	NA	0.22 (0.09–0.44)	85 (71–92)
2b. GI symptoms without large GRV	1	59	7	0.12 (0.05–0.23)	NA	NA
2c. Large GRV	2	83	35	NA	0.42 (0.30–0.54)	NA
3. Insufficient enteral intake	1	50	0	0.00 (0.00–0.09)	NA	NA
Total	17	2072	339	NA	0.19 (0.11–0.30)	90 (86–93)

EN: Enteral nutrition; FI: feeding intolerant GI: gastrointestinal; GRV: gastric residual volume.
[a] Subanalyses of studies with a reported prevalence.
[b] Pooled proportion calculated when >1 study was included and binominal proportion when one study was included.

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Table 3
Causes of feeding intolerance investigated in 8 randomized interventional trials.

Author, year	Definition of FI	N	Population and age range	Study design	Objective	Causes of FI
Cui et al., 2018 [24]	Large GRV (>3 times feeding volume delivered in 3 h), intolerable vomiting, diarrhoea (>4 stools or >10 g/kg/d) or GI bleeding	52	CHD, post-surgery 4 weeks - 12 months	PE-formula vs standard formula gastric EN	Compare nutrition effects and tolerance of the 2 different formulas in infants after congenital heart surgery.	Tolerable diarrhoea higher in PE-formula group 69.2% vs 33.3% No difference in other parameters
Fayazi et al., 2016 [43]	Large GRV (>100 ml after 4 h)	60	Mixed 5–17 years	Intermitted vs continuous gastric EN	Compare intermitted vs continuous feeding in terms of time to reach caloric goal and complications	FI higher in intermittent feeding group ($P = 0.02$) No significant difference in vomiting and diarrhoea
Jacobs et al., 2013 [30]	Achieved energy goal less than 75% of estimated energy expenditure x 1,3 within 48 h of initiation of EN	26	Respiratory failure 1–18 years	Eicosapentaenoic acid, γ-linolenic acid and antioxidants vs standard formula via gastric or post-pyloric route	Pilot study to determine feasibility of eicosapentaenoic acid, γ-linolenic acid and antioxidants feeding	Achievement of energy goal comparable for both formulas (28 −30 h)
Simakachorn et al., 2011 [27]	Inability to reach target caloric intake (70 kcal * kg * day)	94	Mixed diagnosis receiving antibiotics 1–3 years	Probiotic vs standard formula via oral or gastric route	Demonstrate the tolerance and safety of an enteral formula containing a synbiotic blend and to investigate its effect on the intestinal microbiota	1) Median time to reach target caloric goal comparable between probiotic (4.13d) vs standard (4.36d) formula ($P = 0.999$) 2) No difference in abdominal distention ($p = 0.83$), vomiting ($p = 0.59$), and diarrhoea ($p = 0.39$)
Van Waardenburg et al., 2009 [28]	Large GRV (>50% of 4 h feeding volume delivered), distension, vomiting or diarrhoea (>4 watery stools per day leading to a negative fluid balance or hemodynamic consequences)	20	Respiratory failure 4 weeks–12 months	PE-formula vs standard formula via gastric or post-pyloric route	Compare nutritional effects of PE-formula to standard formula (delivery, energy/nitrogen balances, amino acid profiles). Secondary aims were assessing tolerance and safety	No vomiting, distention, diarrhoea in both groups. GRV higher in PE-group vs standard group (9.8 ± 2.8 vs 4.7 ± 2.4 ml/kg; $p < 0.01$)
Meert et al., 2004 [25]	Aspiration, vomiting, diarrhoea (>3 liquid stools in a 24 h period) or abdominal distention	74	Mixed <18	Gastric vs post-pyloric EN	Evaluate the effect of feeding tube position on nutrient delivery and feeding complications	Presence of each symptom did not differ between gastric and post-pyloric EN group (NS)
Horn et al., 2003 [45]	Number of stools, diarrhoea (>3 stools in a 24 h period) or vomiting	45	Mixed 0–13 years	Intermittent vs continuous gastric EN	Assessing tolerance of continuous vs intermitted feeding	The number of stools per day and the prevalence's of diarrhoea and vomiting did not differ between the two groups (NS)
Lyons et al., 2002 [26]	Abdominal distention, diarrhoea, gastroesophageal reflux, pulmonary aspiration or emesis	59	Mixed Mean age 8.9 (±1.5) months	Continuation of post-pyloric feeding during extubation	Examine the safety and efficacy of continuous feeding compared with interrupted post-pyloric feeding at the time of extubation.	No difference between continuation vs withholding EN prior to extubation (NS)

CHD; Congenital heart disease; EN: Enteral nutrition; FI: Feeding Intolerance; GA: gestational age; GI: gastro-intestinal; GRV: gastric residual volume; NEC: necrotizing enterocolitis; NPO: Nil per os; PE: protein and energy enriched; RCT: randomized controlled trial.

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Table 4
Feeding intolerance associated with outcome in 3 non randomized studies.

Author, year	Definition of FI	N	Population and age range	Study design	Objective	Clinical outcomes of FI
Sánchez et al., 2000[a] [14]	EN discontinued due to abdominal distention, large GRV (>50% of 4 h feeding volume delivered), vomiting or diarrhoea	152	Mixed 3 days–17 year	Prospective, receiving post-pyloric EN	Assess the use and complications of post-pyloric EN	- Pulmonary infections (25% vs 8.6%; $p < 0.05$) - Altered hepatic function (100% vs 9.5%; $p < 0.01$) - Hypokalaemia (19 vs 5.5%; $p < 0.05$) - Hypocalcaemia (19% vs 9.5; $p < 0.05$)
Panadero et al., 1998[a] [13]	Vomiting, abdominal distension, large GRV, diarrhoea or pulmonary aspiration	41	Mixed 8 days–12 year	Prospective, receiving post-pyloric EN	Analyze the utility and complications of post-pyloric EN	Mortality higher in FI patients 30% vs 13% (NS)
Wolf et al., 1997 [15]	Abdominal distention, large GRV (>150 ml/h) or diarrhoea (>2.5 L/d) resulting in ≥24 h EN discontinuation.	91	Severe burned children	Retrospective, receiving post-pyloric EN	Determine if FI is associated with sepsis and increased mortality in children with severe burns	FI associated with sepsis ($p < 0.001$) FI associated with mortality ($p < 0.05$)

Abbreviations: EN: Enteral nutrition; FI: Feeding Intolerance; GRV: gastric residual volume.
[a] Studies are secondary analysis of previous published studies with possible overlay in population.

significant association between feeding intolerance and mortality ($p < 0.05$) [15]. In 2 studies, FI in critically ill children was also associated with pulmonary infections ($p < 0.05$) [14] and sepsis ($p < 0.001$) [15]. The association of FI and enteral energy delivery was investigated in four non randomized studies and are reported in Table 5. FI was associated with lower energy delivery [37] and delayed achievement of full EN [33,39].

4. Discussion

Our systematic review revealed several nutritional studies in critically ill children with a focus on the descriptive term "feeding intolerance". However, the methodological quality of these studies was moderate to poor. As hypothesized, FI was inconsistently defined, which precludes any firm conclusions on prevalence, predictors and outcomes. FI was most commonly based on a wide variety of gastrointestinal symptoms. FI was sometimes addressed as not reaching target intakes, however, in other studies this was the outcome determinant of FI. It is remarkable that there is no standardized definition for FI, especially considering the substantial impact it presumably is declared to have on morbidity and mortality during critical illness [14,47]. Unfortunately, no overall prevalence could be calculated to assess the burden if FI in critically ill children. Aside from inconsistency in the use of determinants for

Table 5
Feeding intolerance associated with energy delivery investigated in 4 non randomized studies.

Author, year	Definition of FI	N	Population and age range	Study design	Objective	Outcomes of FI
Martinez et al., 2017 [34]	Large GRV (>3 ml/kg or >150 ml), ≥2 increases in abdominal girth, ≥ 2 emesis episodes, ≥ 3 loose stools or subjective abdominal discomfort in a 24 h period	20	Mixed >1 year	Prospective cohort with acetaminophen absorption test, receiving gastric EN	Explored the feasibility of performing the acetaminophen absorption test and examined its correlation with FI	GRV did not predict delayed vs normal gastric emptying ($p = 0.964$) Other FI signs did not predict gastric emptying ($p = 0.824$)
Canarie et al., 2015 [33]	Large GRV, vomiting, abdominal distention, constipation, diarrhoea	444	Mixed <21 years	Prospective cross-sectional, receiving oral, gastric or post-pyloric EN	Reviewed nutritional practices in six medical-surgical PICUs and determined risk factors associated with delayed EN	Risk factor for delayed EN (OR:2.05; 95% CI 1.14–3.68)
Brasil de Oliveira Iglesias et al., 2007 [37]	Abdominal distention, diarrhoea (≥3 loose stools in a 24 h period), gastroesophageal reflux disease, large GRV, emesis, constipation	55	Mixed	Prospective, receiving gastric or post-pyloric EN	Compare the differences between prescribed and delivered energy and to identify the factors that impede the optimal delivery	FI associated with lower energy delivery ($p = 0.033$)
Mayer et al., 2002 [39]	Large GRV (>125% of 4 h feeding volume delivered)	23	Mixed 1 month–16 years	Prospective interventional, receiving gastric EN	Determine the relationship between amylin levels and gastric emptying	Delayed gastric emptying in FI patients using paracetamol absorption test ($p \leq 0.01$)

Abbreviations: EN: Enteral nutrition; FI: Feeding Intolerance; GRV: gastric residual volume.

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a definition the overall poor description of how these determinants were assessed was of greater concern, leading to a high risk of bias in almost all studies included in our review. This resulted in a large statistical heterogeneity of our pooled prevalence within the definitions (I-squared 85% and 91%) [48]. Despite the substantial heterogeneity of the definitions, the current literature search showed that FI is prevalent (median prevalence 20.0%) in the PICU.

The variety of definitions used in the studies, in combination with the risk of bias of the studies describing them, precluded making even cautious conclusions on potential predictors of feeding intolerance. However, there appeared to be an association between FI and severity of illness [17,39]. Our review further showed that current literature does not provide causation in relation to feeding intolerance. No studies were identified which compared polymeric versus (semi)-elemental formulas. This is remarkable as these formulas are advised in nutritionally vulnerable patients who are unable to achieve adequate nutrition from standard oral diets [49,50]. Despite the high burden and prevalence, no studies investigated motility agents or other treatment for FI. Thus, the current literature does not provide any evidence that feeding intolerance can be influenced by feeding route, mode or the type or composition of enteral nutrition.

Considering feeding intolerance as an aggregate of symptoms of yet another organ failing during critical illness is, again taking the methodological issues into consideration, supported by a few studies which associated feeding intolerance with increased morbidity and even mortality [13–15]. Whether GI dysfunction in itself can determine outcome independent of nutrient intake is an important question. It is unclear if the impact on clinical outcome is caused by the consequences of FI as expression of organ (intestinal) failure, or if it reflects an underlying severity of illness. The studies in our systematic review that defined FI as an inability to achieve enteral target intake did not make associations with outcome. There are two large observational cohorts who have showed that enteral intake below two-third of what was prescribed during the first 10 days of admission in the PICU impaired clinical outcome in critically ill children [51,52]. Unfortunately, these studies did not describe any GI symptoms or gave a description of feeding intolerance otherwise and where therefore not included in our systematic review.

Diverse pathophysiological pathways leading to FI might play a part in the variations in definitions and prevalence at the PICU. Both the GI morphology and function can be altered and aside from nutritional processing the intestines have other immunological, endocrine and barrier functions [22,53,54]. The aetiology of abnormal GI function in critically ill children is largely unknown, but is most likely multifactorial. GI peptides and neurohormones play an important role in the motor function and increased levels of GI peptides (CCK, PYY) have been associated with GI dysfunction [55,56]. A study in cardiac surgery patients found an association between GI symptoms as definition of feeding intolerance, and intestinal barrier function (I-FABP, citrulline, claudin 3). Plasma biomarkers reflecting the epithelial barrier function, together with pro- and anti-inflammatory cytokines, were altered in relation with severity of illness [22]. There is a high need for studies investigating the potential mechanisms of FI during critical illness and unravel the largely unknown aetiology.

A recently published narrative review discusses the need for a consistent definition of FI among the international PICU community [57]. Unfortunately, the evidence from the current paediatric literature is insufficient to provide such definition. Therefore, we want to propose a definition, which can be used for further validation (Table 6). The term feeding intolerance implies a patient who does not tolerate full enteral nutrition due to gastrointestinal symptoms. Thus, in our opinion the descriptive definition of FI should start with the inability to achieve enteral target intakes and secondly should include GI symptoms which indicate GI dysfunction according to expert clinicians and researchers. As previously reported, the evidence of insufficient enteral intake is sparse, however, an intake below two-third of target has been associated with poor clinical outcome [51,52]. Furthermore, the new SCCM-ASPEN clinical guidelines suggest to achieve an energy delivery of at least two-thirds of the prescribed daily requirement by the end of the first week in the PICU [58]. Therefore, this could be a starting point for a proposed definition. We would like to state that the GI symptoms are a direct symptom of the pathophysiological mechanism causing FI, and therefore reflect problems with gastric emptying, motility, enterocyte dysfunction and nutrient absorption or are related to intestinal inflammation or dysfunction of enteric endocrine system. Frequently described GI symptoms ($\geq$10 times) were large GRV, abdominal distention, diarrhoea and vomiting, and these have to be considered in the definition. Also, serious adverse GI symptoms, such as intestinal ischemia and bloody stool have to be taken into account [41]. Usually no cut-off thresholds for frequency and/or volumes of symptoms were reported. Without reporting these thresholds in the definition, besides the issues with inter- and intra-observer reliability, validation will be difficult. The impact of each individual symptom is uncertain, but will probably vary between symptoms. Also, no attempts were made to report the sensitivity or specificity of the symptoms in the included studies of our review. In our review, large GRV was often reported as one of the GI symptoms, which is comparable with the systematic review performed in adults [47]. The implications of GRV measurements in standard practice are debated. Recent studies found no association between GRV

Table 6
Proposed definition for enteral feeding intolerance in critically ill children in whom EN is indicated and attempted; registered over a 24 h period.

1)	**Insufficient enteral intake**	Defined as enteral intake two-third of prescribed daily target or EN is withheld for $\geq$48 h or EN is not increased for $\geq$48 h Excluding interruptions due to procedures
AND		
2)	**Presence of at least one of the following criteria**	
a	GI-symptoms	
	i Large GRV	Defined as $\geq$ 50% of the EN delivered in the last 4 h
	ii Presence of vomiting	Defined as $\geq$ 2 times with gastric content in 24 h period
	iii Presence of diarrhoea	Defined as $\geq$ 4 times loose stool with negative fluid balance in 24 h period
b	Severe GI-symptoms with concern for intestinal ischemia	- Abdominal distention - Abdominal pain - Melena - Haematochezia

Abbreviations: EN: enteral nutrition; GI: gastro-intestinal; GRV: gastric residual volume.
Critically ill children must both fulfill the first and second criteria to be classified as feeding intolerant according to this definition.

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measurements and clinical outcome and current guidelines on critically ill children start to challenge the use of GRV as a marker for feeding intolerance [59–62]. Due to the previously mentioned limitations, further validation of any proposed definitions is needed in critically ill children.

Taking all these concerns into consideration, we propose the definition for enteral feeding intolerance as presented in Table 6, to be used as clinical and research tool. This definition includes the combination of the inability to achieve target intake and the presence of GI-symptoms. For this definition it is essential that EN is indicated and attempted. Additional research is needed for validation of this proposed definition, including cut-off thresholds for enteral target intake and GI symptoms. Furthermore, the impact of each individual criterion needs to be investigated.

There are several limitations of our systematic review that need to be addressed. As described before, the methodological quality of the included studies was overall moderate to poor and conclusions based on these studies need to be made with considerations. Furthermore, our systematic review might be subjected to bias, as a large proportion of our included studies were retrospective observational studies. Our primary aim was to report the most commonly used definitions of FI and if possible provide a universal and standard definition. Unfortunately, the evidence from the current paediatric literature is insufficient to provide such definition and we therefore proposed a definition for further validation based on expert opinion. Despite our elaborate literature search, no causal relationship could be addressed in regard with short-term or long-term effects of FI.

In conclusion, feeding intolerance is inconsistently defined in the current literature, but appears to be a realistic and prevalent problem in critically ill children. FI is mostly defined in studies by the presence of gastrointestinal symptoms, without describing associations between predictors and outcome with FI. We would propose that a definition for FI should include the inability to achieve enteral nutrition target intakes in combination with the presence of GI symptoms indicating GI dysfunction.

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Availability of data and materials

The datasets and analyses used for the current study are available from the corresponding author on reasonable request.

Authors' contributions

All authors contributed to the design of the study; RE and SV acquired and analyzed the data; All authors interpreted the data, drafted and revised the manuscript; All authors approved the final version of the manuscript.

Conflict of interest

The authors declare that they have no competing interest.

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Abbreviations

AC	Agresti-Coull
CENTRAL	Cochrane Central Register of Controlled Trials
CHD	congenital heart diseases
CI	confidence interval
EN	Enteral nutrition
FI	Feeding intolerance
GI	gastrointestinal
GRV	Gastric residual volume
HLHS	hypoplastic left heart syndrome
IQR	Interquartile range
NEC	necrotizing enterocolitis
PICU	paediatric intensive care unit
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
SD	standard deviation
VA-ECMO	venoarterial extracorporeal membrane oxygenation
WFA	weight-for-age

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2019.03.026.

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