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Enteral Feeding Intolerance: Updates in Definitions and Pathophysiology

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Conflicts of interest

A. Reintam Blaser received speaker fees from Fresenius Kabi and Nestlé, and a study grant for University of Tartu from Fresenius Kabi.

A. Deane or his institution has received honoraria from Baxter, Cardinal Health, Nestle and Takeda.

J.-C. Preiser received speaker fees from Fresenius, Nestlé and Nutricia.

Y. Arabi reported that his institution received funding from King Abdullah International Medical Research Center, Riyadh, Saudi Arabia, and King Abdulaziz City for Science and Technology, Riyadh, Saudi Arabia, for the studies on permissive underfeeding and for biomarker substudies.

S. Jakob reported that the Department of Intensive Care Medicine has, or has had in the past, research & development/consulting contracts with Edwards Lifesciences Services GmbH, Phagenesis Limited and Nestlé. The money was paid into a departmental fund, and none of the authors received any financial gain.

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Abstract

Enteral feeding intolerance 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 enteral feeding intolerance 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 enteral feeding intolerance may represent the consequence of various pathophysiological mechanisms, and this heterogeneity may explain varying associations with outcome.

In clinical practice a pragmatic definition may be useful. A pragmatic definition of enteral feed intolerance is that a clinician has decided to reduce the amount of enteral nutrition, specifically because features of gastrointestinal dysfunction which appeared during enteral feeding. For research purposes a more detailed definition of enteral feeding intolerance 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 enteral feeding intolerance in critically ill patients. Based on current knowledge, we propose a conceptual framework for a definition of enteral feeding intolerance for future consensus process.

Keywords: enteral nutrition; critical illness; gastroparesis; gastric emptying; enteral nutrition intolerance; diarrhea

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 patients³. Despite the prevalence, there is no widely agreed-upon definition of EFI³. A major challenge in having a unified definition is the wide spectrum of pathophysiological

mechanisms that affect different parts and functions of 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 outcome⁴. Moreover, there is no robust well-validated and widely used objective methodology to measure GI dysfunction in critically ill. Furthermore, the clinical outcomes may be affected by EFI in several ways: the underlying GI dysfunction, 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 three main categories: ‘large’ gastric residual volumes, gastrointestinal symptoms and ‘inadequate’ delivery of enteral nutrition³ (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 application of different definitions of EFI in the same patient cohort results in wide variability in prevalence and 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 gastric residual volumes - GRV), 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 outcome is currently unclear, as some definitions (e.g. amount of EN) do not include any information on etiopathogenesis. At the same time, differentiation of pathophysiological mechanisms would be central in choosing correct management strategy.

Similar to the literature on adult critically ill patients, literature on EFI in critically ill children report various definitions of EFI, including large GRV, 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.

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 non-precise 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
6. incorporate application of EN, signs of EN intolerance, and consequent action regarding EN

In order 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 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 consistence 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 has 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 have 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, e.g. mortality, should guide 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 system, 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 gastrointestinal motility during critical illness, and can be influenced by a multitude of stressors. The topic has been reviewed elsewhere²⁴⁻²⁷. Besides, also disturbed integrity of the network of the interstitial cells of Cajal, located between the nerve endings and smooth muscle cells in the gastrointestinal tract, may importantly affect gastrointestinal motility²⁸.

GI hormonal pathways regulating motility

Next to neurally mediated pathways, hormonal mechanisms are important, with hormones such as CCK, glucagon-like peptide-1, peptide YY and amylin slowing down gastric emptying, whereas ghrelin and motilin accelerating it^{23,29-33}.

Even though a motilin-agonist erythromycin is frequently administered, and also supported by recent guidelines³⁴, 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 practice³⁷⁻³⁹. The limited efficacy of the pharmacological approach designed to manipulate hormonal pathways highlights the complexity and time-varying pattern of EFI.

Mechanisms related to management of critical illness

Drugs administered to critically ill patients are known to impair GI motility⁴⁰⁻⁴⁵. A detailed review of drug-induced effects on gastrointestinal 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 EFI⁴⁹.

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, benefit of unselectively applied restrictive fluid balance in patients with major abdominal surgery is controversial, possibly due to the risk of hypovolemia and 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 was associated with acute gastrointestinal injury, while 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. Prokinetic agents seem to reduce EFI and the risk to develop large GRV ⁵⁴. Furthermore, the presence of large GRVs is dependent on provided EN, accordingly, a reduction in energy delivery reduces the prevalence of EFI assessed by presence of large GRV ^{55,56}. Associations with poor outcome (pneumonia, ICU stay or mortality) have been observed in a few observational studies for GRV of >500 mL/one measurement ^{17,18} and between 150 and 500 mL at two 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 RCTs investigating different cut-offs (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 enteral nutrition during the ICU stay, with reduced use of prokinetic drugs and less gastrointestinal 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 antrum⁶³, but no monitoring tool has replaced GRV for assessment of gastric filling/emptying so far.

The focus on gastric emptying when identifying EFI has, at least in part, developed due to the greater difficulty to detect GI function distally from the stomach. In the critically ill gastric motility and function is better understood than that of a small bowel. However, the concept of EFI being limited to proximal to the pylorus should be revised, and both hypo- and hypermotility throughout the GI tract (e.g. 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 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}. While there are numerous reasons for diarrhea in critically ill (e.g. antibiotics, hypertonic medications, pancreatic exocrine insufficiency), including enteral nutrition itself^{15,16}, dysregulation of neurohumoral control of GI motility may also contribute.

Indeed, instead of aiming GI tract to move the contents downwards at a predefined rate, appropriate absorption of macro- and micronutrients together with appropriate regulation of water and electrolyte balance should be aimed. The problem here is the lack of tool to assess absorption or detect malabsorption at bedside. The only symptom that has been suggested to reflect malabsorption in critically ill 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 pathobiont 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 development of EFI in critical illness.

Clinical relevance of EFI in critically ill

EFI may represent a maladaptive physiological response that affects outcomes via either a direct effect - on gastrointestinal motility - or an indirect effect - with inadequate nutritional intake increasing the risk of adverse outcome and/or delayed recovery. EFI may conceptually be harmful via a direct effect as gastrointestinal 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 evaluating severity of GI dysfunction and adapting the dosage of EN remains to be 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 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 pathway that EFI promotes a physiological response to reduce nutrient is to the body preserving autophagy (or 'self-eating')⁷³. Autophagy is a ubiquitous cellular pathway of that recycles cytoplasmic material and is considered essential to facilitate adaption to a changing environment^{74,75}. While 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 pathway⁷⁵. It has, therefore, been suggested that EFI may represent an adaptive physiological response to critical illness, with evolution favoring gastrointestinal 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 shock⁷⁶. This hypothesis is based on physiological and pathophysiological processes. In health and critical illness, small intestinal nutrient increases blood flow through the superior mesenteric artery⁷⁷. However, similar to shunting that occurs within the kidney during shock leading to acute kidney failure⁷⁸ 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 ischemia⁷⁹.

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 that the pathophysiological condition should be treated to achieve success of enteral nutrition 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 patient. 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-caloric EN in patients with severe shock⁷⁹.

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 gastrointestinal motility mechanism⁸⁶ or indirect nutrient provision mechanism – improves patient-centered outcomes⁸³.

Conceptually, the pathophysiological responses to critical illness of other organ systems manifest as signs, for e.g. tachycardia, - that are initially adaptive but if left untreated or uncontrolled for extended periods the physiological responses itself 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 (e.g. 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 effective⁸⁴. 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 (dys)function⁴. Nonetheless, a definition of EFI solely on symptoms related to stomach is probably insufficient and may ignore important aspect of safety.

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 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, even though 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, that require different complexity 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 success of EN. Such definition could be created easily based on a cut-off 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 mechanism 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 required⁴. 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 review⁴. We propose a framework for developing a consensus definition in Table 3. Ideally, consensus should be reached for each step presented in this table.

Conclusions

A uniform definition of EFI is lacking. Despite the lack of an agreed-upon definition, EFI occurs frequently and is associated with adverse outcome. A current pragmatic definition - reduction or cessation of enteral nutrition 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 one mechanism are incapable to cover the whole spectrum. We propose a conceptual framework for a definition of enteral feeding intolerance for future consensus process.

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Figure 1. Overview of pathophysiological mechanisms that may lead to clinical signs of enteral feeding intolerance^{46,87-89}.

Legend: CCK – cholecystokinin; Ach - acetylcholin

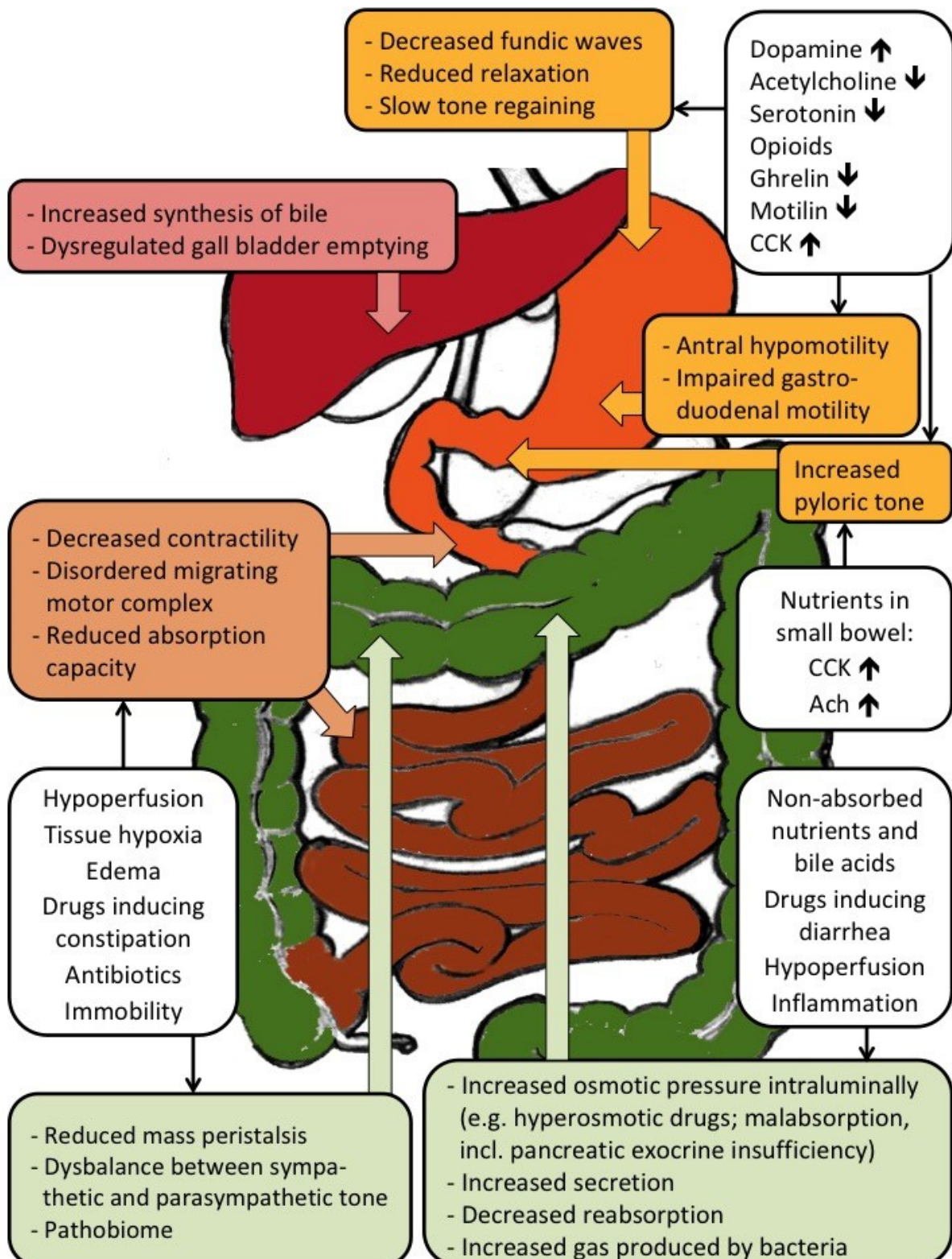


Table 1. Different definitions of enteral feeding intolerance (numbers of studies and reported prevalence of EFI based on a previously published systematic review ³)

Definition	Number of studies	Prevalence of EFI (range)
Large GRV, cut-off 150 mL *	18/63 [§]	8-67%
Large GRV, cut-off 200-250 mL	22/63	
Large GRV, cut-off 300-400 mL	4/63	
Large GRV, cut-off 500 mL	7/63	
Other cut-off (cumulative for 24h 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 calories) or absolute (500 or 750 kcal/24h) amount of calories	6/72	36-37%

Legend: EN – enteral nutrition; GI – gastrointestinal; GRV – gastric residual volume

* Cut-offs presented for single measurement. One single measurement defined EFI in 48/63 studies

§ 63/72 studies used GRV as a criterion, in 30 of them GRV was the only criterion

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	Allow more complex assessment of different aspects and parts of GI tract	Subjective, importance of each single symptom 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 enteral nutrition, 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 calories administered by EN	Possible to easily identify EFI based on a defined cut-off	Is rather a consequence of EFI as the syndrome itself Depends on feeding practices Does not differentiate etiology and is useless for management decisions

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

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 one definition for research and one for clinical practice and whether the clinical practice and research definitions should be integrated into one definition?	Which criteria need to be fulfilled 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?