GI Intolerance to Enteral Nutrition Definitions, Pathophysiology, Etiology and Management: Review and Guidance

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Introduction

Enteral nutrition (EN) is a form of nutrition support for individuals who have a functional gastrointestinal (GI) tract, however, are unable to consume adequate nutrients orally.[1,2] There are different types of EN formulas, including polymeric, (whole protein); blenderized foods which can be whole protein or hydrolyzed protein; partially hydrolyzed (semi-elemental or peptide), and amino acid (elemental). The ability to tolerate EN can be dependent on many factors such as formula delivery rate, type of EN formula and its composition, EN delivery route, EN delivery method, existing medical conditions, existing GI functionality, and influence of medications.[2,3] The literature indicates that GI intolerance(s) to EN is a common outcome as a result of EN in various care settings.[1,4-6] The prevalence of GI intolerance to EN is reported to be between 35-66% in a mix of care settings care settings and between 2-75% in the ICU[1,4,7,8] and in one study, as high as 100% depending on the definition used.[6] Although enteral nutrition intolerance (ENI) occurs on the general hospital ward, in long-term-care and in the home setting, the majority of the published randomized clinical trial literature, focuses on the (ICU) settings and includes gastric residual volume (GRV) as a marker of intolerance.

GI intolerance to enteral formula may lead to symptoms of diarrhea, abdominal distension, and vomiting, resulting in EN formula withdrawal, reductions in EN formula volume, altered delivery method and sometimes a change in formula type.[1,5,6] Individuals experiencing ENI are less likely to achieve their nutrition goal rate, leading to hypocaloric nutrition and negative energy balance, which are associated with poor clinical outcomes and more specifically mortality in the ICU setting.[3,4] As a result, ENI can have serious implications for patient nutrition and health outcomes including dehydration, malnutrition, and quality of life; affecting patients, caregivers and the healthcare system.[1]

The objective of this literature review on enteral nutrition intolerance (ENI) was four-fold:

1. Describe the definitions used in the literature for EN tolerance and intolerance. *Section 1-5*
2. Explain the reported possible etiology and pathophysiology of ENI. *Section 6-7*
3. Report on management strategies described in both clinical studies and RWE. *Section 8*
4. Summarize with suggestions and guidance for consideration for NHSc, when communicating EN tolerance and intolerance related to NHSc products. *Section 9*

This review explored a selection of published literature from 2014-2022 within various clinical practice settings including ICUs, acute care (AC), and home care (HC).

1. Gastrointestinal TOLERANCE to Enteral Nutrition – Definitions

Before defining GI intolerance, it is important to review how the literature describes GI *tolerance*. According to a narrative review by Blaser et al in 2021, GI *tolerance* to EN is defined by the appropriate absorption of all delivered nutrients and the appropriate regulation of water and electrolyte balance. A limitation associated with this tolerance definition is the lack of measurement tool(s) to assess GI absorption capacity. The authors suggest that measuring the weight and macronutrient content of feces may help to better gage intestinal absorption capacity.[5] This measurement may be attainable in an ICU setting and much less so in other health care or home care settings. In another observational study of ICU patients, feeding tolerance to EN was defined as a 7-day persistent EN tolerance where at least 20 kcal/kg of body weight per day via the enteral route could be sustained from 72 hours to 7 days.[9]

Overall, GI tolerance to EN is described as adequate intestinal absorption capacity, appropriate fluid balance, if EN can be sustained without complications and the absence of GI symptoms. Interestingly, meeting energy goals may not be a good indicator of EN tolerance, as there are many factors involved in meeting daily goals such as planned procedures, interventions and other elective or subjective clinical reasons to withhold feeding.[9] Additionally, symptoms used to describe GI tolerance to EN include appropriate stool consistency, and the avoidance of retching, vomiting, abdominal distention, diarrhea and flatulence.[2,9] The defining qualities of GI tolerance are often subjective, lack evidence and are scarcely described in the literature, which is unfortunate given this could help to isolate a good practical working definition of GI intolerance to EN.

2. Gastrointestinal INTOLERANCE to Enteral Nutrition. General Definitions

There is no one universally accepted, clinically relevant, practical definition of GI *intolerance* to EN that covers all care settings. There are a few suggested very simple definitions in the ICU literature, such as, a reduced delivery of EN for whatever reason [10] or one that focuses on a specific GRV measure. [7,] These definitions both lack specificity considering the multitude of factors that cause ENI and the varied symptoms that can arise. Neither definition offer management strategies for ENI. Outside of the ICU, ENI definitions in the literature are often stated simply as, GI symptoms that may interfere with the delivery of EN, or simply presence of GI symptoms [1, 11-14]

The 2012 European Society of Intensive Care Medicine (ESICM) recommendations from a working group, provide a definition of feeding intolerance focused on the ICU and largely based on expert opinion.[10] They describe the general term of intolerance to enteral feeding for whatever clinical reason, including

vomiting, high gastric residuals, diarrhea, GI bleeding, presence of entero-cutaneous fistulas and the inability to achieve 20kcal/kg of energy intake per day within three-days. They caution that ENI should not be considered as present if enteral feeding is electively withheld or interrupted due to procedures. Others also use this working definition.[9] These studies do not explore the role of enteral formula in the ENI or its evidence-based application in managing ENI.

One retrospective study looking at hospitalized patients in both ICU and non-ICU, defined ENI as the development of symptoms that required changes to the feeding protocol or treatment, specifically if reducing the feeding rate, changing the route of feeding or stopping the feeding was required for tolerance. The definition did not include a change to the type of nutrition used.[4]

Definitions of ENI in patients managed outside the ICU are also not consistent. Perhaps the elusive nature of this definition lies partially in the lack of clarity of exactly what GI intolerance to enteral nutrition is amongst Health Care Professionals (HCPs). Is it the negative symptoms caused by the enteral nutrition formula itself (nutritional components, delivery rate or method)? Or is it the GI intolerance experienced while receiving EN, which can be caused by many elements not associated with the actual formula, such as concomitant medications, procedures, severity of illness, disease process, immobility, hydration status or tube type or placement? [6, 7]

Taken a step further, is it GI dysfunction clinicians talk about when referring to ENI. Perhaps it is a combination of both, and without clarity, it is a challenge to land on a working definition. McClave et al clearly discusses the differences in GI dysfunction and feeding intolerance in the ICU patient and provides context to consider when assessing GI dysfunction (Table 1). This comprehensive review article cautions on the potential overlap of the terms, which are often vague and can be misleading.[15]

Table 1

GI Dysfunction	Feeding Intolerance
GI dysfunction usually relates to disordered motility and is most commonly defined by a constellation of symptoms including elevated GRV vomiting/regurgitation, abdominal distention, and absent bowel sounds. Ileus, acute GI injury, chronic intestinal failure	Feeding intolerance is most often defined by the reduced delivery of enteral feeding for whatever reason, with sometimes the addition of GI symptoms or just GI symptoms alone and often include GRV in the definition
For both of these definitions, additional factors such as intra-abdominal hypertension, presence of overt GI bleeding, and diarrhea, are often included in an inconsistent manner.	

McClave also reviews current scoring systems for GI dysfunction used in ICU.[15] Three common scores focus on; either gastrointestinal failure, acute gastrointestinal injury, or chronic gastrointestinal failure. The authors concludes that appropriate feeding intolerance or GI dysfunction scores could be used for prognosis on admission to the ICU, however, cautions on-going use of the scoring system that may guide the nutritional therapy. In a recent study Lin proposed a feeding intolerance scoring system for the ICU that took it one step further than GI symptoms alone. The authors included a points system based on severity of potential feeding intolerance variables (abdominal distention/pain, nausea/vomiting and diarrhea). They demonstrated their novel scoring system was an independent risk factor for 28-day mortality with acceptable predictive accuracy which may help recognize when intervention should happen, ultimately improving nutrition delivery in the ICU.[16]

A search for published literature in the past 5-years on ENI in pediatrics resulted in almost all of the 161 citations focusing on infants, and more specifically pre-term infants. One narrative review by Tume et al on feeding intolerance in critically ill children found 15 articles that defined intolerance, with 11 out of 15 focusing on GVR as the most common factor used in the definition.[17] They summarize the definitions as being inconsistent, nebulous, and arbitrary. The evidence to support the commonly used indicators of feeding intolerance, such as gastric residual volumes (GRV), vomiting, diarrhea, abdominal distention and pain/discomfort, and the use of serum lactate is described as weak or absent. Tume notes, that common actions taken to reduce feed intolerance in critically ill children include changing feed delivery method from intermittent bolus to continuous feeding or from gastric to transpyloric feeding, changing feed formulation (from polymeric to semi-elemental), or administering prokinetic agents. However, they indicate there are no studies on the optimal feeding/formula to support feeding intolerance/tolerance. Interestingly, they conclude with a statement that little progress has been made in defining feeding intolerance in children since a review paper on the topic was published in 2004.

The 2017 ASPEN guidelines for the provision and assessment of nutrition support therapy in the pediatric critically ill patient discusses feeding intolerance and suggests the use of protocols that guide the detection and management of ENI should be used; however, no guidance is provided.[18]

3. **Systematic Literature Review (SLR) Definitions of ENI**

Systematic literature reviews are powerful pieces of literature that provide a compilation of the best available research in a topic and synthesize the scientific evidence to answer a particular research question. We are fortunate to have two SLR's that focus on ENI in adults and one in pediatrics. However, all three target the intensive care unit leaving compiled data on patients outside the ICU lacking.

Two recent SLR's in adults attempted to uncover an evidence-based working definition for this condition in intensive care patients however, both discovered more than 40 varied definitions used in research and were left to proposes their own simple functional definition[5,6] (Table 2). A SLR by Blaser et al in 2014 and a further updated narrative review by the same author in 2021 concluded that definitions of GI intolerance to EN in critically ill patients can be categorized as large gastric residual volumes (GRVs), GI symptoms, and inadequate delivery of EN.[6,7] Blaser's recent update article proposed an iterative conceptual framework consensus process to develop a definition of ENI. [5]

An SLR by Jenkins in 2022 found that 78% of studies use GI symptoms to define GI intolerance to EN, including vomiting, regurgitation, abdominal distention, abdominal pain, GI bleeding, bowel ischemia, perforation, diarrhea, and constipation.[6] However, the most commonly identified symptoms in the literature were vomiting, abdominal distention and diarrhea.[6] They also found the most frequently reported predictors associated with feeding intolerance were vasoactive drugs, sedation or paralysis, intra-abdominal pressure and APACHE II score. Their review found no consistency of thresholds of GRV used to define feeding intolerance and no link was seen between GRV and rates of ENI and do not recommend using GRV to determine ENI. The authors do mention in their discussion that changing enteral feed type to extensively hydrolysed or advancing the enteral tube to provide post pyloric feeding should be considered managing ENI.

Table 2 SLR Proposed Definitions of ENI in Adult ICU[6]

Blaser, 2021 For everyday clinical practice at bedside: A pragmatic definition of, reduction or cessation of EN due to clinical manifestation of GI dysfunction
Jenkins 2022 A failure to reach EN energy and protein targets in addition to presence of GI symptoms. More specifically: EN intake is insufficient (less than 80% of target with 72 h of feed initiation) and at least one of the following symptoms is present: vomiting/ regurgitation, abdominal distension, or diarrhea.

A SLR by Eveleens in 2019, in a pediatric ICU population, categorized the definitions of GI intolerance to EN from the 31 studies they reviewed, as: discontinued EN due to GI symptoms, the presence of GRVs and/or GI symptoms, and the inability to achieve enteral target intake.[8] In the absence of finding a clear ENI definition, they proposed a definition should include:

- the inability to achieve enteral nutrition target intakes of two-third of prescribed daily target and,
- the presence of at least one of the following GI symptoms indicating GI dysfunction: large GRV, presence of vomiting or diarrhea or severe GI-symptoms with concern for intestinal ischemia.

None of the pediatric RCTs, interventional, prospective, or retrospective studies that Everleens reviewed in their SLR compared polymeric versus (semi)-elemental formulas in managing ENI. They further indicate that 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. Of note, there are several real-world-evidence (RWE) publications which have showed improvement in patient's GI symptoms when transitioning from a standard polymeric formula to semi-elemental formula or from casein-based to whey-based formula. [2,11,12, 14, 19-21] Although in these studies the clinical reason for the GI improvement is not well defined, they do contribute to practice-based experience and judgement.

4. **Role of Gastric Residual Volumes in ENI Definitions**

Many studies define GI intolerance to EN using GRVs, or any combination of GRVs, abdominal distention, and GI symptoms. These studies are mainly ICU focused and have used a range of GRV volume of 75-500mL to define problematic GRVs.[6,7] The American Society for Parenteral and Enteral Nutrition (ASPEN 2016) recommends that GRVs should no longer be used as a marker of GI intolerance to EN due to poor correlations with gastric emptying, pneumonia, aspiration, and regurgitation. [22] The European Society for Clinical Nutrition and Metabolism (ESPEN) states that measuring GRVs should only be used to identify GI intolerance during initiation and progression of EN, and not as a continuous marker.[10]

In a recent large multicentre, multiyear retrospective analysis of a comprehensive database of over 15,000 ICU patients, Heyland defined enteral feed intolerance as interrupted feeding due to one of the following reasons: high gastric residual volumes, increased abdominal girth, distension, subjective discomfort, emesis, or diarrhea. They reported that 24% of patients had at least one episode of enteral

feed intolerance and identified higher sustained levels of GRV to be one of the factors associated with ENI. They concluded that enteral feed intolerance is associated with lower enteral nutrition delivery and worse clinical outcomes and that repeated evaluation of GRV using a higher threshold may be warranted to better identify patients that may benefit from interventions to manage EFI. This study did not mention enteral formula or their role in contributing or managing ENI. [23]

5. Real World Evidence (RWE) - Definitions of ENI

Real-world evidence (RWE) publications on enteral formula tolerance/intolerance provides an opportunity to gain insights into day-to-day clinical practice. These non-interventional studies may be a retrospective look at patient charts or healthcare medical-claims data (insurance claims), observational or quality improvement or a prospective survey of opinions and beliefs on the topic. Tolerance data generated from these RWE studies can serve to support product reimbursement submissions in various countries. In fact, countries such as UK and Canada have government agency established criteria on how they define what is measured for formula efficacy, which includes tolerance. The UK Advisory Committee on Borderline Substances (ACBS) criteria to support the submission for prescription usage in the NHS, recommend the following is measured when establishing tolerance; changes during EN feeding in diarrhea, constipation, bloating, nausea, vomiting, burping, flatulence, regurgitation and abdominal pain or discomfort. In Canada, a large provincial reimbursement agency requires evidence of product efficacy and tolerance of a formula. However, they do not define what tolerance means.

Regarding a definition of ENI, RWE publications are often lacking specificity in this area and may not define tolerance or intolerance at all. Rather they simply report on the patients ENI symptom outcome after a formula switch. A between clinical trials or SLRs and RWE clearly exists. Rarely does a clinical trial or SLR discuss impact of an enteral formula in resolving ENI, in fact in most of these studies specific enteral formula is not mentioned. And in RWE rarely is a definition, causation of the ENI or pathophysiology discussed. The focus is often on a specific formula and its tolerance, rather than intolerance relationships.

One recent RWE publications on EN tolerance and healthcare utilization in pediatric patients at home, defined intolerance as the presence or absence of nausea/vomiting, diarrhea, constipation, abdominal distension and gastric residual.[19] Another recent study on a very similar topic does not specifically define ENI, rather reports on changes in symptoms of GI distress, (diarrhea, nausea, abdominal pain and

cramping, bloating and constipation) after a formula switch.[20] Minor et al examined tolerance improvements in a small group of children with development delays, who were switched from one formula to another. They did not specifically define intolerance, rather reported on retrospective pre-and post-switch data of changes in tolerance parameters where children had vomiting, constipation, diarrhea, gagging and retching and high residual volumes.[24] O'Connor looked at a change in feed tolerance in children when a formula was switched. They described tolerance issues to formula as retching, vomiting, flatulence, and/or abnormal stool consistency and frequency and reported tolerance as either improved, no change or worsened.[2] A 2022 retrospective study evaluated usage and tolerance of two commercial blended formula in pediatrics and adults using medical-claims data (insurance claims).[21] They assessed tolerance based on reported symptoms of nausea, vomiting, abdominal distention, constipation, and diarrhea before and after hospital discharge, and concluded the formula was well tolerated if symptoms improved. None of these studies defined intolerance and all used proxies of tolerance if standard symptoms of intolerance were improved.

The RWE evidence in adults is very similar. Mundi et al's retrospective review of a home enteral-claims data base described intolerance as; when clinically patients present with symptoms of GI distress such as gas/bloating, diarrhea, nausea.[12] They reported on improvements in symptoms after a formula switch. They did not define intolerance and like other RWE, used proxies of tolerance to describe intolerance. Hopkins et al described a small retrospective cases series in adults where formula was switched to improve tolerance. Tolerance parameters assessed included volume of formula infused versus goal, and nausea and vomiting, residuals, gagging/ retching, abdominal gas/distention, and stool assessments.[11] Their study reported improved tolerance as either improved, no change, or worsened. An earlier RWE survey by the same author, of 240 dietitians working outside of the ICU, on self-reported prevalence of ENI, focused on GI symptoms of intolerance: nausea, vomiting, reflux, sensation of fullness, abdominal distension, bloating, diarrhea, and constipation.[1] Intolerance was not specifically defined in this study, although they indicated the presence of one or more clinical symptoms was considered indicative of ENI for data collection.

Overall, RWE publications rarely, if ever, define ENI or evaluate ENI against a definition. For the most part they describe symptoms and comparative improvements of symptoms when a formula is switched. Never-the-less, RWE that is published in peer-reviewed journals, using sound research methodology, can be a powerful tool to encourage clinicians to consider new management options to help manage their patients with ENI.

6. Etiology of GI Intolerance to Enteral Nutrition

To further understand GI intolerance to EN and determine the most effective management strategies, it is crucial to acknowledge the causes of ENI and how it emerges in the body. However, the precise etiology of ENI is not well described, and no one study fully explains its probable causes. What is reported in the literature, once again, mainly focuses on the adult ICU patient, often with a heterogeneous study population and varying patient diagnosis. For example, Heyland reported that ENI was more likely to occur in patients with burns, cardiovascular disease, existing GI problems, and sepsis, however the cause of ENI was not elucidated.[23] In some studies ENI is a secondary discussion where ENI treatment modalities are one of the primary objectives of the studies.[5-7,]

Others report predictors of ENI, with the most frequent for their ICU specific study population, being vasoactive or muscle relaxant drugs, sedation or paralysis, intra-abdominal pressure (IAP), the APACHE II score, large GRVs, delayed gastric emptying [25]. A few studies discuss EN delivery method as a predictor of ENI, with it being more prevalent with bolus EN delivery and full-dose regimes early in the feeding process, and other discuss bolus as being tolerated better during the weaning phase. [26,27] Predictors of ENI are just that and should not be confused with what caused the ENI. It appears the best data clinicians have so far has been lists of predictors of ENI along with their clinical experience which may or may not be guided by a facility protocol.

One must not confuse the potential complications of enteral feeing such as postoperative ileus, acute bowel ischemia, bowel obstruction, aspiration pneumonia, and even refeeding syndrome or clinical manifestations/symptoms of ENI as etiology. Nausea, vomiting, bloating, diarrhea, abdominal distension, and/or high nasogastric residuals are symptoms of GI distress. These symptoms could be caused by the process of enteral feeding or the enteral formula itself, although literature on this topic is sparce and largely narrative in real-world evidence reports, where causation is lacking.
Studies on specific etiology of ENI outside the ICU setting are lacking and the exact cause remains unclear, with some literature commenting on the topic based on the authors experience of the specific effects of treatment of the ENI. Overall, the causes of ENI are poorly understood, and poorly defined, making it is difficult to develop effective management and potentially prevention strategies.

7. Pathophysiology of Gastrointestinal Intolerance to Enteral Nutrition

Two recent papers in the critically ill, one in adults and one in pediatrics, do a good job at describing possible pathophysiological processes occurring in those with ENI. [5,17]

Blaser et al discusses that the malfunctioning enteric and autonomic nervous systems, altered hormone regulation, smooth muscle dysfunction, medications, fluid imbalances, glucose abnormalities, and systemic inflammation are all correlated with GI intolerance to EN in the adult ICU patient. [5] More specifically, if the integrity of the interstitial cells, between the nerve endings and smooth muscle cells in the GI tract are disturbed, the risk of GI dysmotility increases. In addition, the increased presence of hormones such as cholecystokinin, glucagon-like peptide-1, peptide YY, and amylin can delay gastric emptying, while ghrelin and motilin accelerate gastric emptying. Also, medications such as antibiotics can alter the gut microbiome, leading to malabsorption and poor digestion, all of which contributes to GI intolerance to EN. Fluid balance in the body is a predictor of GI tolerance as a fluid overload can result in intestinal edema, inhibiting normal bowel motility and causing acute GI injury. Blaser also notes that GI intolerance to EN can occur in individuals with or without primary GI pathology and that many parts of the GI tract may have implications on the pathophysiology of GI intolerance to EN, and its definition should reflect this. [5]

Tume et al 's publication with pediatric critically ill patients, describe a number of factors that can lead to GI intolerance to EN.[17] Alterations of vagal tonus, vasoactive intestinal peptide and nitric oxide secretions are factors that delay gastric emptying. As a result, stomach motor discoordination, antroduodenal discoordination, and gut contraction/relaxation discoordination occurs, leading to ENI. Although serum lactate is frequently used as a marker of GI intolerance as increased serum lactate typically indicates inadequate tissue perfusion, they caution it use to determine the incidence of ENI as variable/inconsistent lactate thresholds are used in the literature and in professional practice.[17] Medications such as opiates, sedatives, neuromuscular blocking agents, and catecholamines slow transit time, depending on dosage, leading to delayed gastric emptying and possible ENI. In addition, gut tissue alteration due to gut inflammation or hypoperfusion can lead to malabsorption and bowel movement alterations. Tume also describes how pressure changes resulting from positive pressure ventilation or other traumas may impact the renin-angiotensin system in the body and therefore reduce splanchnic perfusion, which is the blood flow to GI organs. Reduced splanchnic perfusion can alter one's tolerance to EN by causing functional and structural changes in the GI tract. They indicate this is due to the fact that EN increases the oxygen and metabolic demands of the gut, which may result in oxygen supply and

delivery imbalances due to the decreased blood supply. Finally, the authors further describes how gastroesophageal reflux and vomiting, key indicators of GI intolerance to EN, may be the result of an obstructed bowel or a paralytic ileus, irritation of the endotracheal tube, incorrect gastric tube positioning, and/or inadequate gastric decompression.[17]

Emerging evidence suggest gut microbiota may be associated with GI intolerance to EN, particularly when the body is under a stressed state of systemic inflammation.[21] It is suggested an increased prevalence of declining alpha-diversity of gut microbiota is present in ICU patients with GI intolerance to EN, resulting in a decline of health-promoting bacteria such as Faecalibacterium, Ruminococcus, and/or Pseudobutyrivibrio, and overgrowth of pathobionts like Enterococcus, Escherichia, Staphylococcus, Enterobacteriaceae, and Pseudomonas.[28] However, causal effect for GI intolerance has not been firmly demonstrated yet.

8. Managing Gastrointestinal Intolerance to Enteral Nutrition

In addition to a non-existent clear working definition of ENI, there is a paucity of literature on how to effectively manage ENI, with clinical practice and clinical judgement the main driver of management strategies. A number of retrospective reviews have described patients with varying degrees of intolerance to EN based on a list of symptoms, and some report on suggestions to help improve ENI based on an association between symptom and formula. [1,11,12,19,24,] These suggestions are mainly grounded in type of EN formula with a theoretical reason for success in a particular patient population prior to, and after a formula switch was made. The etiology and pathophysiology of the ENI is rarely defined in these retrospective studies making it difficult to draw solid clinical conclusions on reason for the results. However, in the absence of solid clinical data on how to manage ENI, these retrospective studies serve to inform practice and help health care providers develop their own clinical experience and judgement.

The literature describes a number of strategies to help manage ENI with the approach varying depending on if the patient is in ICU or not. These include the use of medications, reducing the volume of formula delivered, switching either EN formulas, feeding schedules or tube placement, and even discontinuation of EN and use of Parenteral Nutrition. [1,4,6,24,25]

One RWE publication of dietitians practice outside the ICU reported that 20% of the time formula is changed due to ENI.[1] As described in section 5 of this review, a number of researchers using retrospective data, show GI symptom improvement when a formula is switched from a standard formula to one that possibly offers better GI tolerance, and they offer theoretical reasons for the described improvement. One recent guideline of on the evaluation and treatment of gastrointestinal and nutritional complications in children with neurological impairment cited, among their recommendations, one specifically related to EN, which suggested for gastroesophageal reflux, a trial of whey-based formula if the patient has gagging and retching. [29]

A very common ENI management strategy in most of the ICU literature is the use of prokinetic agents, which can helps reduce GRVs. [4,25] However, these medications have not shown positive effect on vomiting, diarrhea, pneumonia, or mortality, and the side effects and tachyphylaxis associated with prokinetic agents can be undesirable.[6,9,19,25] Additionally, when gastro-prokinetics improve gastric emptying, it can worsen bowel distension, leading to other complications that can be mistaken for GI intolerance to EN.[7,24,,25]

Metheny provides a much-appreciated nursing perspective on the area of enteral feeding intolerance in both the ICU and outside the ICU. Her paper reviews recommendations and guidelines for enteral feeding from six international organizations and provides her perspective on best nursing practices for monitoring and managing ENI in adults. [13]

It is evident that much of the management strategies for GI intolerance to EN are challenged with the discrepancies in defining characteristics, etiologies and pathophysiology that belong to this condition. Current management strategies outside the ICU are often grounded in experience and practice with the goal to improve GI symptoms.

9. Considerations for Nestlé Health Science

The objective of this literature review on enteral nutrition intolerance (ENI) was four-fold:

1. Describe the definitions used in the literature for EN tolerance and intolerance
2. Explain the reported possible etiology and pathophysiology of ENI
3. Report on management strategies described in both clinical studies and RWE
4. Summarize with suggestions and guidance for consideration for NHSc, when communicating EN tolerance and intolerance related to NHSc products

This review confirms that a wide range of definitions are used to represent GI tolerance and intolerance to EN, with no one standardized approach to management in the ICU or outside the ICU. Interestingly, the literature demonstrates minimal progression in establishing a clear clinical and practical definition of ENI with research findings remaining similar over the past ten plus years. Literature in the ICU area generally talk about EN intolerance with no mention of enteral formula as a cause or possible treatment, while RWE studies on patients outside the ICU often describe tolerance before and after a formula switch. In RWE, rarely is mentioned a definition, causation of the ENI, pathophysiology, or evidence of why the switch was successful. The focus is often on a specific formula and its tolerance, rather than intolerance relationships. It is clear a gap exists between clinical trials or SLRs and RWE approach to ENI.

Suggestions for consideration by NHSc, when communicating EN tolerance and intolerance related to NHSc products. Nestle would be well positioned to:

1. **Adopt a pragmatic and harmonized approach** in the way all platform teams assess the literature and communicate about tolerance/intolerance of products in scientific collateral. Our position should include referencing to applicable literature as well as guidelines such as ESPEN/ASPEN.

   In the absence of a clear and well-defined definition of intolerance, we should consider the following as our guidance:

   - **EN can be described as well tolerated if**: there is an absence of GI symptoms during EN feeding, including an absence of diarrhea, constipation, bloating, nausea, vomiting, belching, flatulence, regurgitation and abdominal pain or discomfort.
   - **GI intolerance to EN can be described as**: the occurrence of one or more of the above listed symptoms, may suggest ENI is present.

2. Increase efforts in the area of **professional education** on ENI, creating awareness of scientific aspects of tolerance to EN and GI intolerance to EN as well as management strategies to manage ENI. Become the leader in this clinical area.
3. **Engage prominent researchers and subject matter experts** in the area of ENI to help develop an approach to a consistent scientific message for enteral products use in the area of ENI.
4. **Help support the development of standardized and validated measurement tools** for diagnosing GI intolerance to EN and measuring its signs/symptoms. This may include creating thresholds for signs/symptoms of ENI symptoms

5. **Design research /evidence generation,** that either NHSc does, or when NHSc supports investigators to do research, that includes:
    a. a definition of ENI or tolerance (be clear what we are assessing)
    b. be clear on the hypothesized outcome and how the outcome was met including potential pathophysiology that supported the effective outcome
    c. if the research design is focused on switching from one formula to another to show improved tolerance, establish clear parameters for outcomes, particularly if the terms “better” or “improved” tolerance/intolerance is to be used.
    d. in the absence of a comparator formula in the research design, establish well defined baseline characteristics and avoid the terms “better” or “improved” tolerance/intolerance if a baseline is not established.
    e. In the care area studied, (ICU, hospital or homecare) – focus on the value (economic) of impacting improvement of ENI in that care area

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