Gastrointestinal function in critical illness—a complex interplay between the nervous and enteroendocrine systems

Enid E. Martinez1,2,3, Alessio Fasano2,3,4, Nilesh M. Mehta1,3,5

1Department of Anesthesiology, Critical Care and Pain Medicine, Division of Critical Care Medicine, Boston Children’s Hospital, Boston, MA, USA; 2Department of Pediatrics, Mucosal Immunology and Biology Research Center, Massachusetts General Hospital, Boston, MA, USA; 3Harvard Medical School, Boston, MA, USA; 4Department of Pediatric Gastroenterology and Nutrition, Massachusetts General Hospital for Children, Boston, MA, USA; 5Center for Nutrition, Boston Children’s Hospital, Boston, MA, USA

Contributions: (I) Conception and design: EE Martinez; (II) Administrative support: NM Mehta, A Fasano; (III) Provision of study materials or patients: EE Martinez; (IV) Collection and assembly of data: EE Martinez; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Enid E. Martinez, MD. Boston Children’s Hospital, 300 Longwood Avenue, Bader 634, Division of Critical Care Medicine, Boston, MA 02115, USA. Email: enid.martinez@childrens.harvard.edu.

Abstract: Gastrointestinal (GI) dysfunction affects 40-80% of critically ill children and is associated with morbidity and mortality. GI function, specifically GI motility, is dependent on a complex interplay between the extrinsic and intrinsic nervous systems and the endocrine system. During critical illness the coordinated actions of these systems are disrupted resulting in GI dysmotility. The extrinsic parasympathetic nervous system is inhibited, thereby directly and indirectly contributing to GI dysmotility, whereas the sympathetic nervous system is upregulated. The enteric nervous system (ENS) is altered by local inflammatory and altered extrinsic nervous system signaling and the enteroendocrine system is dysregulated with variable up- and down-regulation of different GI hormones. Current approaches to diagnose GI motility at the bedside are primarily based on clinical assessments, which can be unreliable. Application of modalities such as ultrasound or serum biomarkers are promising diagnostic tools and may provide real-time guidance on GI motility for critically ill patients. Treatments for GI dysmotility remain limited, though research on the pathophysiology of GI dysmotility is guiding the development of novel therapies such as targeted GI hormone therapeutics to treat GI dysmotility. In this review, we present an overview of the physiology of GI motility during health and critical illness, the currently available modalities to diagnose GI motility in critical illness and available therapies. Understanding the role of the nervous and endocrine systems on GI dysmotility in critical illness will guide innovations in clinical practice and research, thereby advancing the diagnostic and therapeutic alternatives for this condition.

Keywords: Gastrointestinal (GI); motility; critical care; hormones; parasympathetic

Received: 28 July 2020. Accepted: 23 November 2020; Published: 30 November 2020.

doi: 10.21037/pm-20-74

View this article at: http://dx.doi.org/10.21037/pm-20-74

Introduction

Gastrointestinal (GI) dysfunction affects between 40% and 80% of critically ill children (1-3). Physiologically, GI function includes complex and coordinated interactions between the neurologic and endocrine systems resulting in digestion, absorption, and peristalsis. In critical illness, both, digestion, secondary to dysmotility, and absorption, secondary to epithelial barrier disruption, can be affected (2,4). GI dysfunction results in enteral nutrition (EN) intolerance which leads to an inability to achieve EN targets and has been associated with greater length of stay in the intensive care unit (ICU), acquired infections, and mortality (2,4,5). In this review we present an overview of GI
Physiology

GI motility is the result of a complex interplay between the nervous system (extrinsic and intrinsic) and the endocrine system both of which are differently modulated by feeding versus fasting states (6-10).

The extrinsic nervous system is present throughout the GI tract and includes spinal afferents and the autonomic nervous system (ANS) that both parasympathetic and sympathetic innervation. The parasympathetic innervation is provided by the vagus nerve from the esophagus to the proximal large intestine, and the pelvic nerve for the remaining distal GI tract. Afferent innervation of the ANS provides signals from mecha- and chemo-receptors in the GI tract and the efferent nerves act on smooth muscle and secretory and endocrine cells. The enteric nervous system, the intrinsic nervous system of the GI tract, can also integrate motor and sensory input and act on motor, secretory and endocrine functions of the GI tract but independently of the central nervous system. Cells of the enteric nervous system are in the myenteric and submucosal plexi, where they act on motor and secretory functions, respectively, and can interact with components of the ANS. The interplay among these neural networks is demonstrated most prominently in patients with vagotomies who develop gastroparesis despite an intact enteric nervous system, and patients with Hirschsprung's disease, who have ineffective colonic motility despite an intact ANS. In addition to the extrinsic and intrinsic nervous systems, GI motility is regulated by the interstitial cells of Cajal (ICC) and the enteroendocrine system (7,11). The ICCs, primarily present in the submucosal layers of the GI tract, serve as pacemakers generating constant slow waves that can be transformed into complete depolarizations and GI contractions with secondary stimuli (11). The enteroendocrine system is composed of different types of enterochromaffin cells (ECCs) which account for <1% of the cells of the epithelial barrier and are selectively distributed throughout the whole GI tract. Enterochromaffin cells can sense nutrients either in the apical or basolateral surface of the epithelial mucosa and release hormones or hormone-like substances that regulate GI function including motility and secretory functions (7). Figure 1 depicts the distribution of these neurologic and enteroendocrine components in the layers of the GI tract.

**Fasting (Interdigestive) state**

Under fasting conditions, or the interdigestive period, the GI tract goes through a cycle of phasic contractions known as the migrating motor complex (MMC). The MMC serves a housekeeping function whereby residual luminal content is propelled forward to clear the GI tract. The MMC is primarily initiated in the distal stomach and small intestine and is composed of three phases, a quiescent phase (45–60 minutes), a phase of irregular contractions (35–50 minutes) and a short phase of regular contractions (5–15 minutes) (6). The MMC is controlled by parasympathetic input, GI hormones, specifically motilin, ICCs, and the enteric nervous system.

**Feeding state**

Upon ingestion of a meal, neural and GI hormone signaling significantly change to facilitate digestion and absorption of nutrients. The MMC ceases and stretch mechanoreceptors in the proximal stomach trigger “receptive relaxation” via vago-vagal reflexes accommodating up to 1.5 L of volume in adults (6). Simultaneously, the distal stomach undergoes cycles of contraction and relaxation to break down a solid meal (6). Exposure of the small intestine to macronutrients and an osmolar load activates feedback loops within the ANS and enteroendocrine signaling, that increase the contraction and relaxation cycles and control pyloric relaxation. Pressure gradients between the antrum and the duodenum allow for controlled periodic transfer of digested food bolus into the duodenum for nutrient absorption. Parasympathetic and enteroendocrine signaling also slows down gastric emptying and the transfer of chyme from the stomach into the small intestine to ensure complete absorption of nutrients in the small intestine. GI hormones serve as a regulating mechanism for multiple phases of digestion and are released or suppressed, depending on their function, in the presence of luminal macronutrients or after absorption in different segments of the GI tract (7). The secretion of some GI hormones is also either triggered or regulated by parasympathetic input (7). Table 1 summarizes the site of and trigger for secretion or suppression of GI hormones as well as described effects on GI motility. Gastric emptying of a standard meal will take 2–3 hours, however, differences in the digestive patterns are present when comparing solid versus liquid meals and meals with different osmolar loads (6).
Large Intestine Motility

The large intestine reabsorbs electrolytes and water, and allows for controlled waste of unabsorbed luminal content (12). This process, unlike that of stomach and small intestinal digestion, is prolonged and transit of luminal contents from cecum to rectum can take over 48 hours in healthy patients. Motility in the large intestine is also regulated by the enteric nervous system, ANS and GI hormone signaling. An important role of the large intestine in GI function is the secondary metabolism of nutrients by commensal bacteria. Significant advances have identified how bacterially derived metabolites contribute to GI, immune and neurologic health (13-15).

Pathophysiology

GI motility can be greatly altered in the setting of critical illness secondary to the effect of inflammation and medications on the neurologic and enteroendocrine systems. The majority of studies have demonstrated that in critically ill patients there is a slowing of gastric emptying, a loss of coordination between the antrum and the duodenum, and a slowing of colonic motility (2,3,16,17). Figure 2 presents a schematic of the multiple alterations of the extrinsic and intrinsic nervous systems and the enteroendocrine system that result in GI dysmotility during critical illness.

In critical illness, the sympathetic arm of the ANS is primarily activated, resulting in a suppression of parasympathetic input (18). Furthermore, medications administered in critical care have an anticholinergic effect which can further suppress the parasympathetic system (19). Inhibition of the parasympathetic nervous system results in an overall slowing down of GI functions as has been noted in patients with vagotomies and in animal models (20-22). The parasympathetic nervous system, the vagus nerve specifically, has been shown to modulate GI hormones levels. For example, experimental models have shown that vagotomy or cholinergic inhibition results in reduced ghrelin and peptide-YY (PYY) secretion (23,24). Abnormal GI hormone levels have been reported in critical illness independent of the effect of the ANS on their secretion. Table 2 summarizes adult and pediatric studies of critically ill patients where GI hormone levels were examined and correlated with GI motility or EN tolerance as a proxy.
The most commonly studied GI hormones in critical illness are cholecystokinin (CCK), PYY, and ghrelin (26,28-32). Results vary among studies and this may be secondary to differences in study design such as sampling of hormone levels during fasting versus fed states, assays utilized for measuring hormone levels or the definition applied for GI dysmotility.

The enteric nervous system can locally control smooth muscle action and interacts with the ANS to regulate motility. Enteric neurons interact with innate immune cells of the GI tract and therefore, under conditions of inflammation the activation of innate immune cells and their signaling on the enteric nervous system can result in changes in GI motility (14,35). In animal models, activated
pro-inflammatory macrophages and their interactions with the enteric nervous system have been implicated in the development of post-operative ileus (36). A contributing factor to the activation of the innate immune cell population of the GI tract is the increase in intestinal trafficking of microbial products across the epithelial barrier (15). Epithelial barrier disruption and increased intestinal trafficking have been reported in critical illness, and therefore secondary GI tract inflammation via this pathway may also affect the enteric nervous system and motility (1,37). Similarly, the microbiome and associated metabolites modulate the innate immune system and secondarily regulate the enteric nervous system and its function (14). Dysbiosis has been described in critical care and therefore, regulation of the enteric nervous system and secondary GI dysmotility in this context is also possible (38).

**Diagnosis**

Although many clinically-approved methodologies exist to examine GI motility, few are feasible in critically ill patients. Esophageal, antro-duodenal and colonic manometry all measure pressure changes associated with regional motility, whereas the ingestible wireless motility capsules can measure whole GI transit, and Sitz markers distal GI transit (39). Studies examining GI motility in critically ill patients have focused on measuring gastric emptying. Scintigraphy, the clinically used and gold-standard test, has been employed with the use of a portable gamma-camera in an adult ICU (40–42). However, the majority of ICUs do not have the
ability to perform portable scintigraphy. The 13-C octanoic acid breath test and the acetaminophen absorption test have both been moderately to strongly correlated with scintigraphy (41-43). In both assays a known concentration of either a 13-C octanoic tagged meal or acetaminophen is administered in the stomach where neither is metabolized nor absorbed. As the stomach empties, the 13-C octanoic tagged meal or acetaminophen are then transferred into the small intestine where they are absorbed and metabolized in the liver. 13-C octanoic levels are measured in exhaled breath, whereas acetaminophen levels are measured in the blood, and the concentration of these markers over time reflects gastric emptying. These assays are non-invasive and can be nearly universally applied, except in patients with liver dysfunction and/or with severe malabsorptive disorders, either of which may alter the metabolism and absorption of each agent, respectively. Ultrasound (US) has become a common diagnostic adjunct in the ICU and may

Table 2 Summary of studies on gastrointestinal hormones and gut function in adult and pediatric critical illness

<table>
<thead>
<tr>
<th>Authors (Ref)</th>
<th>Study population</th>
<th>Clinical methods</th>
<th>Hormone studied</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crona et al. (25) *</td>
<td>20 adult patients with feed intolerance; 10 without</td>
<td>GE by AAT; Feed tolerance by GRVs</td>
<td>Ghrelin, CCK, motilin</td>
<td>Ghrelin levels were greater in feed intolerant patients; Feed intolerance correlated with delayed GE</td>
</tr>
<tr>
<td>Nguyen et al. (26) *</td>
<td>39 adult patients</td>
<td>GE by CO13 breath test</td>
<td>CCK, PYY</td>
<td>CCK and PYY levels greater in patients with delayed GE while fasting and feeding</td>
</tr>
<tr>
<td>Summers et al. (27) *</td>
<td>26 adult patients; 23 controls</td>
<td>GE by CO13 breath test; Feed tolerance by GRV and emesis</td>
<td>Amylin, GLP-1, glucose</td>
<td>GLP-1 levels were greater in feed intolerant patients</td>
</tr>
<tr>
<td>Nguyen et al. (28) *</td>
<td>19 adult patients; 24 controls</td>
<td>Feed intolerance by GRV</td>
<td>CCK, PYY</td>
<td>PYY and CCK levels were greater in feed intolerant patients during fasting and feeding</td>
</tr>
<tr>
<td>Santacruz et al. (29) *</td>
<td>30 adult patients; 10 controls</td>
<td>Feed intolerance by GRV</td>
<td>PYY, ghrelin</td>
<td>Ghrelin levels were lower in critically ill than in controls; No difference by feed intolerance</td>
</tr>
<tr>
<td>Martinez et al. (30) **</td>
<td>14 pediatric patients</td>
<td>GE by AAT; Feed intolerance by EN delivery</td>
<td>CCK, GLP-1, PYY, GIP, glucagon, ghrelin, amylin</td>
<td>Greater levels GLP-1, glucagon and amylin correlated with feed intolerance; Lower PYY and ghrelin levels correlated with delayed gastric emptying</td>
</tr>
<tr>
<td>Mayer et al. (3) **</td>
<td>23 pediatric patients</td>
<td>GE by AAT; Feed tolerance by GRV</td>
<td>Amylin</td>
<td>Amylin levels were greater in feed intolerant patients; Feed intolerance correlated with delayed GE</td>
</tr>
<tr>
<td>Shanahan et al. (31) **</td>
<td>64 preterm infants &lt;30 weeks GA</td>
<td>Feed intolerance by time to reach full enteral nutrition</td>
<td>Amylin, GIP, GLP1 GLP-2, Ghrelin, Insulin, Leptin, PYY</td>
<td>PYY and GIP levels were lower in feed intolerant patients</td>
</tr>
<tr>
<td>Sharman-Koendjibaharie et al. (32) **</td>
<td>8 preterm infants with NEC and ileostomy; 11 controls</td>
<td>Feed intolerance by volume of feed provided</td>
<td>Gastrin, CCK, PYY</td>
<td>CCK levels were greater and PYY levels were lower when feeding volume was lower</td>
</tr>
<tr>
<td>Hanekamp et al. (33) **</td>
<td>12 neonates on ECMO</td>
<td>Change between PN and EN</td>
<td>CCK, PYY, Gastrin</td>
<td>Gastrin, CCK, PYY levels were greater when EN was initiated</td>
</tr>
<tr>
<td>Kairamkonda et al. (34) **</td>
<td>70 Preterm neonates</td>
<td>Feed intolerance by GRV and time to goal EN</td>
<td>Amylin</td>
<td>Amylin levels were greater in feed intolerant patients</td>
</tr>
</tbody>
</table>

*, indicates adult studies; **, indicates pediatric studies. GE, gastric emptying; AAT, acetaminophen absorption test; GRV, gastric residual volume; CO13, 13-C octanoic test; PN, parenteral nutrition; EN, enteral nutrition; NEC, necrotizing enterocolitis; ECMO, extracorporeal membrane oxygenation; CCK, cholecystokinin; GLP-1, glucagon like peptide 1; GLP-2, glucagon like peptide 2; PYY, peptide-YY; GIP, total gastric inhibitory polypeptide.
serve as a non-invasive tool to examine gastric emptying in critically ill patients. More than one US approach has been used to measure gastric emptying, including measuring a change in circumference of the stomach or the width of the antrum over time after a meal or assessing the presence or absence of contents in the stomach (44-47). The majority of studies have been completed in adult or neonatal critically ill patients, therefore additional studies to examine the use of US in the pediatric ICU are needed.

In the absence of these diagnostic methods the most common proxy measures for GI dysmotility are bedside clinical assessments for EN intolerance (5,48). In pediatric critical care studies, GI symptoms such as diarrhea, emesis, abdominal distension and gastric residual volume (GRV), are the most common bedside proxy markers for EN intolerance and GI dysfunction (5). In addition, some studies utilize discontinuation of EN as a marker for GI dysfunction. Of these markers, GRV and EN delivery have been compared with a measure of gastric emptying, the acetaminophen absorption test. One study reported no difference in the median GRV between patients with and without delayed gastric emptying but identified a correlation between gastric emptying and EN delivery (2). Another study reported that patients with GRVs greater than 125% of the instilled bolus of formula had delayed gastric emptying (3). Furthermore, a study comparing EN advancement between two pediatric ICUs with differing practices on measuring GRV found no difference in the frequency of aspiration events and greater EN delivery when GRV was not measured (49).

**Treatment**

Despite advances in the understanding of the physiology of GI dysmotility in critical illness, the available treatment strategies are limited. Prokinetic agents have been reported to be used in 79% of critically ill children with EN intolerance (50). The most common agents used are erythromycin, metoclopramide and domperidone (51). These agents act on one or multiple of the pathways responsible for GI dysmotility. Specifically, erythromycin is a motilin agonist, and metoclopramide and domperidone are dopamine antagonists. A meta-analysis of randomized-controlled trials including critically ill adults concluded that prokinetic agents reduced EN intolerance and the risk for high volume GRVs (52). There are insufficient pediatric ICU data on the efficacy of these medications, despite their wide use. In addition, the efficacy of these agents is short-lived as they are prone to tachyphylaxis and they carry the risk of moderate to severe side effects including prolonged QTc and tardive dyskinesia for metoclopramide, and antibiotic resistance for erythromycin. Novel prokinetic agents have been developed based on research advances on the role of GI hormones on motility. These have included ghrelin agonists, motilin agonists and serotonin agonists with reduced side effect profiles. Early clinical trials on such alternative drugs have been promising with some showing similar efficacy in improving EN tolerance and delivery compared to current agents (53-57).

An alternative strategy to administration of prokinetic agents is post-pyloric feeding to bypass EN intolerance due to delayed gastric emptying. Post-pyloric feeding has been reported in 36% of pediatric critical care patients (50). A single-center experience has shown that post-pyloric tube placement can be feasible at the bedside and safe (58). However, some argue that post-pyloric feeding, and continuous over bolus feeding, contribute to GI dysmotility in the ICU. Post-pyloric and continuous feeds both deviate from normal GI physiology and therefore may alter the complex neuro-hormone signaling that promotes normal GI motility. Compared to healthy subjects, critically ill adults on post-pyloric nutrition had slowed gastric emptying and greater antral-duodenal discoordination (17). In a cross-over study of healthy adults, continuous as compared to bolus EN was associated with lower peak of serum levels of PYY and a lesser decrease in ghrelin levels from the fasting state (59). Gastric emptying, based on gastric volume measured by magnetic resonance imaging (MRI), had a significant greater change over time in the bolus than the continuously fed cohort (59).

Conclusions

GI dysfunction is prevalent in critical illness and is secondary to an alteration in the complex coordination of the nervous and endocrine systems in the setting of inflammation, medications and non-physiologic alternatives to EN. Research advancements on the interplay between these systems will continue to promote the development of innovative approaches to manage GI dysfunction and
prevent associated adverse outcomes.

**Acknowledgments**

**Funding:** None.

**Footnote**

**Provenance and Peer Review:** This article was commissioned by the Guest Editors (Lyvonne Tume, Frederic Valla and Sascha Verbruggen) for the series “Nutrition in the Critically Ill Child” published in *Pediatric Medicine*. The article was sent for external peer review organized by the Guest Editors and the editorial office.

**Conflicts of Interest:** The authors have completed the ICMJE uniform disclosure form (available at [http://dx.doi.org/10.21037/pm-20-74](http://dx.doi.org/10.21037/pm-20-74)). The series “Nutrition in the Critically Ill Child” was commissioned by the editorial office without any funding or sponsorship. Dr. Fasano reports the following relationships or activities: Alba Therapeutics - Alternative treatments to gluten free diet (GFD) for celiac patients | Stock holder; Mead Johnson Nutrition - Role of nutrition on inflammation | Speaking Agreement; Viome - Role of microbiome in CID | Scientific Advisory Board. The authors have no other conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Open Access Statement:** This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: [https://creativecommons.org/licenses/by-nc-nd/4.0/](https://creativecommons.org/licenses/by-nc-nd/4.0/).

**References**

1. Martinez EE, Zurakowski D, Pereira L, et al. Interleukin-10 and Zonulin Are Associated With Postoperative Delayed Gastric Emptying in Critically Ill Surgical Pediatric Patients: A Prospective Pilot Study.


41. Chapman MJ, Besanko LK, Burgstad CM, et al. Gastric emptying of a liquid nutrient meal in the critically ill:
relationship between scintigraphic and carbon breath test measurement. Gut 2011;60:1336-43.