Gastrointestinal dysmotility in critically ill patients

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Abstract	Gastrointestinal (GI) motility disorders are commonly present in critical illness. Up to 60% of critically ill patients have been reported to experience GI dysmotility of some form necessitating therapeutic intervention. It has been attributed to various factors, related to both the underlying disease and the therapeutic interventions undertaken. The assessment of motility disturbances can be challenging in critically ill patients, as the available tests used to detect abnormal motility have major limitations in the setting of an Intensive Care Unit. Critically ill patients with GI dysmotility require a multifaceted treatment approach that addresses multiple causes and utilizes multiple pharmacological pathways. In this review, we discuss the pathophysiology, assessment and management of GI dysmotility in critically ill patients.

Keywords Gastrointestinal motility, gastrointestinal dysmotility, critically ill

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Introduction

Gastrointestinal (GI) motility disturbances are common in critical illness. Up to 60% of critically ill patients have been reported to experience GI dysmotility of some form necessitating therapeutic intervention. GI dysmotility has significant clinical consequences, being associated with feeding intolerance and malnutrition, gastroesophageal reflux (GER), bacterial overgrowth, and translocation. Recently, remarkable progress has been made in understanding the pathophysiology of GI motility in critical illness. Predominant motility abnormalities seen in Intensive Care Unit (ICU) patients include esophagus dysmotility, antral hypomotility, delayed gastric emptying, and reduced migrating motor complexes (Fig. 1).

The diagnosis of GI motility disturbances can be challenging in critically ill patients, as the available tests used to detect abnormal motility have significant limitations in the ICU setting. Recognition of the type and site of an intestinal motility disorder is essential to guide the therapy and improve the outcome (Table 1). Reintam *et al* studied the prognostic

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value of the GI failure (GIF) score, a combination of intra-abdominal pressure and feeding intolerance. They showed that the GIF score might serve as an independent risk factor for ICU mortality. GIF score may also have a predictive value in addition to the sequential organ failure assessment score in outcome prediction [1]. Nevertheless, at present, there is a lack of evidence regarding clinical validation of the GIF score. Clinical symptoms such as nausea, vomiting, pain, flatus, and distention may be underestimated in the vast majority of ICU patients. Amongst the clinical signs, bowel sound auscultation has been proposed as a means of monitoring bowel motility in critically ill patients, though its sensitivity and specificity in identifying ileus are relatively low [2]. Over the last few years, novel methods of electronic monitoring have been tested, aiming to eliminate the background noise and standardize the evaluation of bowel sounds, though at present they are used mainly for research proposals [3].

Concerning treatment, new general and therapeutic measures have been introduced during the last decade. Prokinetic pharmacotherapies are currently the mainstay for the management of disordered upper GI motility.

The purpose of the current review is to discuss the pathophysiology, clinical manifestations, assessment, and treatment options of GI motility disturbances in critically ill patients.

Esophageal motility disorders

The main functions of the esophagus are to transport food and fluids from the pharynx to the stomach, to prevent the passive diffusion of substances from the food into the blood, and to prevent the reflux of gastric contents into the
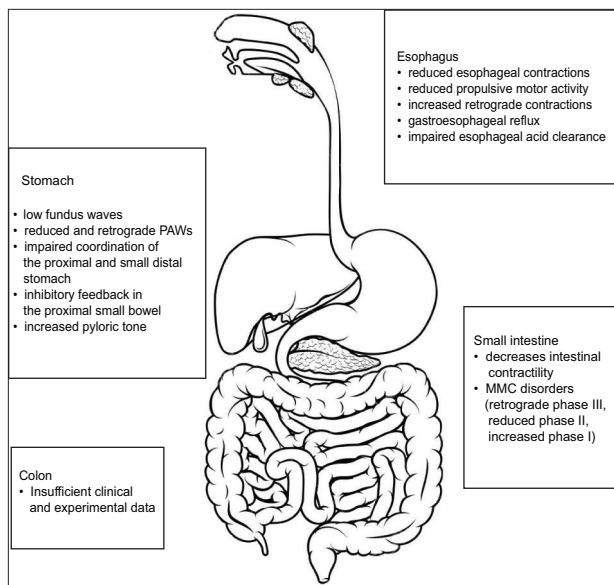
Figure 1 Causes of motility disorders in the gastrointestinal tract
PAWs, propagated antral waves; MMC, migrating motor complex

esophagus. Food transportation from the pharynx to the stomach is attained by coordinated peristaltic contractions initiated in the upper esophagus, which temporally follows a descending wave of inhibition. The tone of the lower esophageal sphincter is critical to esophageal function. Maintenance of adequate sphincter tone is crucial for preventing the reflux of gastric contents, under positive pressures relative to the esophagus due to their location in the peritoneal cavity. The esophagus musculature consists of skeletal muscles in the upper third, smooth muscles in the lower third and a mixture of skeletal and smooth muscles in the middle part. The propulsive activity of the upper esophagus is controlled by the nucleus ambiguus of the vagus nerve, whereas the dorsal motor nucleus of the vagus nerve and the myenteric plexus control smooth muscle peristalsis [4].

Quantitative and qualitative esophageal motility disorders are commonly seen in critically ill patients, mainly in the form of reduced esophageal contractions, reduced propulsive motor activity and increased retrograde contractions, attributed to various factors related to both the underlying disease and numerous pharmaceutic interventions. Kolbel *et al*, in a pilot study of 15 mechanically ventilated patients, reported that, regardless of the underlying disease, the administration of sedatives and opioids is associated with a significant reduction in esophageal propulsive motility, thus implicating opioids and sedatives in the pathophysiology of esophageal motility disturbances in critical illness [5].

In critically ill patients, esophagus motility disorders are associated with significant clinical consequences related to GER and impaired esophageal acid clearance. The incidence of GER is substantially higher in the majority of patients during mechanical ventilation. Numerous potential mechanisms have been implicated in the presence of GER during mechanical ventilation, including the dynamic deterioration of salivary

clearance, the pharmacological inhibition of esophageal motility—mainly with sedatives and paralyzing agents—the presence of high gastric volume and a supine body position. Nasogastric intubation, a common intervention in critically ill patients, has been proposed as a causative factor of GER [6], and a positive correlation has been reported between the duration of nasogastric intubation and the degree of erosive esophagitis. Furthermore, Nind *et al* have shown that reflux episodes in mechanically ventilated patients occur predominantly as a result of low or absent lower esophageal sphincter pressure (LESP), often with a superimposed cough or strain [7]. Factors that are associated with low LESP, such as sepsis, hypoventilation or hemorrhagic shock, may also contribute to the pathogenesis of GER in mechanically ventilated patients [8,9]. GER may significantly affect the mobility of critically ill patients, leading to gastric content aspiration and erosive esophagitis. Approximately 50-75% of mechanically ventilated patients experience at least one episode of pulmonary aspiration due to GER during mechanical ventilation [10].

Numerous diagnostic tests have been proposed for the assessment of esophagus dysmotility in critically ill patients, though with limited feasibility in the ICU setting [11]. Multichannel intraluminal impedance is a catheter-based method of detecting intraluminal bolus movement within the esophagus, using differences in resistance to alternating electrical current at various sites in the esophagus. In combination with liquid esophageal manometry, it can provide functional details about bolus transit in patients with esophageal motility abnormalities. It measures both viscous and liquid impedance [12], and it has been reported that the viscous test solution detects more esophageal function abnormalities than liquid testing alone [13]. High-resolution manometry has a higher number of pressure sensors and can measure the pressure pattern throughout the entire esophagus [14]. High-frequency endoluminal ultrasound has also been proposed as a means of evaluating motor abnormalities. In ambulatory patients, motility disorders, such as achalasia and esophageal spasm, have been investigated with this method, since it provides clear images of the components of the high-pressure zone of the distal and proximal esophagus, though its usage in the ICU setting is limited to research purposes only.

Stomach

The primary gastric functions are mixing and propelling food particles at a rate that facilitates the absorption of nutrients by enhancing the time they are in contact with the mucosa. Two distinct motor functional zones are recognized in the stomach: the proximal zone, which includes the fundus and the proximal third of the corpus of the stomach acting as a reservoir, and the distal zone, comprising the antrum and pylorus, which together with the proximal duodenum delivers chyme at a metered rate into the absorptive mucosa of the small intestine. The gastric reservoir function is mainly vagally and intrinsically mediated, implicating the importance of the intact function of the vagus for gastric motility. The

distal stomach mixes the food with the antral contractions and regulates the outflow to the duodenum [15]. The gastric peristalsis and mixing are induced by slow waves and action potentials produced by the interstitial cells of Cajal. They are also influenced by hormonal and extrinsic neural signals and reflexes (e.g., enterogastric, gastrocolic) [1]. Gastric reservoir function and peristalsis occur during and shortly after meals, whereas during fasting the main motility pattern that is observed is the migrating motor complex.

Gastric motility can be markedly abnormal in critically ill patients, resulting in slow and delayed gastric emptying, food intolerance, and inadequate nutrition. Delayed gastric emptying is the most common gastric dysmotility pattern, in critically ill patients and has been associated with increasing severity of illness. The main pathophysiological mechanisms underlying the delayed gastric emptying in these patients are primary motor dysfunction, impaired coordination of the proximal and distal stomach, inhibitory feedback in the proximal small bowel, and a combination of the above. The impaired proximal gastric function is characterized by delayed and excessive relaxation and abolition of a dose-dependent increase in proximal gastric volume. Furthermore, fundus waves are significantly low, both at baseline and during duodenal nutrient infusion. Distal stomach dysmotility mainly involves an impaired antro-pyloro-duodenal response. A prospective case-controlled study has demonstrated a quantitative reduction in propagated antral waves (PAWs) with markedly abnormal characteristics. PAWs in critically ill patients were spread over a shorter distance, were more likely to be retrograde, rarely involved the duodenum, and in most instances they appeared to be associated with a closed pylorus [16,17].

Intrinsic myogenic activity, neural signals from the gastric myenteric plexus, parasympathetic and sympathetic nervous systems, and several hormones regulate smooth muscle activity in the stomach [18]. Common metabolic disorders associated with critical illness may induce gastric dysmotility. Hyperglycemia (glucose >140 mg/dL) has been associated with a significant reduction in gastric duodenum and jejunum motility. Hyperglycemia-induced gastric dysmotility is characterized by a reduction of phase II migrating motor complex waves [19]. Hypoxia and hypercapnia induce a significant decrease in gastric tone and motility, effects that are probably mediated by both arterial chemoreceptors and direct metabolic effects of hypoxia in muscle cells and enteric neurons.

Delayed gastric emptying has also been attributed to factors related both to the underlying disease that led to critical illness and to specific therapeutic interventions. Delayed gastric emptying is more frequently present in the elderly and in patients with brain and spinal cord injury. Up to 50% of mechanically ventilated patients and 80% of patients with intracranial hypertension will present delayed gastric emptying [20-22]. An additional factor for GI dysmotility is the administration of inotropes (dopamine, adrenergic agonist), sedatives and opiates. Propofol has been reported to be an independent predictor of gastric feeding intolerance, whereas there are conflicting results for the use of opioids [23,24]. Several studies suggest that hormones secreted by the GI tract may be implicated in the regulation of GI motility, metabolism, mucosal growth

and immune function [25]. Ghrelin, an orexigenic hormone, has been shown to accelerate gastric emptying when given exogenously. Critically ill patients have been reported to have a more than 50% reduction in ghrelin's plasma levels, suggesting that ghrelin probably contributes to delayed gastric emptying, weight loss, and decreased appetite in critically ill patients [26]. Increased levels of cholecystokinin and peptide YY, which both typically slow gastric emptying, have also been reported in the acute phase of critical illness [27]. Recent evidence suggests that gastric motility is mainly regulated by the hormone motilin. In healthy subjects, motilin accelerates gastric emptying by inducing anterograde contractions in the stomach. Motilin plasma levels increase cyclically every 90-120 min during the interdigestive fasting period, and this cyclical release of motilin disappears after ingestion of a meal. These cyclical peaks of plasma motilin are synchronized with strong peristaltic contractions initiated from the stomach and migrating to the duodenum and small intestine (phase III activity). Although fasting motilin plasma concentrations have been shown to be similar in critically ill patients and healthy subjects, plasma motilin levels are significantly higher in the patients during nutrient infusion. Furthermore, in critically ill patients there is an inverse relationship between the peak increase in plasma motilin concentrations and the peak change in proximal gastric volume induced by duodenal nutrient stimulation—a finding that may explain the persistence in interdigestive GI contractile activity and the impaired proximal gastric relaxation during enteral feeding in these patients [28].

Gastric dysmotility in critical illness may be assessed using both direct and indirect methods; in general, the preference of the method depends on the requirements of the physician/investigator. Intermittent measurement of gastric residual volumes (GRVs) is the most common practice for evaluation of gastric motility and feeding tolerance in ICU patients receiving enteral feeding. However, despite its widespread use, the utility and the significance of GRVs remain controversial, as substantial evidence is lacking regarding the correlation between GRV and gastric emptying. Moreover, this practice is deficient in standardization and is exceedingly affected by patient positioning, technique, tube location and diameter, the use of prokinetic drugs, and the composition of the liquid nutrient. In an observational study, 25% of ICU patients with GRV >150 mL—considered a cutoff for the interruption of enteral feeding in many ICUs—had normal gastric emptying [29]. Furthermore, regular GRV monitoring seems to be the main reason for discontinuation of the enteral nutrition [30]. A randomized study (NUTRIA), showed that the absence of gastric volume monitoring was not inferior to routine residual gastric volume monitoring regarding ICU-related infections, diarrhea, duration of the mechanical ventilation, length of ICU stay and mortality rates [31,32]. Additionally, several randomized controlled trials showed that a lower GRV cutoff was no safer than a higher cutoff. Consequently, the 2006 SCCM/ASPEN guidelines raised the GRV target to <500 mL. More recently, two randomized controlled trials concluded that it was safe to stop checking GRVs entirely [33,34]. In the light of this evidence, SCCM/ASPEN currently recommend the elimination of GRVs

Table 1 Diagnostic methods of gastrointestinal dysmotility in critically ill patients

Gastrointestinal part	Method	Applications	Clinical syndrome
Esophagus	Liquid-esophageal manometry	Intraluminal pressures	Esophageal dysmotility
	High resolution manometry	Intraluminal pressures	Esophageal dysmotility
	Multichannel intraluminal impedance	Esophageal transit	Esophageal dysmotility
	High frequency endoluminal ultrasound	Clear images of sphincters	Esophageal dysmotility (achalasia and esophageal spasm)
Stomach	Gastric residual volumes	Gastric emptying	Delayed gastric emptying
	Scintigraphy	Gastric emptying	Delayed gastric emptying
	Paracetamol absorption test	Gastric emptying	Delayed gastric emptying
	Radioisotope breath tests ($^{13}CO_2$)	Gastric emptying	Delayed gastric emptying
	Carbohydrate absorption (3-OMG)	Gastric emptying	Delayed gastric emptying
	Ultrasonography	Gastric volumes and contractions	Delayed gastric emptying
	Magnetic resonance imaging	Gastric emptying	Delayed gastric emptying
	Gastric motility recording electrogastrography	Gastric wall electrical activity	Delayed gastric emptying
	Wireless motility capsule	Gastric emptying	Delayed gastric emptying
Small intestine	Lactulose breath hydrogen test	Small intestinal transit time	Paralytic ileus
	Manometry	Intraluminal pressures	Paralytic ileus
	Wireless motility capsule	Small intestinal transit time	Paralytic ileus
Colon	^{13}C- (and ^{14}C)-substrate breath tests	Orocecal transit	Decreased colon contractions
	Scintigraphy	Colonic transit	Decreased colon contractions
	Plain abdomen radiography	Colon dilation	Ogilvie's syndrome

completely from routine care. GRVs should probably be monitored only in high-risk patients (e.g., abdominal surgery patients) [35]. In the research setting, particularly when studying smaller cohorts, GRVs are too imprecise, so usually direct or indirect methods are used (Table 1). Indirect tests, such as carbohydrate absorption (3-OMG) or radio-isotope breath tests ($^{13}CO_2$), are minimally invasive and have modest intra-subject variability. They are useful when studying the effect of an intervention thought to have a potent effect on gastric emptying in larger cohorts, particularly when researchers use a crossover design. The breath test is based on the detection of ^{13}C-octanoate in the exhaled air following the consumption of a ^{13}C-octanoic-acid–labeled test meal. The ^{13}C-labeled substrate is absorbed in the duodenum, metabolized in the liver, and excreted as breath $^{13}CO_2$. This test correlates gastric emptying with the $^{13}CO_2$ enrichment of breath that can be measured at regular intervals over a 3-4-h period [36]. Ghoos *et al* have reported an excellent correlation between the gastric emptying parameters determined by the breath test and scintigraphy in healthy subjects [37]. However, in ICU patients with multi-organ dysfunction, the accuracy of the method is significantly low.

The paracetamol absorption test (PAT) is an alternative indirect method of assessing gastric emptying through peak plasma concentrations of paracetamol and can be easily performed in the ICU setting. Paracetamol is absorbed quickly and completely by the small intestine; hence, rapid gastric emptying is correlated with early peak concentrations of paracetamol [38]. A significant correlation between PAT and scintigraphy has been reported regarding the evaluation of gastric emptying. PAT is contraindicated in patients with hypersensitivity, hepatic or renal dysfunction, because of the increased risk of toxicity.

Ultrasonography is a noninvasive method that has recently been introduced for the evaluation of gastric emptying, antral wall motion, transpyloric flow and gastric accommodation [39]. Studies have shown high correlation in t1/2 liquid emptying time between ultrasonography and scintigraphy [40,41]. However, the accuracy of this method depends on the experience and skills of the operator and so far it lacks validation in critically ill patients [42].

For studying the effect of a less potent gastrokinetic drug, for a parallel design study, or when more precise measurement is required, direct tests, such as scintigraphy, are more suitable and remain the gold standard. Gastric scintigraphy evaluates gastric emptying by measuring the gastric transit of a radio-labeled meal with a gamma camera. Nevertheless, the feasibility of scintigraphy in the assessment of critically ill patients is limited, as it is time-consuming (average duration of 2-4 h) and necessitates the transportation of patient outside the ICU [43].

Magnetic resonance imaging is a newer method that has been used to measure gastric emptying [44] and accommodation [45]. Gastric emptying is measured after administration of a liquid meal containing gadolinium tetra-azacyclododecane tetra-acetic acid. It is a noninvasive test but has significant limitations, such as the transfer of the ICU patients, the cost, and the fact that it can only be performed with the patient in a supine position, which is a drawback for gastric emptying, especially of liquids [46]. Gastric motility recording electrogastrography has been used to evaluate the basic electrical activity of the stomach, but it is impractical in the ICU setting because of the prolonged recordings [47]. Manometry has been employed in ICU patients to measure gastric antrum, proximal and distal duodenum pressures [48], whereas barostat methods have not been used in trials.

Small intestine

Normally the primary motility functions in the small intestine are peristalsis, segmentation, and the migrating motor complexes during fasting periods. Motility function in the small intestine is controlled by myogenic characteristics, extrinsic and intrinsic nerve circuits, interstitial cells, hormones, and reflexes mediating the central nervous and immune system. The enteric nervous system, and mainly the myenteric plexus, seems to be the dominant regulator of the small intestine. The pathogenesis of small intestine motility disturbances in critical illness remains mostly uncertain. Sepsis overall slows upper GI transit and decreases intestinal contractility by causing dysfunction of small bowel muscularis. Excessive fluid administration has been demonstrated to cause intestinal edema, which may contribute to small bowel dysmotility [49]. Small intestine dysmotility may have a significant impact on critically ill patients' outcomes, since previous studies have shown that it influences nutrient and drug absorption rates [50-52]. Moreover, intestinal stasis has been linked to bacterial overgrowth, potentially leading to bacterial translocation, systemic inflammatory response syndrome, sepsis, and multiple organ dysfunction syndromes. The most common clinical manifestation of small intestine dysmotility in critically ill patients is the presence of paralytic ileus.

Several diagnostic methods have been proposed for the assessment of small intestine dysmotility. The lactulose breath hydrogen test measures small intestinal transit indirectly through orocecal transit. This test is based on the fact that lactulose, administered orally, cannot be absorbed by the GI and is metabolized by colonic bacteria. The hydrogen produced is absorbed from the circulation and excreted through the lungs, indirectly indicating the orocecal transit [53]. A series of studies have shown a good correlation between lactulose breath hydrogen testing and scintigraphy when performed simultaneously with lactulose in the test meal [54-56]. However, Miller *et al* showed that lactulose directly accelerates small intestinal transit [57]. Small bowel manometry has also been used successfully to measure small bowel pressure waves in ICU patients.

An alternative novel technique, the wireless capsule technology, may be useful for evaluating intestinal motility in critical care patients. Measurement of GI motility with this technique is accomplished with an ingested radiocapsule that measures pressure, pH, and temperature and transmits these signals to a receiver outside the body. The method was first introduced for the evaluation of motility and transit time in ambulatory patients suffering from functional motility disorders, such as irritable bowel syndrome, functional dyspepsia, and chronic idiopathic constipation. The efficacy of the wireless motility capsule in critically ill patients was recently evaluated in two prospective studies [58,59]. Rauch *et al* reported a statistically significant delay in gastric emptying, intestinal transit and whole-gut transit time in a group of critically ill trauma patients. The main advantage of the wireless motility capsule in critically ill patients is that it provides an evaluation of the motility of the whole gut, eliminating the use of multiple methods. However, the presence of only one pressure sensor limits its efficacy in the evaluation of propagation and contractile forms of GI dysmotility [60].

Colon dysmotility in critical illness

There is limited evidence with regard to colon dysmotility in critical illness. During sepsis, the colon has its distinct characteristics in comparison with the small bowel, as different types of leukocyte infiltrate, and varying levels of inducible nitric oxide synthase and cyclooxygenase-2 are expressed. Although the amplitude and frequency of both colon and small intestine contraction are suppressed during endotoxin injection (or cecal ligation and puncture), there may be an anatomical explanation for these pathophysiological differences [44].

Although constipation represents the most common clinical manifestation of colon dysmotility in critically ill patients, colon dysmotility in these patients may rarely present in the form of acute pseudo-obstruction. Acute pseudo-obstruction (ACPO), also referred to as Ogilvie's syndrome, is defined as a clinical syndrome characterized by impairment of intestinal propulsion, which may bear a resemblance to intestinal obstruction, in the absence of a mechanical cause. Acute intestinal pseudo-obstruction may also involve the small intestine and most frequently occurs in patients with stroke, myocardial infarction, peritonitis, sepsis, and postoperatively in orthopedic surgery, cesarean section, cardiovascular or lung surgery [61-63]. The pathophysiology underlying ACPO remains rather unclear, with the prevailing hypothesis being an imbalance in colonic autonomic innervation in the setting of other predisposing factors. The clinical hallmark of ACPO is the presence of dilation of the colon on a plain radiograph. The dilation favorably involves the cecum and the ascending and transverse colon, although the left colon, including the rectum, may also be affected. The prognosis of acute intestinal pseudo-obstruction varies with the underlying clinical condition.

Management of GI dysmotility

In the context of the general management of the ICU patient, several measures have been proposed for the treatment and prevention of gut dysmotility. These include patient posture, adjustment of electrolyte imbalances, control of blood glucose, appropriate management of catecholamines and drugs used for analgosedation, early enteral feeding, and use of prokinetic agents (Table 2) [64].

Glucose control

Hyperglycemia has been shown to have a negative effect on antral motor activity. Reduced fundic tone, inhibition of antral pressure waves and stimulation of pyloric pressure waves have been observed with glucose levels above 15 mmol/L. Additionally, several studies showed that a high blood glucose concentration is a positive predictor of delayed gastric emptying. Although evidence is currently lacking regarding the effect of hyperglycemia on GI motility in critically ill patients, glucose control should be considered as a measure to prevent GI dysmotility [65,66].

Table 2 Prokinetic drugs used in management of gastrointestinal dysmotility

Prokinetic agent	Dosage
Metoclopramide	10-20 mg IV, 4-6 hourly (5 mg in case of renal failure)
Erythromycin	200 mg or 70 mg IV, 12-hourly
Naloxone	8 mg, 6-hourly
Tegaserod	6 mg, 12-hourly
Neostigmine	0.4-0.8 mg/h infusion
Insufficient data	
Alvimopan	6 mg, 12-hourly
Mitemcinal	10-30 mg, 12-hourly
Domperidone	10-20 mg, 6-hourly
Ghrelin	10 pmol/kg/min infusion
Dexloxiglumide	200 mg, 8-hourly

Enteral feeding tubes

Enteral nutrition is a conventional method for nutritional supplementation in critically ill patients with intestinal failure. Percutaneous endoscopic gastrostomy (PEG) is indicated for patients with an intact functional GI tract requiring long-term nutritional support (>30 days) [67]. Feeding tubes can be inserted directly into the stomach, endoscopically or under radiological guidance. PEG tube insertion has been shown to be the most cost-efficient and safe method compared to surgical gastrostomy [71]. It has been reported that 13-40% of patients with PEG placement experience minor complications, such as maceration due to leakage of gastric contents around the tube and peristomal pain [68-70]. Serious complications have been reported in only 0.4-4.4%, including peristomal leakage-associated peritonitis, necrotizing fasciitis of the anterior abdominal wall, gastric bleeding, internal organ injury, tumor seeding at the PEG site, and death. Post-pyloric tubes are appropriate for patients with severe GER and gastroparesis [88]. Long-term jejunal feeding can be achieved endoscopically with jejunal tubes through the PEG and direct percutaneous endoscopic jejunostomy. Retrograde dislodgement of the jejunal extension tube, tube obstruction and mechanical failure have been described as the most common device-related complications [72].

Prokinetic agents

The second therapeutic approach involves the administration of prokinetic agents such as metoclopramide, cisapride, and, more recently, erythromycin.

Metoclopramide

Metoclopramide is a drug commonly used for its antiemetic and prokinetic effects. It is a D2 antagonist—in both the central

nervous system and peripheral tissues—a 5-hydroxytryptamine (5HT) 3 antagonist and 5HT4 agonist. The prokinetic effect is pharmacologically caused by the D2 receptor blockade and by the 5HT4 agonism [73]. It improves GI peristalsis, while increasing gastric emptying and patients' tolerance of enteral nutrition [74,75]. It should be noted that prokinetic agents (metoclopramide, domperidone) given either intravenously or intramuscularly have been proven to facilitate the post-pyloric placement of nasojejunal tubes [76]. Although well-designed clinical trials are lacking, current evidence suggests that metoclopramide has a moderate prokinetic effect in critically ill patients. Compared to erythromycin, metoclopramide has a lower prokinetic effect [77]. Concerning the effect of metoclopramide in reducing the incidence of ventilator-associated pneumonia in patients receiving nasogastric enteral feeding, two randomized studies failed to prove any positive effect [78,79]. The primary side-effects of metoclopramide are nausea and extrapyramidal symptoms (dyskinesia, dystonia, convulsions, hypertonia, and tremor). Extrapyramidal manifestations are very rare (0.003%) and are mainly present in patients who require chronic use of metoclopramide.

Erythromycin

Erythromycin is a macrolide antibiotic that increases gastric motility by stimulating enteric nerves and smooth muscle and triggering a phase of the migrating myoelectric complex. Because of that effect, it has been used in diabetics with gastroparesis who were unresponsive to other treatment [80]. The antral motor effects of erythromycin in humans are mediated via different pathways. The induction of a premature activity front is mediated through activation of an intrinsic cholinergic pathway, while the induction of enhanced antral contractile activity may be mediated via a pathway potentially involving activation of a muscular receptor. These effects on gastric motility have been measured in the past by paracetamol absorption (PAT) in critically ill patients [81]. A double-blind, randomized controlled trial concluded that erythromycin is useful in the short term for delayed gastric emptying. Compared to placebo, administration of erythromycin was associated with more successful enteral feeding at both 1 and 12 h. No significant difference between the two groups was found 24 h after infusion, suggesting that administration once or twice daily may be sufficient to provide the prokinetic effect [82]. Similar results were reported in previous studies in critically ill patients and trauma patients [83,84]. Prolonged administration (>3-4 days) of erythromycin is associated with reduced efficacy. Nguyen *et al* found that by 24 h of erythromycin administration successful enteral feeding was achieved in 87% of ICU patients. However, the treatment became significantly less effective on day 3 (47%), while on day seven only 30% of patients were still feeding tolerant [77]. Erythromycin's effect as a prokinetic agent is dose-dependent [85]. Low doses stimulate an antral activity front (phase III), which migrates into the duodenum and is possibly mediated by activation of an intrinsic cholinergic pathway, whereas high doses induce strong contractions of the antrum, which are not propagated and thus transit may

be slower [86]. These contractions are possibly mediated via a pathway that involves activation of a muscular receptor. However, the optimal dosage for accelerating gastric emptying in the critical care setting remains uncertain. The recent cloning of the motilin receptor may help to clarify the correct dose at a molecular level [87]. One concern regarding the use of erythromycin as a prokinetic is the possible development of resistance to it as an antibiotic agent. Nevertheless, the dosage of erythromycin that is usually required to increase gastric emptying has no antibiotic effect and the risk remains theoretical. Erythromycin may promote cardiac arrhythmias through prolongation of the QT interval, including the potentially fatal ventricular arrhythmia *torsades de pointes* [88]. QT prolongation is due to the delayed repolarization that is thought to be the result of the blockage of *human ether-a-go-go-related gene* (*HERG*) potassium channels [89]. Several risk factors are known to increase the risk of *torsades de pointes,* including age, female sex, hypokalemia, history of previous QT prolongation or cardiac arrhythmia, structural heart disease and poor left ventricular function. The risk of arrhythmias is also increased with the concurrent administration of antifungal drugs (ketoconazole, itraconazole, fluconazole, astemizole and terfenadine), antiarrhythmic drugs (disopyramide, procainamide, amiodarone, sotalol, and quinidine), calcium channel blockers (diltiazem and verapamil), haloperidol and pimozide [90]. However, no serious cardiac toxicities have been reported in clinical trials, probably because of the short duration of administration [77,91]. Other non-serious adverse effects include hypotension, abdominal pain, nausea, vomiting, and diarrhea [92,93]. Watery diarrhea is the most common and can occur in up to 25% of enterally fed patients. The use of erythromycin is contraindicated in patients with myasthenia gravis, since it may trigger a myasthenic crisis [94].

Recent studies in critically ill patients support the efficacy of a combination of different prokinetics as first-line therapy for feeding intolerance. The combination of erythromycin and metoclopramide has been shown to achieve the highest efficacy of feeding tolerance with the lowest incidence of tachyphylaxis. In a double-blind, randomized study, the use of combination therapy was significantly more effective than erythromycin alone. Combination therapy was also associated with a lesser degree of drug tachyphylaxis and up to 60% of patients remained responsive at day 7 of treatment [95]. A more recent study demonstrated that combined treatment with metoclopramide 10 mg/6 h and a single low-dose IV erythromycin (10 mg/h) best facilitates gastric emptying in critically ill, mechanically ventilated patients [96]. Other novel gastrokinetic drugs, such as non-antibiotic motilin agonists, ghrelin agonists, or cholecystokinin antagonists (e.g., dexloxiglumide), could be of interest but have yet to be investigated.

Concluding remarks

GI dysmotility and feeding intolerance are common amongst critically ill patients and have been associated with significant complications that may lead to increased morbidity and mortality. Currently, treatment with prokinetics is considered as the first-line therapeutic option, as it may improve gastric emptying and nutrition delivery. Novel methods for GI motility assessment and management are required to reduce the incidence of GI dysmotility-induced complications and improve patients' outcomes.

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