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Pathophysiology and treatment of gastrointestinal motility disorders in the acutely ill

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Abstract:	Gastrointestinal dysmotility causes delayed gastric emptying, enteral feed intolerance, and functional obstruction of the small and large intestine – the latter two which are frequently termed ileus and Ogilvie's syndrome respectively. In addition to meticulous supportive care drug therapy may be appropriate in certain situations. There is however considerable variation between individuals as to what gastric residual volume that identifies gastric dysmotility and would encourage use of a pro-motility drug. While the administration of either metoclopramide or erythromycin is evidence-based, dual drug therapy (erythromycin and metoclopramide) reduces the rate of treatment failure. There is a lack of evidence to guide drug therapy of ileus but neither erythromycin nor metoclopramide appear to have a role. Several drugs, including ghrelin agonists, highly selective 5-hydroxytryptamine receptor agonists and opiate antagonists are being studied in clinical trials. Neostigmine, when infused at a relatively slow rate in patients receiving continuous haemodynamic monitoring may alleviate the need for endoscopic decompression in some patients

ABSTRACT

Gastrointestinal dysmotility causes delayed gastric emptying, enteral feed intolerance, and functional obstruction of the small and large intestine – the latter two which are frequently termed ileus and Ogilvie's syndrome respectively. In addition to meticulous supportive care drug therapy may be appropriate in certain situations. There is however considerable variation between individuals as to what gastric residual volume that identifies gastric dysmotility and would encourage use of a pro-motility drug. While the administration of either metoclopramide or erythromycin is evidence-based, dual drug therapy (erythromycin and metoclopramide) reduces the rate of treatment failure. There is a lack of evidence to guide drug therapy of ileus but neither erythromycin nor metoclopramide appear to have a role. Several drugs, including ghrelin agonists, highly selective 5-hydroxytryptamine receptor agonists and opiate antagonists are being studied in clinical trials. Neostigmine, when infused at a relatively slow rate in patients receiving continuous haemodynamic monitoring may alleviate the need for endoscopic decompression in some patients

INTRODUCTION

Gastrointestinal motility describes the process of smooth muscle contraction and relaxation within the gastrointestinal tract. Gastrointestinal motility regulates movement of luminal contents, with the predominantly antegrade movement occurring because of coordination of peristaltic and non-peristaltic flow. This coordination of gastrointestinal smooth muscle, and the propagation of its contractions, is modulated by neural and humoral mechanisms.

Enteral nutrition is part of standard care provided to critically ill patients (1, 2). Gastrointestinal motility is frequently disordered in these patients (3-5). Not only does dysmotility diminish the provision of enteral nutrition but it is also associated with adverse important patient-centred outcomes and healthcare utilization, such as increased mortality and duration of ICU admission (6). While dysmotility *per se* can result in a life-threatening condition due to intestinal ischemia and perforation (7), these associations are not proven causative relationships, as dysmotility is more prevalent as illness severity increases (8).

Within this review we will summarise the gastrointestinal motility pattern that occurs in health, describe how this differs during critical illness and outline the mechanisms underlying these differences. We will emphasise conditions in the critically ill that relate to disordered gastrointestinal motility - such as delayed gastric emptying, enteral feed intolerance and intestinal functional (sometimes termed pseudo-) obstruction - describe the medications available, summarise the best-available evidence to inform clinical practice and the latest research using newer drugs.

In clinical practice monitoring of dysmotility is challenging to identify and measure, with bedside techniques to quantify dysmotility being imprecise (9). Nonetheless, awareness and understanding of pathophysiological mechanisms is important, so that clinicians can avoid or promptly treat conditions

caused by dysmotility and prevent the life-threatening complications as intestinal ischemia and perforation.

CLINICAL PRESENTATION OF DYSMOTILITY

Differing clinical presentations may occur due to gastrointestinal dysmotility, because of a pathophysiological process in a defined region or a generalised dysmotility throughout the entire gastrointestinal tract (Table 1). While retrograde or excessively rapid movement of luminal contents occurs as part of the spectrum of critical illness associated dysmotility (10, 11), the more frequently observed phenomenon is deceleration of antegrade movement (3), which reflects a decrease in propulsive force (peristaltic flow) and/or increased resistance to flow (4).

There is no agreed taxonomy to describe pathophysiology associated with dysmotility in the critically ill. To highlight this point, in a systematic review of enteral feed intolerance in the critically ill there were 43 different definitions for enteral feed intolerance used in the literature (6). Trying to group these definitions it seems that enteral feed intolerance is diagnosed using at least one of three categories: (1) presence of 'large' gastric residual volumes (GRVs); and/or (2) presence of gastrointestinal symptoms; and/or (3) inadequate delivery of enteral nutrition (6). According to this systematic review the prevalence of enteral feed intolerance and the association between this condition and mortality depended on the definition used but the presence of large GRVs and other gastrointestinal symptoms (vomiting, abdominal distension or diarrhoea) provided the strongest relationship between the presence of enteral feed intolerance and mortality (12). However, it has been recently recommended by a group of experts (The Working Group on Abdominal Problems of the European Society of Intensive Care Medicine) that enteral feed intolerance should be the general term for patients who cannot tolerate enteral nutrition regardless of clinical reason or category (large GRVs, vomiting, gastrointestinal bleeding, diarrhea, etc.) (13).

Ileus is similarly a term lacking an agreed definition in the critically ill. It generally refers to hypomotility and a functional obstruction in the absence of a discreet luminal narrowing or stricture, usually including the small intestine but any segment of the gastrointestinal tract can be implicated (14). Given the lack of an agreed definition it is not surprising that ileus can be challenging to identify in clinical practice, with a range of possible signs, including abdominal distension, increased GRV and absent bowel sounds (7). Since many of these signs may be attenuated in mechanically ventilated patients receiving sedation and/or analgesia the European Society of Intensive Care Medicine Working Group recently suggested to use the term 'paralysis of lower gastrointestinal tract' defined as the absence of stool for three or more consecutive days (13), but this definition is based solely on expert opinion and does not differentiate between dysmotility in small bowel and large bowel. Clinical relevance of such 'paralysis' depends on presence of bowel dilatation and distension (15).

When there is no physical obstruction, but functional obstruction due to bowel paralysis in the large intestine, distension may be even more prominent (16). Acute functional obstruction of the large intestine is described using a variety of terms, including acute colonic pseudo-obstruction and the eponymous Olgilvie's Syndrome (17). This condition, which is diagnosed radiologically, is important because it is more frequently associated with intestinal ischemia and perforation (7). While there are limited data regarding the prevalence and mortality rate of acute functional obstruction of the large intestine for patients already admitted to ICU, a study using a large US hospital-wide database of > 100,000 cases provided a mortality point estimate of 8% (18). It is important, however, to note that this is all-cause mortality and is not attributable risk specifically due to functional obstruction of the large intestine.

We will consider each clinical scenario on an anatomical basis, but it is important to recognise that these clinic-physiological states may often overlap in an individual patient.

STOMACH

Gastric motility in health

Gastric motor function has evolved to perform three major physiological functions:

(1) A fasting motility pattern to intermittently expel ingested non-nutrient material which also avoids stagnation of content and subsequent bacterial proliferation;

(2) Preparation of solid digestible nutrient for the small intestine by reducing the size of the food particles and mixing with gastric fluid to facilitate digestion. This subsequent grinded matter is termed chyme; and

(3) Receiving and storage of nutrient (chyme), and then regulating the delivery of this matter, ideally to match the absorptive capacity of the small intestine, via the rate of gastric emptying.

Myogenic control of gut peristalsis is independent of the central nervous system (19). The frequency of myogenic initiation of peristalsis varies according to the region of the gut, and has been variously named the basal electrical rhythm or gastric pacemaker. The interstitial cells of Cajal initiate this electrical activity (20). Whether or not the electrical activity initiates mechanical contraction is determined by the influence of exogenous and endogenous factors.

The fasting motility pattern that commences in the stomach and progresses throughout the small intestine has been arbitrarily divided into three phases, which have been termed the Migrating Motor Complex (21). The 'housekeeping' role or propulsion of luminal contents occurs mainly during phase III of the Migrating Motor Complex.

To prepare solid digestible nutrient for the small intestine, ingesta must be mixed with gastric fluid and processed into particles of a sufficiently small size to pass through the pylorus. This occurs as antral contractions grind solid food into particles because the contractions occur against a closed pylorus or the particles are too large to pass through an open pylorus (21).

Finally, gastric emptying regulates movement of chyme into the duodenum. Nutrients interact with the small intestinal mucosa, which induce the release of a number of neurotransmitters and hormones that modulate gastric emptying through feed-back inhibition (21, 22). Accordingly, gastric motility and emptying varies considerably depending on whether the fasting or fed state is being evaluated (23). The rate of gastric emptying of a meal is modified by its composition and macronutrient content, with relatively little effect of meal volume (21, 24). Liquid emptying by the stomach follows an exponential pattern whereas solid emptying, after an initial lag phase, follows a linear phase (25).

Gastric emptying is regulated by multiple neural and hormonal pathways (21). The neural regulation of gastric emptying is mediated by extrinsic inputs from the central nervous system via the vagus nerve, and intrinsic modulation via enteric nerves. The extrinsic or parasympathetic input from the vagus nerve is particularly important in the upper gastrointestinal tract. The vagus nerve communicates information using complex circuitry involving both afferent and efferent components, by release of excitatory neurotransmitters (e.g. acetylcholine) and inhibitor neurotransmitters (e.g. nitric oxide) (23). The intrinsic pathway mediates responses via ascending and descending enteric nerves and also by release of both excitatory and inhibitory neurotransmitters.

Compared to these neurally-mediated effects, there may be more persistent endocrine-mediated mechanisms. Hormonal pathways are also important and include hormones that slow gastric emptying - such as amylin, cholecystokinin, glucagon-like peptide-1 and peptide YY - and hormones that accelerate emptying rate - such as ghrelin and motilin (26-29). Such endocrine targets may represent a focus of future therapy, with the most likely candidates being ghrelin and motilin (which are discussed in detail under the sub-heading ‘drug therapies’).

Targeting amylin is unlikely to be a high priority. In an observational study of 26 critically ill patients and 23 healthy participants as ‘controls’ fasting amylin concentrations were comparable between

critical illness and health and the rate of gastric emptying was not related to fasting amylin concentrations (27), suggesting other targets are more appealing.

In the critically ill pharmacological administration of glucagon-like peptide-1 has slows gastric emptying and lowers blood glucose (30-32). In health, administration of an antagonist to glucagon-like peptide-1 does accelerate gastric emptying and increases blood glucose (33, 34). Given the likely increase in blood glucose that will occur with administration of glucagon-like peptide-1 antagonists, such agents are unlikely to be a useful therapy.

Some but not all studies report that plasma cholecystokinin concentrations are increased in the critically ill (35, 36), which raises the possibility that specific antagonists, such as loxiglumide, may be effective. However, in the critically ill small intestinal absorption of nutrient is substantially impaired (11, 28, 37) and antagonism of cholecystokinin could diminish pancreatic exocrine function. Any studies of cholecystokinin antagonists like loxiglumide should therefore also measure the impact on nutrient absorption.

Gastric motility during critical illness

Gastric emptying is delayed in a proportion of critically ill patients and the magnitude of delay is substantially more severe than in many other conditions, such as diabetic gastroparesis, where gastric emptying of nutrient liquid may be abnormally slow, but usually occurs nevertheless (38). Precise quantification of gastric emptying is limited to the research setting: a summary of these techniques can be found elsewhere (24).

In the clinical setting the rate of emptying is most frequently estimated using intermittent aspirates of the gastric feeding tube the so-called GRV (24, 39). Using any continuous variable to separate patients into binary categories of either having, or not having, a disease has been criticized in other areas of medicine (40). Consistent with the concept, aspirating the GRV and categorizing patients as having normal or delayed gastric emptying according to a single volume is somewhat simplistic – e.g. two patients with aspirated GRVs of 249 and 251 ml will have similar, rather than different, rates of gastric emptying. Moreover, GRVs may not be a specific marker for delayed gastric emptying, as many critically ill patients with slow gastric emptying will have GRVs < 250 ml (41). Once GRVs are > 250 ml the test appears a relatively sensitive marker of delayed gastric emptying, having been measured against the gold standard of scintigraphy (42). Accordingly, the greater the GRV the more certain clinicians can be that a particular patient has disordered motility. While recent guidelines have included recommendations to use a threshold of 500 ml to identify those patients who may require discontinuation or a reduction in feed rate (1, 2), this value should not be interpreted has defining those with gastric dysmotility. Using large cross-sectional datasets it has been reported that up to one third of all enterally-fed mechanically ventilated critically ill patients experience a moderate form of delayed gastric emptying presenting as enteral feed intolerance (43). Many more patients may have subclinical gastrointestinal dysmotility, with estimates of the proportion of patients with disordered motility detected using more sophisticated research tools being as high as 80% (4, 44-47). The variability in the literature of the proportion of patients having gastrointestinal dysmotility is likely to reflect the precision of the research methodology to detect dysmotility and that many of the studies are single centre studies with the risk of selection bias.

Mechanisms underlying critical illness associated gastric dysmotility

To evaluate the mechanisms underlying disordered motility, researchers can undertake studies in patients or utilise animal models of critical illness, both of which require sophisticated methodologies (48). To precisely determine the effect of an endogenous neurotransmitter or hormone the researcher

must then administer the specific antagonist to the neurotransmitter or hormone (49). For example, the substantial slowing of gastric emptying that occurs with endotoxin administration to rats is almost abolished with co-administration of capsaicin, which is used in neuroscience laboratories to blunt vagal afferent responses (50, 51). Assuming that the response in an animal model reflects the response in a critically ill patient, these animal data are consistent with the concept that the vagal afferent pathways are an important mediator of gastroparesis in the critically ill.

Because of the challenges of conducting studies of acute physiology in the critically ill, researchers may also look for associations between physiological variables, e.g. hyperglycemia, or administered therapies, e.g. opiate drugs, and gastric dysmotility, and then extrapolate evidence from health – e.g. higher blood glucose concentrations, even minor perturbations within normal physiological range (gastric emptying is slower at 8 mmol/l than at 4 mmol/l) (52) and opiate drugs, even modest doses, both impair motility patterns to identify risk factors for gastric dysmotility (Table 2) (19).

One method that has been used to quantify mechanism/s underlying dysmotility in the upper gastrointestinal tract in the critically ill involves multi-lumen water-perfused manometric catheters. The recording of increased pressure will identify luminal occlusive contractions at various locations, with organised and propagated luminal occlusive contractions resulting in peristaltic. Certain motor patterns are known to slow transpyloric flow (e.g. antral atony and/or isolated pyloric pressure waves) (10). This technique allows researchers to study motility patterns whilst nutrient is infused directly into the small intestine and thereby understand feed-back mechanisms (4).

In the critically ill this nutrient stimulated feed-back mechanism is potentiated, so that after small intestinal infusion of liquid nutrient (even at relatively low rates such as 1 kcal/min) the frequency of antral waves is less than in healthy subjects, with marked increases in pyloric tone and in the number of isolated pyloric pressure waves (i.e. strong contractions of the pyloric sphincter) (4, 10). These motility patterns retard further trans-pyloric flow (i.e. slow gastric emptying) (4, 10). It is therefore clear that not only is gastrointestinal dysmotility present during fasting but, perhaps of greater

relevance to clinical care, this is exacerbated during the delivery of nutrition. The content of the liquid nutrient further influences gastric emptying, with formulae high in fat or osmolarity more likely to slow gastric emptying (53, 54). This 'hypersensitivity' to the presence of nutrient in the small intestine is mediated via hormonal (and probably neurotransmitter) responses (22).

Hormones are usually evaluated according to their endocrine effect (i.e. related to the concentration of hormone in plasma). However, it is likely that most/all of the hormones that regulate gastric emptying have an additional paracrine effect/s that are mediated via vagal afferents or enteric nerves (55). Consequently, the magnitude of hormone-mediated effects may be underestimated (49).

SMALL INTESTINE

Small intestinal motility in health

As the predominant site for digestion and absorption of nutrient, small intestinal motility has two major motor functions: mixing and propulsion of ingesta. Similar to the stomach, intestinal motility also depends on presence of nutrient, with the fasting phase – the Migrating Motor Complex, as described above – and a fed or postprandial phase (19). The postprandial phase of intestinal motility facilitates mixing, aids digestion, and prolongs exposure of chyme to absorptive epithelium (28). In the postprandial state the speed at which contents are propelled varies within the small intestine, e.g. transit is more rapid in the duodenum and jejunum and slower in the ileum, to allow for absorption of nutrient within the small intestine (11).

Intrinsic pathways (i.e. enteric nerves) are the major determinant of small intestinal motility but additional extrinsic parasympathetic pathways are also important. Extrinsic parasympathetic pathways, which to the upper gastrointestinal tract are via the vagus nerve and to the lower tract via the sacral nerves, accelerate motility when stimulated, whereas sympathetic activation, via thoracic splanchnic nerves, retard motility. Similar to the stomach, the enteric nervous system contains a

number of neurotransmitters that are responsible for stimulation of motility, e.g. acetylcholine, or relaxation, e.g. nitric oxide.

Small intestinal motility during critical illness

Because of the difficulties with passing manometric catheters into the distal small intestine there is a lack of granular detail regarding motility patterns distal to the duodenum in critically ill humans. Even coarse information related to small intestinal transit (duodenal-cecal) times are challenging to obtain, with only sparse data available. A cohort of 8 critically ill mechanically ventilated patients admitted following a traumatic brain injury were studied using a wireless motility capsule (56). The capsule was placed in the stomach and data compared to a cohort of healthy volunteers who had participated in a separate trial (56). Enteral nutrition was commenced at least 12 hours after the capsule was placed in the stomach. Small intestinal transit time was almost two-fold greater in the critically ill (56). The same investigators also studied 16 critically ill mechanically ventilated patients with intracranial haemorrhage using a video telemetry capsule placed directly into the small intestine and compared to 16 healthy volunteers (57). This study was conducted in the fasted state, with data collected for 8 hours. Transit times were not statistically different between groups but there was considerably greater variability in transit times in the critically ill (57). There were also a proportion (5/16) of the critically ill patients in whom the capsule had not reached the caecum at the end of the study period, whereas all healthy volunteers had, and a smaller proportion of critically ill patients who had very rapid transit (57). Using a scintigraphic technique we (AMD and MJC) measured duodenocecal transit time of radiolabelled nutrient over a 4-hour period in 28 mechanically ventilated critically ill patients and compared these data to healthy volunteers. Interpretation was limited by the fact that tracer had not reached the cecum by the end of the study (240 min) in 12 of 28 patients and 6 of 16 healthy subjects (11). Similar to the study by Rauch and colleagues, we observed greater variability in transit times in the critically ill but the median times were not statistically different (11).

Mechanisms underlying critical illness associated small intestinal dysmotility

The mechanisms underlying critical illness associated small intestinal dysmotility are largely extrapolated from animal models and from humans suffering a discrete insult, e.g. surgery. The pathogenesis of post-operative ileus is held to occur in three phases. Firstly, a surgical stimulus causes activation of inhibitory spinal reflex arcs, specifically those involving the prevertebral ganglia, and long reflexes involving the spinal cord (58). Subsequently, endocrine and inflammatory cytokines augment inhibitory neurotransmitters and nitric oxide to paralyse gut peristalsis (59). The final phase involves parasympathetic (vagal) activation, which mediates resolution of ileus via an anti-inflammatory mechanism (60). There is a complex interaction within the gut between inflammatory components of the mucosa (mast cells, neuroglial cells) and submucosal tissue (enteric neurons, myocytes). This occurs through Toll-like receptors and intracellular signalling pathways involving neurotransmitters as diverse as nitric oxide, cytokines, growth factors, proteases, prostaglandins and hormones. Furthermore, bidirectional signalling between enteric neurons and central nervous system neurons cause systemic inflammation to have gastrointestinal consequences, which in turn perpetuate the inflammation.

Opioids and postoperative stress contribute to the symptom elaboration (61). It has been speculated that exogenous opioids have the capacity to promote virulence within the microbiome of critically ill patients but this hypothesis requires confirmatory evidence (62). There are μ-opioid receptors throughout the gastrointestinal tract. Activation of μ-receptors delays gastric emptying, slows intestinal and colonic propulsion and coordination of peristalsis, increases fluid absorption in the small and large intestine and also increases anal sphincter tone. The net symptomatic result of these pharmacological effects is nausea, vomiting, loss of appetite, abdominal pain, hard stool and rectal evacuation difficulty. While opioid induced constipation has recently been characterised by expert consensus (Rome IV), the criteria reliance on subjective symptoms mean that this definition is less relevant to the critical care environment (13).

Additionally, fluid and electrolyte administration may contribute to postoperative ileus. Excessive fluids lead to intestinal edema and intra-abdominal hypertension, whereas reduction of serum

potassium concentrations affect the opening of calcium channels, attenuating neuromuscular function and hence slowing small intestinal transit (63). Another factor influencing gut motility in ICU patients is the alteration of intestinal microbiota that occurs secondary to antibiotic use, leading to antibiotic-associated diarrhea or even colitis due to *Clostridium difficile*.

LARGE INTESTINE

The motor functions of the large intestine are to provide conditions for fermentation of fibre and undigested nutrient by microbes, and thereby produce faeces, to absorb water from faeces, which is then stored and finally excreted. Unlike the gastric and small intestinal regions there is no clear separation between nutrient-stimulated and non-nutrient patterns, rather periodic large propulsive contractions sweep through the colon to move the contents into the rectum and promote the urge to defecate (64).

Large intestinal motility in health

In health the motility patterns allow sufficient time for resorption of luminal fluid that was secreted in the small intestine. During mixing short duration contractions move contents within haustra and longer propagated contractions progress contents from one haustra to the next. A distinct pattern of high amplitude propagating contractions causes aboral movement of feces longer distances to the rectum.

Large intestinal motility during critical illness

Colonic transit and/or large intestinal motility have rarely been quantified in the critically ill. In the wireless motility capsule study of 8 patients conducted by Rauch and colleagues, the excretion of the capsule was markedly slower in the critically ill than in health (median [lower and upper interquartile range respectively] 10 [8.5-13] days vs. 1.2 [0.0-1.9] days; P <0.001) (56), suggesting transit through the large intestine is delayed.

Given the lack of precise data much of the current orthodoxy comes from clinical observations. Such observational data are, however, imprecise, as there are no consensus definitions, or even the terminology that should be used. Because patients are frequently unable to communicate their symptoms several observational studies have defined constipation as the failure to pass stool within 72 hours of admission to the ICU (65). Using this definition to identify the proportion of patients who have slow colonic transit, disordered motility may occur in at least 20 and up to 60% of patients (5, 66, 67). However, given the frequent periods of inadequate delivery of enteral nutrition, prolonged immobility, sparse dietary fiber and volume depletion, disordered large intestinal motility may be even more common. The European Society of Intensive Care Medicine Working Group on Abdominal Problems recommended avoiding the term constipation in the critically ill: instead, they advocated for the term paralysis of lower gastrointestinal tract, which they defined as the inability of the bowel to pass stool due to impaired peristalsis and required an absence of stool for three or more consecutive days without mechanical obstruction (13).

Similar to the variability in measured small intestinal transit time, based on observational data alone, large intestinal motility is likely to be variable, as both the infrequent passage of stool and, the converse, diarrhoea are reported to occur frequently. Often, diarrhea reported in the ICU actually represents low volume incontinence, and not true diarrhea (defined by >200 gm/day) (68). Regardless of the definition of diarrhea, regular passage of formed stools is less common (69, 70).

Mechanisms underlying critical illness associated large intestinal dysmotility

The mechanisms underlying large intestinal dysmotility in the critically ill have been rarely studied but are likely to be complex and be similar to those influencing gastric and small bowel motility as detailed earlier (71).

DRUG THERAPIES

Pro-motility drugs are frequently administered to critically ill patients and have an established role as an effective treatment to accelerate gastric emptying, improve feed tolerance and increase the delivery of calories administered via the gastric route (43, 72). However, it should be noted that none of the drugs described (Table 3) have been approved for the specific indication of treating critical illness associated dysmotility and their use remains 'off-label'. Moreover, even when a pro-motility drug increases delivery of enteral nutrition or reduces enteral feed-intolerance this has not been proven within a randomized clinical trial to reduce mortality and morbidity. This may be because these outcomes are influenced by a variety of pre-hospital, in-hospital and post-hospital factors; such that even a well-designed trial including a large number of participants is unlikely to detect a statistically significant difference for these outcomes when evaluating a pro-motility drug (73, 74).

Motilin agonists

Motilin is secreted from the duodenum and the proximal small intestine during fasting and the peak plasma motilin concentration coincides with the onset of phase III of the migrating motor complex (75-77). Receptors to motilin are found predominately in the smooth muscle in the gastric antrum and proximal duodenum and, when stimulated, induce isolated smooth muscle contractions. Exogenous motilin induces contractions in this region and thereby accelerates gastric emptying in healthy individuals and patients with gastroparesis (38). When compared to those tolerating enteral nutrition, critically ill patients with enteral feed intolerance had similar plasma motilin concentrations (26).

Macrolide antibiotics such as erythromycin exert pro-motility effects via stimulation of motilin receptors (38). In the critically ill erythromycin accelerates gastric emptying, reduces feed-intolerance, and increases the delivery of calories administered via the gastric route (78-83). The pro-motility effects of erythromycin vary with dose but even lesser doses of erythromycin (e.g. 40mg IV) have pro-motility effects (19). Measuring gastric emptying with using an isotope breath test in 35 critically ill patients, the use of erythromycin at 70 mg did not appear to accelerate gastric emptying

substantially less than 200 mg (84). While the use of a lesser dose when using erythromycin it is our experience that the majority of clinicians that prescribe intravenous erythromycin do so in the range of 100-250 mg twice to three times daily (85). Administration of erythromycin may also increase small intestinal carbohydrate absorption independent of the effect on gastric emptying, with the likely mechanism being minor variations in luminal flow reducing the depth of the 'unstirred layer' within the small intestine (86). Motilin agonists have no role in the treatment of ileus, as erythromycin appears to slow, rather than accelerate, global small intestinal transit times (86).

The use of erythromycin can prolong the QT interval and precipitate cardiac arrhythmias (38). In critically ill patients who are continually monitored the use of low doses (100-250mg) infused over longer periods (e.g. 20 min) rather than intravenous injection may reduce the risk of adverse outcomes (87). Nonetheless, it is prudent to avoid erythromycin in patients with established prolonged QT interval. As a potent inhibitor of CYP3A there is the potential for drug-drug interactions when administering erythromycin (88). There is also concern that widespread use of erythromycin could promote the development of microbial resistance (38). Due to the concerns about side effects we (AMD and MJC) recently completed two trials using a non-macrolide motilin receptor agonist. In a single center study of 23 critically ill patients with established feed intolerance, a single dose of the motilin receptor agonist, camicinal, when compared to placebo, appeared to accelerate gastric emptying and increase carbohydrate absorption (89). In a subsequent international, multi-center, parallel-group, blinded, randomized controlled trial of 84 critically ill patients the pre-emptive administration of enteral camicinal did not significantly augment the provision of goal enteral nutrition (90). Based on these data, non-macrolide motilin receptor agonists, which are not currently available, may have a future role as treatment for patients with established feed-intolerance but do not appear effective as a pre-emptive strategy to prevent enteral feed intolerance.

Ghrelin agonists

Ghrelin is a peptide that is structurally similar to motilin (49). Ghrelin is secreted primarily by the stomach with plasma concentrations greatest during fasting and suppressed by nutrient (49). Receptors to ghrelin are distributed widely, including the hypothalamus, pituitary, and stomach (49). Fasting plasma ghrelin concentrations have been reported to be reduced by more than 50% in the early phase of critical illness, with suppression continuing up to day 28 post admission (91). Moreover, a subsequent analyses of two studies that included a total of 30 critically ill patients reported that when compared to those tolerating enteral nutrition, those with enteral feed intolerance had greater total ghrelin concentrations but that feed intolerant patients had lesser acyl-ghrelin concentrations and acyl-ghrelin to non-acyl-ghrelin ratios (26). This is relevant as the acylation process and subsequent transformation is required for ghrelin to have a physiological effect. Ghrelin is a potent acute stimulant of appetite: indeed, markedly increased ghrelin concentrations are likely to mediate the hyperphagia observed in some patients with the Prader-Willi syndrome (92). Ghrelin increases muscles mass as it is the natural ligand for the growth hormone secretagogue receptor thereby stimulating growth hormone secretion (49). In addition, exogenous ghrelin accelerates gastric emptying in ambulant patients with gastroparesis (93). A multicenter, blinded randomized clinical trial is currently enrolling patients to evaluate the use of an intravenous ghrelin agonist (ulimorelin) in patients with enteral feed intolerance (clinicaltrials.gov NCT0278439).

Dopamine antagonists

Metoclopramide is a frequently prescribed prokinetic and antiemetic drug with complex actions. It acts predominantly as a dopamine (D2 receptor) antagonist with both central and peripheral effects. The dominant mechanism underlying the prokinetic effect is via the dopamine receptor antagonism in the myenteric plexus (94). Metoclopramide also has weak mixed serotonergic effects, partial antagonism of 5-hydroxytryptamine (5-HT^3), partial agonism of 5HT^4 receptors and is a weak cholinesterase inhibitor (38, 94, 95).

In the critically ill intravenous metoclopramide accelerates gastric emptying and is an effective treatment for enteral feed intolerance (96-99). In non-critically ill patients, adverse central nervous system effects are reported not infrequently (95). The frequency of complications in the critically ill is unknown but administration via infusion over longer time periods and reduced frequency of dosing in renal failure are likely to reduce the frequency of complications (95).

Domperidone is a more specific and peripherally acting dopamine receptor antagonist that does not cross the blood–brain barrier and so central nervous system adverse effects are rare (38). The antiemetic effects of domperidone occur via the area postrema chemoreceptor trigger zone (i.e. outside the blood-brain barrier) (94). In ambulant patients with delayed gastric emptying domperidone is an effective therapy that is associated with fewer central nervous system effects (100) but its use as a pro-motility drug in the critically ill has not been evaluated.

Serotonin agonists

Serotonin, or 5-hydroxytryptamine (5-HT) is secreted from enterochromaffin cells throughout the gut (94, 101). Serotonin stimulates 5-hydroxytryptamine receptors, which modulates a number of neurotransmitters including acetylcholine.

Cisapride markedly accelerates gastric emptying in the critically ill (96, 97, 102, 103). However cisapride is not a selective serotonin agonist and also stimulates the cardiac ether a-go-go (hERG) potassium channels, which prolongs the QT interval leading to cardiac dysrhythmia (101). This effect resulted in cisapride being withdrawn from the market. The non-selective 5-hydroxytryptamine Tegaserod was also evaluated in off-label audits and was reported to reduce gastric residual volumes in the critically ill (104). However it was also withdrawn from the market due to concerns about adverse cardiovascular effects (104).

Newer highly selective 5-hydroxytryptamine receptor agonists have recently become available such as the highly-selective 5HT-4 receptor agonist, prucalopride (105). While prucalopride is only available as a enteral formulation, in patients with functional transit problems the drug is a powerful accelerator of transit, and reduces symptoms of constipation (106), and there are intravenous highly-selective 5HT-4 receptor agonists that have been studied in the critically ill We (AMD and MJC) were involved in a single center pilot trial of 13 critically ill patients who were randomised to a highly selective 5-hydroxytryptamine agonist (TAK-954) or metoclopramide, both administered intravenously, in a blinded double-dummy parallel group fashion (107).

Opioid antagonists

Opioids are frequently prescribed in the critically ill to alleviate pain and are likely to cause gastrointestinal dysmotility (62). Opioid antagonists, administered either enterally or parenterally, attenuate the effect of exogenous opioids on gastrointestinal motility. If they do not cross the blood brain barrier they will not interfere with analgesia. In health, co-administration of opioid antagonists with opioids accelerates gastric emptying and small intestinal transit and is an effective treatment for constipation (108).

There is a lack of well conducted clinical trials evaluating the use of opioid antagonists in the critically ill (62). A single-center parallel-group blinded clinical trial randomised 84 critically ill patients who were receiving fentanyl to receive either enteral naloxone or placebo. Patients receiving naloxone had lower median daily gastric residual volume with no difference in time to defecation (109). A placebo-controlled, parallel group, blinded, randomized, clinical trial to evaluate the use methylnaltrexone was recently completed (http://www.isrctn.com/ISRCTN75305839) (110). When available these results are likely to inform further work in this field.

Cholinesterase inhibitors

Cholinesterase inhibitors increase availability of acetylcholine at neuromuscular junctions, which increases contractility of the gastrointestinal tract and accelerates intestinal transit (38). Adverse effects include autonomic cholinergic effects such as bradycardia, bronchospasm and salivation. Three trials have evaluated the use of the cholinesterase inhibitor neostigmine as a pro-motility drug in the critically ill (111-114). In total, the effects of neostigmine on gastric emptying appear modest. However, neostigmine is an effective treatment for acute colonic pseudo-obstruction (115, 116) and a single center blinded randomized controlled trial of 30 critically ill patients with acute colonic ileus reported that continuous infusion of 0.4-0.8 mg/h of neostigmine markedly reduced time to defecation and was well tolerated (117). The use of a continuous infusion at 0.4-0.8 mg/h appears to reduce the rate of adverse effects, particularly bradycardia, when compared to bolus dosing. The continuous monitoring and immediate availability of resuscitation equipment, drugs and personnel that is standard for all Intensive Care Units provide a relatively controlled environment to implement this intervention. Accordingly, cholinesterase inhibitors when administered as an infusion may be useful as a rescue therapy for functional obstruction of the large intestine prior to more invasive therapies (e.g. colonoscopy).

RECOMMENDATIONS

We are of the opinion that attention to general care of the patient - such as avoiding or treating marked hyperglycemia, prolonged starvation, excessive intravenous volume administration, electrolyte disturbances and excessive opiate drugs – will reduce the frequency and severity of gastrointestinal dysmotility.

Recent American Society for Parenteral and Enteral Nutrition/Society of Critical Care Medicine guidelines recommend that in patients with observed upper gastrointestinal dysmotility pro-motility drugs should be initiated (1). However, these guidelines provided no recommendation as to which drug should be used.

In trials of critically ill patients, albeit small numbers, erythromycin appears to be a more potent pro-motility drug than metoclopramide and leads to more frequent resolution of enteral feed intolerance (82, 83). However, erythromycin use is associated with rapid tolerance to its effect, which may explain why administration of both drugs (erythromycin and metoclopramide) appears to be more effective than erythromycin alone (99, 118, 119).

There is considerable variation between individuals as to what GRV that defines gastric dysmotility that warrants administration of a pro-motility drug. Even amongst 'experts' there is considerable variation with the threshold value that represents large GRVs ranging from 200 to 500 ml (1, 13). As a group of authors who work in a variety of settings there are differences in our practices; but, in general, we are of the opinion that, for the majority of patients and in the absence of symptoms, a single GRV < 500 ml should not lead to a reduction in the rate of enteral nutrition. Rather, this identifies a patient who may benefit from administration of a pro-motility drug. However, when a large GRV is associated with other features of gastrointestinal dysmotility (vomiting, diarrhoea or abdominal distension), or is excessively large (> 500 ml), administration of a pro-motility drug should be considered along with a temporary reduction in the rate of, or stopping, feed.

When possible avoidance of rapid bolus injections and dose reduction during renal failure (metoclopramide) are likely to reduce adverse effects and appear a prudent strategy. In a prospective cluster randomized trial and a subsequent multicenter quality improvement initiative the use of pre-emptive pro-motility drugs when incorporated into a bundle of care increased nutrient delivery (120, 121). However, in the blinded NUTRIATE trial administration of a pre-emptive motilin agonist did not increase nutrient delivery. Given the risk of adverse events with any drug in the critically ill, our interpretation of the current literature is that there is insufficient evidence to support the use of pre-emptive pro-motility drugs. While either metoclopramide or erythromycin are supported by evidence as first line treatment, based on a trial that report fewer treatment failures with dual drug therapy (erythromycin and metoclopramide) when compared to erythromycin alone (122), we favour initiating both drugs. On the available evidence there is currently no second-line drug that can be recommended

and for patients who remain enteral feed intolerant on dual drug therapy and we favour alternative approaches to gastric feeding, i.e. small intestinal feeding or parenteral nutrition as determined by availability at individual institutions (123-126). The effect of drugs on gastrointestinal motility is substantially modified by glycemia (127) such that pro-motility drugs are less effective at higher blood glucose concentrations (128). Accordingly, minimising other systemic factors that contribute to gastrointestinal dysmotility, such as excessive exogenous opiates and hyperglycaemia, may improve response to drugs. Given that all drugs have potential side effects and issue of tolerance, it seems sensible to discontinue pro-motility drugs once patients are tolerating enteral feeds for at least 24 hours and limit duration of therapy to no greater than 7 days.

There is a lack of evidence to guide drug therapy of ileus. Erythromycin does not accelerate small intestinal motility and may even exacerbate ileus (86). Based on studies in other patient settings highly selective 5-hydroxytryptamine receptor agonists may be of use for ileus in the critically ill but need to be studied before they can be recommended. There are inadequate data to provide strong recommendations to guide treatment for functional obstruction of the large intestine. However, neostigmine, when infused in an ICU environment for a short duration at a relatively slow rate, may alleviate the need for endoscopic decompression in some patients and appears a reasonable strategy.

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TABLES

Region of gastrointestinal tract	Clinical problem	Motility in health	Motility during critically ill	Diagnosis of dysmotility: clinical - research -	Interventions/drugs administered in clinical practice
Stomach	Delayed gastric emptying Enteral feed intolerance	Fasting pattern (Migrating Motor Complex) Fed pattern	Gastric emptying frequently delayed 'Pump' - via antral motility suppressed 'Brake' via pyloric resistance increased	Gastric residual volume, vomiting Breath tests Acetaminophen absorption 3-O-methylglucose scintigraphy ultrasound	Erythromycin (motilin agonist) Metoclopramide
Small bowel	Substantial inter-patient variability in transit times but a proportion of patients ileus is present	Fasting pattern (Migrating Motor Complex) Fed pattern	Uncertain but appear to not transition from fasting motility pattern to fed pattern ±retrograde ± disorganized	Abdominal distension, increased gastric residual volumes, absent stool for ≥ 3 days, supported by confirmatory radiology Scintigraphy, manometry, Pill cam, Magnetic	None routinely used

			motility	Resonance Imaging	
Large bowel	Functional obstruction	Large periodic propulsive movements a few times per day	Uncertain but clinical appearance of a proportion of patients with paralysis (too slow) and diarrhoea (too rapid)	Abdominal distension and absolute constipation, supported by confirmatory radiology Pill cam, Magnetic Resonance Imaging	Neostigmine

TABLE 1: Summary of dysmotility, presentation and pharmacotherapy used in current practice

Factors on admission	Pre-existing medical problems (diabetes, Parkinson's Disease) Presenting problem (spinal cord injury, burn injury, pancreatitis, intra-abdominal surgery) Age
Dynamic endogenous factors	Hyperglycemia Hypokalemia Pain Severity of illness Gastrointestinal hormone (excessive or suppressed secretion) Inflammation
Dynamic exogenous factors	Opiate analgesia Catecholamines/vasopressors Excessive volume resuscitation Electrolyte disturbances Intraduodenal lipid

TABLE 2: Risk factors for gastrointestinal dysmotility

Drug	Mechanism of action	Dose and route	Adverse effects
Erythromycin	Motilin agonist	100-250 mg intravenous twice to three times daily	QT prolongation, Cardiac dysrhythmia (at higher dose) and potential for bacterial resistance
Camicinal	Non-Macrolide Motilin agonist	50 mg per oral/naso-gastric once daily	Insufficient numbers to accurately describe adverse effects in the critically ill
Ulimorelin	Ghrelin agonist	600-1200 mcg/kg intravenous three times per day	Insufficient numbers to accurately describe adverse effects in the critically ill
Metoclopramide	Dopamine (D2) antagonist 5-hydroxytryptamine-3 antagonist 5-hydroxytryptamine-4 agonist	10 mg intravenous three to four times per day	Dystonia, Tardive Dyskinesis
Domperidone	Dopamine agonist	10 mg three times per day	QT prolongation Extrapyramidal effects

Cisapride	5-hydroxytryptamine agonist (low selectivity)	No longer available	Cardiac dysrhythmia and removed from market
TAK-954	5-hydroxytryptamine agonist (high selectivity)	0.5 mg intravenous daily	Insufficient numbers to accurately describe adverse effects in the critically ill
Naloxone	Opioid antagonist	8 mg per oral/naso-gastric four times per day	Insufficient numbers to accurately describe adverse effects in the critically ill
Methylnatrexone	Opioid antagonist	8-12 mg subcutaneous once daily	Insufficient numbers to accurately describe adverse effects in the critically ill
Neostigmine	Cholinesterase inhibitors	0.4-0.8 mg/h intravenous infusion	Bradycardia, hypotension and cholinergic symptoms

TABLE 3: Pro-motility drugs that have been evaluated in the critically ill