Alternatives to prokinetics to move the pylorus and colon

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Purpose of review
Gastrointestinal motility disorders (GMDs) are common in the ICU. When encountering these problems, one typically thinks of prokinetics. This review summarizes current evidence of treatments.

Recent findings
Prokinetics are not the first-line therapy for GMDs. In fact, the clinical implications of using prokinetic agents are rather controversial. Current evidence on alternative treatment modalities such as fluid and electrolyte management, laxatives, opioid antagonists, purgative enemas, acupuncture, physical therapies and probiotics is growing.

Summary
Current state of the art to treat GMDs is primarily focused at the elimination of underlying trigger factors. Fluid and electrolyte management as well as laxatives and peripherally acting μ-opioid receptor antagonists are the recommended first-line therapies that can be complemented with prokinetics. Acupuncture as well as physical modalities, such as massage or warming of the abdomen, is promising with few side-effects and should be considered as well.

Keywords
critically ill, motility, μ-opioid receptor antagonists, prokinetics, therapies

INTRODUCTION

Gastrointestinal motility disorders (GMDs) are common in the ICU, occurring in approximately 50% of mechanically ventilated critically ill patients [1▪]. The occurence of delayed gastric emptying is particularly increased in patients with head injuries, burns, multisystem trauma, and sepsis [2]. The severity of illness, quantified by the Acute Physiology and Chronic Health Evaluation Score II score (based on age, physiological variables and chronic health conditions) also directly correlates with the incidence of delayed gastric emptying [2]. Several mechanisms are involved in the etiology of bowel dysfunction including parenteral nutrition, mechanical ventilation, hypoperfusion, shock, dehydration, secretion of inflammatory mediators as well as endogenous and exogenous opioids [3].

Motility disorders may involve any part of the gastrointestinal tract, including the esophagus, stomach, small intestine, and colon, and are commonly associated with delayed gastric emptying, constipation, paralytic ileus and diarrhea. Factors that favor symptoms of delayed gastric emptying, constipation and paralytic ileus include the admission diagnosis (such as head injuries, burns, multisystem trauma, and sepsis), electrolyte abnormalities, age, sex, drugs (such as narcotics or catecholamines), recent abdominal surgery, sepsis and shock with circulating cytokines [2]. Malnutrition, caused by delayed gastric emptying and gastroesophageal

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KEY POINTS

- Gastrointestinal motility disorders are common in the ICU.
- Elimination of factors inhibiting gastrointestinal motility remains the principle therapeutic approach.
- Fluid and electrolyte management as well as laxatives and peripherally acting μ-opioid receptor antagonists are the next therapeutic steps that can be complemented with prokinetics.
- Acupuncture as well as physical modalities are promising with few side-effects.

reflux, is still a cause of increased patient morbidity and mortality in the ICU.

Although less frequent than constipation, diarrhea is also a common finding in critically ill patients, regardless of the initial cause of admission to the ICU with incidences between 15 and 38% [4▪]. Causes of diarrhea in the critically ill patient include enteral feeding with short-chain carbohydrates [5▪], drugs such as magnesium and sorbitol [6], antibiotic therapy [4▪], fever or hypothermia [6], malnutrition [7] and physiological factors associated with stress [8]. *Clostridium difficile* colonization remains the most common cause of infectious diarrhea in the critically ill patients, triggering inflammation and potentially followed by detrimental complications such as bowel necrosis and colon dilation with perforation.

The underlying pathophysiology for the development of impaired gastrointestinal motility is complex and multifactorial involving the neuronal, hormonal, endocrine, muscular, inflammatory, and homeostatic systems, and including effects of surgery, immobilization, mechanical ventilation and medication (i.e. opioids) [9]. Particularly opioid-induced effects play a key role in the mechanisms of constipation in the ICU setting. Besides their desired analgesic mode of action, opioids also interact with opioid receptors within the enteric nervous system. In fact, gastrointestinal motility correlates indirectly with the number of enteric neurones that release opioidergic peptides and express opioid receptors. These substances are the key players in the enteric regulation of motility and secretion [10]. Impaired gastrointestinal motility therefore seems to be a consequence of increased opioid receptor agonists (opioids) disconnecting the physiological neuroenteric regulation of the gut [11]. Endogenous and exogenous opioids cause a presynaptic decrease of acetylcholine and other excitatory transmitters leading to tonic cramps of the intestinal muscle, which inhibits propulsive gut motility [12]. More specifically, muscular cramps of the intestine are either a consequence of a decreased release of nitric oxide from inhibitory enteric neurones or a direct activation of intestinal myocytes through opioid receptors [13]. In addition, prolonged intestinal transit, increased muscle tone (also at the anal sphincter) and decreased gut secretions form the clinical characteristics of constipation.

DIAGNOSIS

The diagnostic possibilities in the ICU setting are limited; the most important evaluations being clinical history and examination. A detailed patient's history may avoid further diagnostic procedures. Stool frequencies and appearance are generally daily monitored by nurses and doctors. At the beginning of symptoms, a rectal palpation is part of the basic examination. A very helpful tool to facilitate the diagnosis of functional constipation is the Rome III-criteria [14].

PROKINETICS

Prokinetics such as dopamine antagonists [metoclopramide (MCP), domperidone], cholecystokinin, serotonin agonists (MCP or erythromycin) are commonly used in critically ill patients with intestinal dysfunction [15]. The $5HT_4$ receptor agonist MCP is the most widely used prokinetic agent in patients with gastric feeding intolerance and stimulates gastric and duodenal motility, predominantly via an action on efferent myenteric cholinergic neurons releasing acetylcholine [16▪▪]. MCP is also a D2-receptor antagonist and therefore contraindicated in Parkinson's disease.

The short-term administration of MCP 10 mg given four times a day intravenously may be more effective than placebo [17], but the desired prokinetic effects rapidly decrease after 3 days [18], then bearing the risk of irreversible tardive dyskinesia, which is directly related to the length and dosage of administration [16▪▪] and/or pre-existing extrapyramidal symptoms. Patients with brain injury seem to be less responsive to its prokinetic effects.

The macrolide antibiotic erythromycin acts as a motilin agonist, and in a single dose of as low as 70 mg has been shown to stimulate antral, pyloric, and duodenal motility [19]. Studies have shown that this therapy is superior to MCP and highly successful in promoting enteral feeding in patients with high gastric residual volumes [18]. However, prolonged erythromycin administration (>3 or 4 days) is associated with reduced efficacy [18]. This is

supported by animal studies showing downregulation of motilin receptors after long-term erythromycin administration [20]. Recent data from humans confirm that the success of enteral feeding is inversely proportional to plasma erythromycin concentrations [16▪▪].

ALTERNATIVES TO PROKINETICS

The clinical implications of using prokinetic agents remain controversial, as a few studies in the past have lacked showing their efficacy in the treatment of intestinal dysmotility [21▪]. Several alternative agents and methods are currently available for the treatment of gastrointestinal motility disorders when prokinetic agents are contraindicated or simply have not resulted in the desired outcome. This review summarizes the current evidence on alternative treatment modalities such as fluid and electrolyte management, laxatives, opioid antagonists, purgative enemas, acupuncture, physical therapies and probiotics.

The initial treatment approach for gastrointestinal motility disorders in any case should focus on a thorough clinical evaluation targeting the possible elimination of underlying causes, that is mechanical obstruction, opioids or other medications.

BASIC REMEDIES

Symptomatic therapy of inhibited gut motility offers a broad range of possibilities. Basic remedies should include an aggressive fluid management clinically applicable, and if appropriate an adapted nutrition as well as physical movement of the body. In most cases, however, these options are not sufficient or clinically feasible. Increased fluid administration has been shown to be one of the most effective but also clinically one of the most difficult treatment options. Fluid management should always be in accordance with the current clinical situation of the critically ill patient [22]. Pathophysiological parameters such as cardiovascular status, circulation, infections, and electrolyte balance have to be taken into consideration at all times. Nutrition in the critically ill patient remains a controversial topic by itself [23▪] and should be adjusted to the patient's caloric needs. Early enteral nutrition has been shown to benefit bowel function and has not yet been linked to major side-effects when administered correctly [23▪]. Although enemas and rectal irrigation may play an important role in releasing impacted stool, the evidence regarding its potential to actually improve gastrointestinal motility is very limited [24].

MEDICATIONS

Current pharmacological treatment options for gut dysmotility include either a nonspecific combination of laxatives and prokinetics or a specific treatment option with opioid receptor antagonists.

Laxatives

The use of laxatives in the treatment of constipation is widespread and well described [25]. Laxatives are divided into osmotically and nonosmotically acting substances (Table 1) [26▪]. In general, they aim to increase the water content in the intestines in order to soften the stool consistency. Several algorithms regarding the sequence of administration have been described (e.g. Klaschik *et al.* [27]). Clinical evidence suggests that laxatives have stronger effects than placebo [28]. Polyethylene glycol is superior to conventional lactulose in the treatment of chronic constipation [29].

There is growing evidence that laxatives can improve constipation in the ICU setting. van der Spoel *et al.* [30] reported that the administration of lactulose and polyethylene glycol thrice a day was more effective in promoting defecation than placebo; patients receiving polyethylene glycol had a slightly lower incidence of acute intestinal pseudo-obstruction, whereas length of ICU stay was shorter in lactulose-treated patients. Patanwala *et al.* [31] published that ICU patients suffering from constipation given a stimulant laxative (senna, bisacodyl) and/or an osmotic laxative (lactulose, milk of magnesia) were more likely to have a bowel movement than nonlaxative treated patients.

Masri *et al.* [32▪] have recently shown that a prophylactic dose of lactulose 20 ml enterally every 12 h for the first 72 h successfully prevented constipation in 18% compared with 4% in a control group without intervention in critically ill patients, ventilated ICU patients.

Prokinetics should only be initiated as a second-line therapy when treatment options with laxatives have been exhausted.

Opioid antagonists

Constipation is a common problem, occurring in 40–95% of patients treated with opioids and can occur even after a single dose of morphine [33–35].

When opioid-induced gut dysmotiliy is clinically suspected, opioid receptor antagonists are a potential treatment option. Opioid receptor antagonist administration remains controversial in the critically ill because drugs such as naloxone or nalbuphine also counteract the analgesic action of opioids resulting in an undesirable increased pain perception [36,37].

Table 1. Overview laxatives

Category	Laxatives	Mechanism(s) of action	Onset of action, h	Dosage (adult)	Side-effects
Osmotics	Lactulose	Increase lower gastrointestinal motility and anal sphincter tone by causing local mucosal irritation	24–48	15–60 ml/day	Dehydration, incontinence, impaired electrolytes
	Sorbitol		24–72	30–50 g/day	
	Polyethylene glycol	Stimulate the mucosal nerve plexus.	24–48	15–60 ml/day	
Bulk-forming laxatives	Methylcellulose	Dissolve in lower gastrointestinal tract fluid, causing lubrication that pushes intestinal contents forward and stimulates peristalsis. Additional water intake necessary (2 l/day)	12–48	1–3 × per day (4–6 g/day)	Obstruction if additional water is inadequately supplied, meteorism, flatulence, impaired electrolytes
	Calcium polycarbophil		12–48	1–4 × per day (4–8 g/day)	
	Psyllium		12–48	varies with formulation	
	Agar-agar, flax seed, wheat bran, bassorin				
Salts	Magnesium citrate	Modulation of intraluminal ion transport	0.5–3	200–300 g/day	Cramps, flatulence, nausea, impaired electrolytes
	Milk of magnesia		0.5–3	15–60 ml/day	
	Sodium phosphate		0.5	1 Clyster	
Stimulant laxatives	Bisacodyl	Augment water dispense to the gut	Oral: 6–12	10–15 mg 3 × per day	Colic-like pain, alteration of the skin, discoloration of the urine. Impaired electrolytes
			Rectal: <0.5		
	Senna		6–12	2–4 × per day = 120 g	
	also: Sodium picosulfate,				
	Castor oil				
Emollients	Docusate sodium or calcium	Anionic surfactants that help mix together intestinal fluids, water and other hydrophobic fecal substances to maintain soft fecal texture	24–72	100–400 mg/ 1–2 × per day	Nausea
	Paraffin wax		24–72	1–8 g/day	Lipid pneumonia, malabsorption

Products may vary and the dosing of laxatives varies with each agent and the desired therapeutic effect. Refer to product labeling or manufacturer's product information for specific prescribing and dosing information for each product. A complete list of adverse effects, warnings and precautions can be found in the manufacturer's product information. Adapted with permission from [26▪].

Hence, a very promising alternative may be peripherally acting μ-opioid receptor antagonists (PAMORA).

Methylnaltrexone and alvimopan

Methylnaltrexone – a quaternary amine derivative of the nonselective opioid receptor antagonist naltrexone – is a peripherally acting PAMORA with restricted ability to cross the blood-brain barrier. Promising data has been released showing a potential to relieve opioid-induced constipation (OIC) without reversing analgesia. A randomized placebo-controlled study in 154 patients with advanced illness showed that a single subcutaneous injection of

methylnaltrexone (0.15 or 0.3 mg/kg) elicited a laxation response within 4 h in 62 and 58% of patients for methylnaltrexone 0.15 and 0.3 mg/kg, respectively, compared with a laxation response of 14% for placebo within the same timeframe. Approximately, half of the methylnaltrexone responders defecated within 30 min of dosing [38]. Although currently using methylnaltrexone may increase total costs, methylnaltrexone and standard care seem cost-effective in treating advanced-illness patients with OIC [39].

So far, available data are still limited but strongly suggest that methylnaltrexone causes laxation in less than 24 h for at least half of palliative care patients over the first 2 weeks of usage without impairing pain control or causing serious adverse effects [40▪▪,41]. Methylnaltrexone is contraindicated in patients at risk for gastrointestinal perforation. Methylnaltrexone recently received approval by the US Food and Drug Administration (FDA) and the European Medicines Agency for treatment of opioid-related bowel dysfunction in patients with advanced illness [42]. However, data on critically ill patients in an ICU setting is currently lacking.

Alvimopan – a different PAMORA – has also shown promising results in the treatment of OIC and postoperative paralytic ileus [43]. Due to the higher occurrence of adverse events (myocardial infarction, neoplasms, and fractures) compared with placebo in a 12-month safety study of alvimopan 0.5 mg twice daily for the treatment of OIC, it is currently limited by the FDA to in-hospital treatment after bowel resection surgery [42,26▪]. The dosing of alvimopan is 12 mg orally once before surgery, then 12 mg twice daily until discharge up to a maximum of 7 days (15 total doses). So far, the potential risks of the long-term (>2 weeks) treatment with alvimopan 12 mg twice daily are unknown; neither have the effects and risks of this treatment in critically ill patients in the ICU setting been investigated [26▪].

In addition, at least four new oral PAMORA (NKTR-118, TD-1211, ADL-7445 and ADL-5945) are currently under clinical development [44].

In summary, insufficient evidence exists for the safety or efficacy of centrally acting opioid antagonists naloxone or nalbuphine in the treatment of opioid-induced bowel dysfunction [40▪▪]. Long-term efficacy and safety of any of the opioid antagonists is unknown, as is the incidence or nature of rare adverse events [40▪▪]. Alvimopan and methylnaltrexone both peripherally acting opioid antagonists show promise in reversing opioid-induced increased gastrointestinal transit time and constipation, but further data will be required to assess the efficacy, safety and optimal dosing in critically ill patients.

ACUPUNCTURE

Several favorable effects of acupuncture on the gastrointestinal tract have been described [45]. Zou *et al.* [46] demonstrated that electrical acupoint stimulation at acupoint Neiguan (volar forearm) in healthy volunteers significantly inhibits the frequency of transient lower esophageal sphincter relaxations, one possible cause of delayed enteral nutrition in critically ill and mechanically ventilated patients. This inhibition may be mediated via efferent vagal innervation, which is modulated by higher cortical and subcortical circuitries, specifically activated by stimulation of Neiguan [47–49]. Patients with systemic sclerosis have unique and persistent alterations in gastric myoelectrical activity with acupressure to Neiguan [50]. Chang *et al.* [51] reported that cutaneous electrical stimulation of acupuncture points may enhance gastric myoelectrical regularity in healthy volunteers [52] and diabetic patients with gastric dysrhythmia. Furthermore, several experimental studies on animals have demonstrated a possible modulating effect of acupoint stimulation on various parameters of gastric motility as well as acid secretion [53–56]. Finally, acupuncture and other forms of acupoint stimulation on acupoint Neiguan were found superior to placebo procedures for postoperative nausea and vomiting (PONV), symptoms for which prokinetic drugs have been used to resolve this problem with only limited success [57]. Acupuncture at Neiguan has also been shown to be highly effective against chemotherapy-induced or pregnancy-related nausea and vomiting [58▪,59,60].

A recent study adapted an acupuncture-stimulation technique to the ICU setting and evaluated its effect on delayed gastric emptying in comparison with the current standard prokinetic drug treatment [61▪]. Acupuncture at Neiguan was shown to be superior to conventional prokinetic drug treatment in improving delayed gastric emptying and preventing malnutrition in a neuro-ICU patient population. The described prolonged intermittent transcutaneous electrical acupoint stimulation proved to be a feasible, low-risk method, which could serve as an adjunct to common drug regimens aimed at reducing overall medication exposure and critical care patient morbidity.

Previous studies have found that acupuncture modulates important components involved in the pathogenesis of delayed gastric emptying, such as relaxation of the lower esophageal sphincter and gastric myoelectrical activity [45,62,63]. Ultimately,

although the underlying pathophysiology of delayed gastric emptying and malnutrition in critically ill patients differs somewhat from acute PONV, both relate to autonomic nervous system activity and both may be amenable to acupuncture therapy.

PHYSICAL THERAPIES

Heat application and massage – although some of the oldest therapeutic methods – are starting to collect evidence for efficacy for the treatment of GMDs.

Heat

Warming of the abdomen has been shown to experimentally influence peripheral hemodynamics (superior mesenteric artery blood flow) and autonomic regulation, thereby inducing a feeling of comfort in the abdomen and providing a beneficial environment for the improvement of gastrointestinal motility [64,65].

Massage

A recent survey evaluating the current clinical practice in treating motility disorders in adult critically ill patients on German ICUs showed that 39% used massage as a therapeutic option [66].

Experimental and clinical studies point toward the ability of massage to stimulate peristalsis, decrease colonic transit time, increase the frequency of bowel movements in constipated patients and decrease the feelings of discomfort and pain that accompany it. Its effectiveness, lack of side-effects, and low cost (especially if self-administered) make abdominal massage an attractive option in bowel management programs for persons with chronic constipation [67▪,68,69].

One set of guidelines for holistic management of chronic constipation in primary care combines abdominal massage with education of patients regarding toileting habits, exercise and diet, monitoring use of possibly constipating medications and prescribing laxatives if other methods have not been successful [70]. One study also points toward effectiveness in a palliative care setting showing decrease of constipation and associated abdominal discomfort in hospice patients with massage [71]. Another study showed reduced postoperative pain and shortened duration of paralytic ileus with massage of the abdominal wall in patients after colectomy [72].

PROBIOTICS

Various therapeutic effects have been ascribed to probiotics like *Lactobacillus reuteri* and other probiotics including correction of functional dysmotility, moderation of inflammation-associated disease states and hypertension [73–77].

The evidence for the use of probiotics is discussed elsewhere in this journal. In general, the efficacy of probiotics in infection prevention among critically ill patients is still not unequivocally determined and it remains uncertain whether probiotics/synbiotics are beneficial or even dangerous to the clinical outcome in critically ill patients; the safety profile differs per probiotic strain and should not be generalized among different strains and patient populations [78,79▪].

CONCLUSION

The elimination of factors inhibiting gastrointestinal motility remains the principle therapeutic approach when treating gut dysmotiliy. Fluid and electrolyte management as well as laxatives and PAMORAs are the next therapeutic steps that can be complemented with prokinetics. Acupuncture as well as physical modalities, such as massage or warming of the abdomen, is promising with few side-effects, and should be considered as well.

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None.

Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 207).

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