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Prevention and Treatment of Gastrointestinal Complications in Patients on Mechanical Ventilation

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Abstract

There exists a complex, dynamic interaction between mechanical ventilation and the splanchnic vasculature that contributes to a myriad of gastrointestinal tract complications that arise during critical illness. Positive pressure-induced splanchnic hypoperfusion appears to play a pivotal role in the pathogenesis of these complications, the most prevalent of which are stress-related mucosal damage, gastrointestinal hypomotility and diarrhea. Furthermore, characteristics of the splanchnic vasculature make the gastrointestinal tract vulnerable to adverse effects related to positive pressure ventilation. While most of these complications seen in mechanically ventilated patients are reflections of altered gastrointestinal physiology, some may be attributed to medical interventions instituted to treat critical illness.

Since maintenance of normal hemodynamics cannot always be achieved, pharmacologic prophylactic therapy has become a mainstay in the prevention of gastrointestinal complications in the intensive care unit. Improved understanding of the systemic effects of mechanical ventilation and greater application of lung-protective ventilatory strategies may potentially minimize positive pressure-induced reductions in splanchnic perfusion, systemic cytokine release and, consequently, reduce the incidence of gastrointestinal complications associated with mechanical ventilation. Herein, we discuss the pathophysiology of gastrointestinal complications associated with mechanical ventilation, summarize the most prevalent complications and focus on preventive strategies and available treatment options for these complications.

The most common causes of gastrointestinal hemorrhage in mechanically ventilated patients are bleeding from stress-related mucosal damage and erosive esophagitis. In general, histamine H_2 receptor antagonists and proton pump inhibitors prevent stress-related mucosal disease by raising the gastric fluid pH. Proton pump inhibitors tend to provide more consistent pH control than histamine H_2 receptor antagonists. There is no consensus on the drug of choice for stress ulcer prophylaxis with several meta-analyses providing conflicting results on the superiority of any medication. Prevention of erosive esophagitis include careful use of nasogastric tubes and institution of strategies that improve gastric emptying. Many mechanically ventilated patients have gastrointestinal hypomotility and diarrhea. Treatment options for gastrointestinal motility are limited, thus, preventive measures such as correction of electrolyte abnormalities and avoidance of medications that impair gastrointestinal motility are crucial. Treatment of diarrhea depends on the underlying cause. When associated with *Clostridium difficile* infection antibacterial therapy should be discontinued, if possible, and treatment with oral metronidazole should be initiated.

More studies are warranted to better understand the systemic effects of mechanical ventilation on the gastrointestinal tract and to investigate the impact of lung protective ventilatory strategies on gastrointestinal complications.

The outcome of critically ill patients depends not only on the treatment of underlying disease, but also on prevention and treatment of complications that occur in the intensive care unit (ICU). The characteristics of the splanchnic vasculature place the gastrointestinal (GI) tract at particularly high risk for complications in critically ill patients.[1] Figure 1 summarizes the possible GI complications that may be encountered in critically ill patients. While most of these complications are reflections of altered GI physiology, some may be attributed to medical interventions instituted to treat critical illness.

Mechanical ventilation, although life saving, is associated with a number of complications that may hinder recovery from critical illness.[1] The complexity of interactions between critical illness and mechanical ventilation, and their effects on the GI tract necessitate better understanding of the pathogenesis of GI complications. It is conceivable that critical illness 'primes' the GI tract thereby creating an environment conducive to the development of mechanical ventilation-induced complications. In this article, we discuss the pathophysiology of GI complications associated with mechanical ventilation and focus on preventive strategies and available treatment options for these complications.

1. Pathophysiology

Current knowledge about the influence of mechanical ventilation on the GI tract is limited. While some GI complications may be directly attributable to mechanical ventilation, most occur as a consequence of the underlying pathophysiologic changes associated with critical illness.[2] The complexity and heterogeneity of critical illness makes it impossible to specifically implicate mechanical ventilation as being the immediate cause of GI complications. Nevertheless, as mechanical ventilation can contribute to the pathogenesis of GI complications in much the same way as critical illness, it is reasonable to conclude that mechanical ventilation may potentiate the adverse effects of an underlying critical illness and worsen GI physiology.

1.1 Splanchnic Hypoperfusion

Impaired splanchnic perfusion plays a pivotal role in the pathogenesis of GI complications associated with mechanical ventilation (figure 2). The splanchnic vasculature lacks vasomotor autoregulation, which leads to persistent vasoconstriction following resolution of hemodynamic instability. The vascular architecture of the gut mucosa is similar to the renal medulla in permitting oxygen shunting which, under normal conditions, can cause hypoxia at the tips of villi.[3,4] Additionally, gut mucosal oxygen

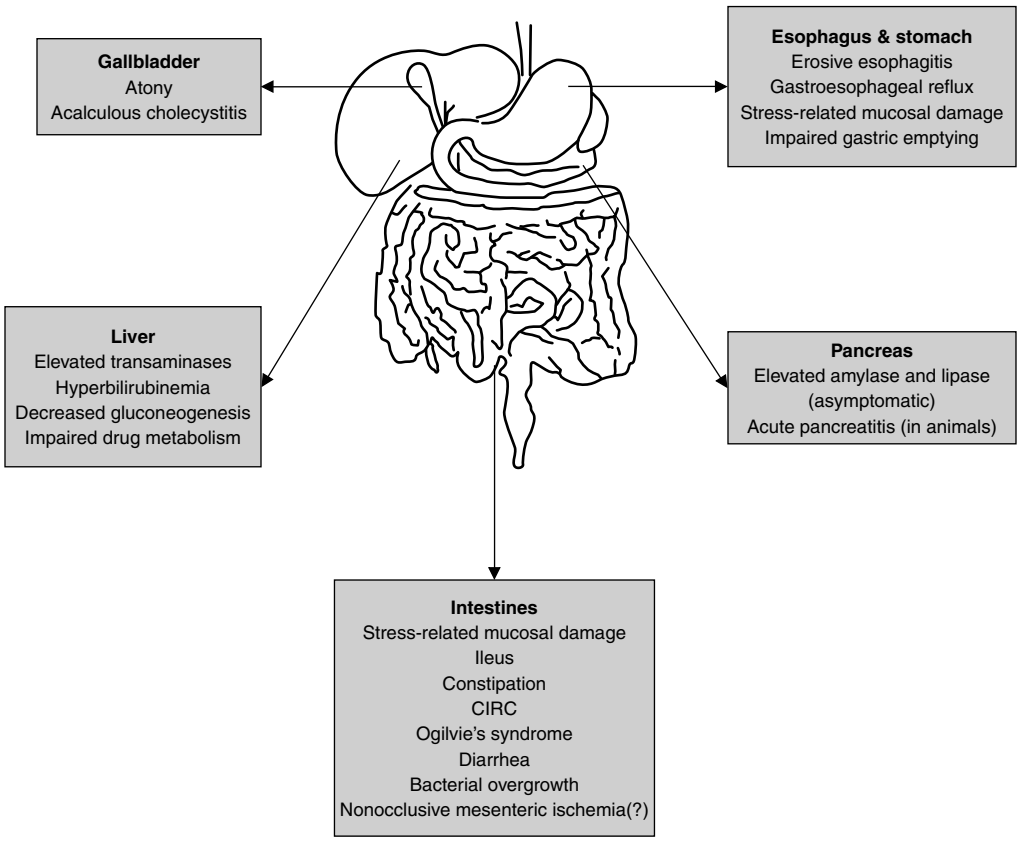

Fig. 1. Organ-specific gastrointestinal (GI) complications in critically ill patients on mechanical ventilation. Both hollow and solid organs in the GI system can be affected by mechanical ventilation. **CIRC** = critical illness-related colonic hypomotility.

content is low due to a hematocrit of approximately 10% that results from dilutional effects of absorbed fluid and nutrients.[5] All of these factors place the GI tract at increased risk of ischemic events.

Mechanical ventilation may lead to splanchnic hypoperfusion by decreasing mean arterial pressure. Mechanical ventilation, especially with high levels of positive end-expiratory pressure (PEEP), decreases venous return by reducing the pressure gradient between systemic veins and the right atrium. Reduced preload results in decreased cardiac output and hypotension, particularly in patients with hypovolemia and impaired venoconstriction. Mesenteric blood flow parallels this reduction in cardiac output. PEEP-induced reductions in mesenteric blood flow can be corrected by restoration of cardiac output following fluid resuscitation.[6]

Another mechanism by which mechanical ventilation may affect splanchnic perfusion is a PEEP-induced increase in intra-abdominal pressure as a result of diaphragmatic descent. Intra-abdominal pressure is normally subatmospheric to 0mm Hg. In animals, gradual increases in intra-abdominal pressure up to 40mm Hg decrease blood flow in all organs in the GI tract.[7] In another animal study, both mesenteric and mucosal blood flow and intramucosal pH (pHi) diminished once intra-abdominal pressure reached 20mm Hg.[8] These reductions in intestinal mucosal blood flow parallel the rise in intra-abdominal pressure. Conceivably, a PEEP-induced increase in intra-abdominal pressure may lead to similar reductions of splanchnic perfusion. It is noteworthy that PEEP-related rises in intra-abdominal pressure may offset the negative effect of PEEP on venous return and cardiac output.[9]

In addition to reduced mean arterial pressure and PEEP-induced increase in intra-abdominal pressure, mechanical ventilation may adversely affect GI perfusion by reflex vasoconstriction of GI vasculature. Positive pressure ventilation is associated with elevated plasma renin-angiotensin-aldosterone activity and increased serum catecholamine levels, as a result of sympathetic activation.[10,11] These neurohormonal alterations contribute to splanchnic hypoperfusion by causing vasoconstriction and redistribution of blood away from the splanchnic vascular bed.[12,13] Whether due to decreased cardiac output and/or increased vascular resistance, splanchnic hypoperfusion produces an imbalance between oxygen supply and demand that may contribute to mucosal

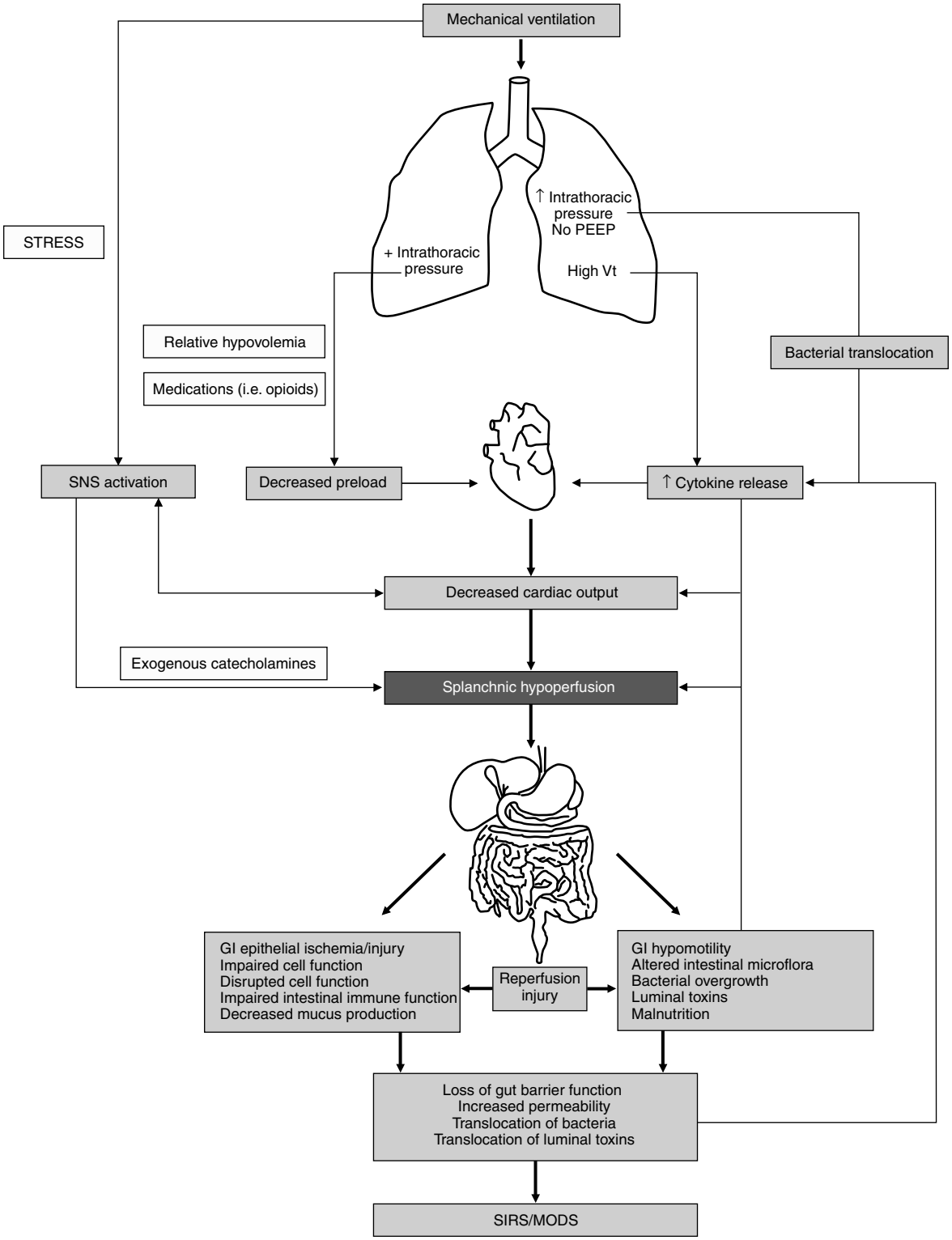

Fig. 2. Proposed mechanisms for the development of gastrointestinal (GI) complications associated with mechanical ventilation. Similar to underlying critical illness, mechanical ventilation can contribute to the pathogenesis of GI complications by altering splanchnic blood flow and leading to increased release of proinflammatory mediators. **MODS** = multiple organ dysfunction syndrome; **PEEP** = positive end-expiratory pressure; **SIRS** = systemic inflammatory response syndrome; **SNS** = sympathetic nervous system; **Vt** = tidal volume; ↑ = increase.

damage (e.g. stress ulcer) and/or hypomotility (e.g. ileus).[12,13] Perhaps more concerning than splanchnic hypoperfusion is reperfusion injury to GI epithelial cells that may occur after restoration of blood flow.[14] Repetitive episodes of hypoperfusion followed by reperfusion may contribute to acute nonocclusive mesenteric ischemia in the critical care setting.[15]

1.2 Increased Cytokine Release and Bacterial Translocation

The influence of positive pressure ventilation on the GI tract is not limited to reduced splanchnic blood flow due to impairment of cardiac output. Mechanical ventilation with 'injurious' ventilatory strategies (i.e. high end-inspiratory lung volumes) may also play an important role in the pathogenesis of GI complications. High tidal volume ventilation leads to an increased release of cytokines, which may amplify inflammatory responses and contribute to the development of multiple organ dysfunction syndrome (MODS).[16] Cytokines may indirectly contribute to splanchnic hypoperfusion and directly impair intestinal smooth muscle function.[12,17,18]

Both high-peak airway pressures and lack of PEEP have been shown to cause translocation of bacteria from the alveolar space into the bloodstream in animals, providing another mechanism by which mechanical ventilation can produce systemic manifestations.[19] Growing evidence regarding increased cytokine release during 'injurious' ventilatory strategies suggests a potentially critical role for mechanical ventilation in the initiation and propagation of a systemic inflammatory response syndrome (SIRS) that may include dysfunction and damage to the GI tract as a part of MODS.[20]

1.3 Impaired Gut Barrier Function

Gut barrier function can be affected by reduced splanchnic blood flow and increased proinflammatory mediators, independent of mechanical ventilation.[5] Gut barrier function is dependent on the function of mucosal cells and intracellular junctions, mucus production, gut-associated lymphoid tissue and secretory immunoglobulin (Ig)A production, all of which may be impaired during critical illness.[21] Other consequences of critical illness, such as malnutrition and altered intestinal microflora, may also threaten GI epithelial cells. Moreover, impaired barrier function may allow the passage of proinflammatory mediators (e.g. endotoxin), and possibly micro-organisms, from the intestinal lumen to the bloodstream.[14] This process can become self-sustaining if the underlying disease that initiates the cascade is not controlled.

1.4 Medications

Medications used to facilitate mechanical ventilation, such as opioids and benzodiazepines, may decrease GI motility and impair venous return via venodilation and/or depressed responsiveness to catecholamines. Opioids slow gastric emptying and cause intestinal hypomotility in critically ill patients.[22,23] Hypotension associated with propofol infusions is dose related and occurs more frequently after bolus dosing. Propofol may lead to hypertriglyceridemia, particularly at high doses or with long-term use,[24,25] and may result in the elevation of pancreatic enzymes.[26,27] Other frequently used medications that may adversely affect the GI tract include vasopressors (particularly dopamine), antibacterials, and additives in oral medications (e.g. sorbitol)

2. Gastrointestinal (GI) Complications in Mechanically Ventilated Patients

2.1 GI Hemorrhage

Acute respiratory failure requiring mechanical ventilation for longer than 48 hours is one of the two strongest independent risk factors for clinically significant GI bleeding in the ICU.[28,29] The most common causes of GI hemorrhage in mechanically ventilated patients are bleeding from stress-related mucosal damage (SRMD) and erosive esophagitis.

Mechanically ventilated patients almost invariably develop SRMD and subepithelial hemorrhage within 24 hours of admission to ICU.[30-32] SRMD occurs within a few hours of critical illness; SRMD can present as lesions ranging from subepithelial petechiae to superficial erosions and can progress into true ulcers. These lesions are usually multiple and occur predominantly in the fundus of stomach, typically sparing the antrum.[32] The mucosa distal to the fundus (antrum and duodenum) can also be affected, although these lesions typically appear later, tend to be deeper, and may be associated with a higher incidence of bleeding.[31,33]

The majority of lesions associated with SRMD are asymptomatic and clinically insignificant (figure 3). Patients with clinically evident bleeding present with frank hemorrhages in the form of hematemesis, melena, coffee-ground material or hematochezia. Clinically significant or life-threatening bleeding is defined as bleeding that causes hemodynamic changes or necessitates transfusion.[34] Mechanically ventilated patients who develop clinically significant bleeding generally do so within the first 2 weeks of their ICU stay.[35]

Clinically evident bleeding due to SRMD occurs in up to 25% of critically ill patients who do not receive prophylactic therapy.[29,32,36] Of those, approximately 20% (corresponding to ~5% of all patients) are clinically significant in that they require inter-

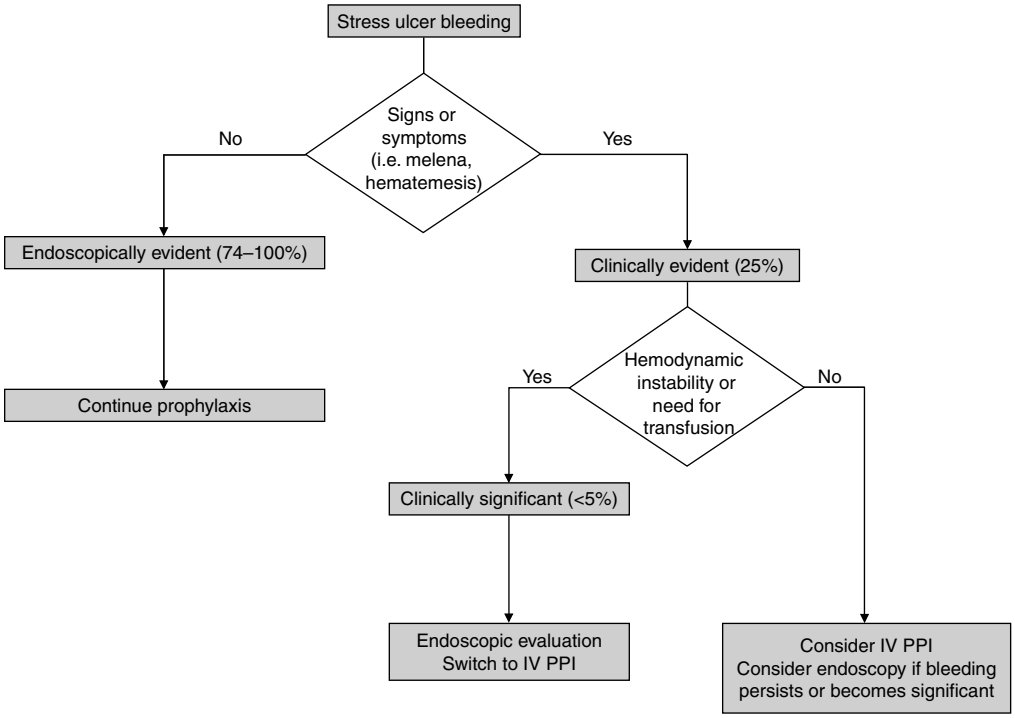

Fig. 3. Features of stress ulcer bleeding in mechanically ventilated patients.The majority of critically ill patients with stress ulcer are asymptomatic. Clinically evident bleeding is found in up to 25% of patients who do not receive prophylactic therapy. Clinically significant bleeding occurs in fewer than 5% of patients. **IV** = intravenous; **PPI** = proton pump inhibitor.

vention and/or transfusion.[29,37-39] Not surprisingly, clinically significant stress ulcer bleeding is associated with an increased length of ICU stay (up to 11 more days), morbidity and mortality.[28,29,35]

Erosive esophagitis occurs in almost 50% of mechanically ventilated patients and accounts for 25% of all upper GI bleeding in ICU patients.[40] The etiopathogenesis of esophageal injury in critically ill patients is multifactorial and includes the use of nasogastric tubes, gastroesophageal reflux and duodenogastroesophageal (bile) reflux.[41,42] Nasogastric tubes cause mechanical irritation and interfere with normal esophageal motility and sphincter function leading to a higher incidence of gastroesophageal reflux.[41,42] It is noteworthy that gastroesophageal reflux occurs independent of body position and is not influenced by the size of the nasogastric tubes.[43] The standard use of stress ulcer prophylaxis makes acid-induced mucosal damage a less likely explanation,[41,44] suggesting that erosive esophagitis probably results from bile-induced damage from duodenogastroesophageal reflux, combined with direct trauma caused by nasogastric tubes.[40] The severity of esophagitis correlates with the volume of residual gastric contents. Gastric colonization with bacteria, which alters bile composition and increases the percentage of injurious unconjugated bile, may contribute to esophageal damage.

2.2 Non-Hemorrhagic Complications

2.2.1 GI Hypomotility

Many mechanically ventilated patients have abnormal upper GI motility[45] that affects the stomach more than the duodenum. Although dysfunction of antral Cajal cells, which regulate gastric contractility, has been proposed as the mechanism responsible for gastric dysmotility,[22,23] it is more likely due to a complex interaction between local enteric afferent neurotransmitter imbalance, autonomous (especially vagal) dysfunction, and abnormal central processing.

In general, patients with hypomotility present with decreased bowel sounds or abdominal distention[46] (table I). In one study,

Table I. Motility-related gastrointestinal complications in mechanically ventilated patients

Complication	Incidence (%)[a]
Decreased bowel sounds	Up to 50
Abdominal distention	13–46
High gastric residuals	32–39
Constipation	15
Ileus	4–10

a Data from Pingleton and Hadzima,[48] Raff et al.,[49] and Gurman et al.[36]

many ICU patients experienced some degree of intolerance to enteral feeding, manifested as high gastric residuals (39%) and constipation (16%).[47] Furthermore, abnormal peristalsis favors the development of duodenogastric reflux and subsequent colonization of the stomach by *Enterobacteriacea* species.

Other less common, but more challenging, clinical problems include critical illness-related colonic hypomotility (CIRC) and Ogilvie's syndrome.[50] Both are characterized by the absence of defecation in combination with colonic distension in Ogilvie's syndrome or no physical or radiographic abnormalities in CIRC. Patients with CIRC lack colonic prokinetic movements, whereas the upper GI tract functions properly. It has been suggested that Ogilvie's syndrome is preceded by CIRC, or may be a variant of CIRC.

2.2.2 Diarrhea

Diarrhea affects up to half of critically ill patients, and those with acute respiratory failure appear to be particularly at risk.[46,51] The etiology of diarrhea in the ICU is multifactorial and, as such, is probably a reflection of the severity of the underlying illness and gut dysmotility (table II).

Diarrhea associated with enteral feeding affects up to 25% of ICU patients.[52,53] The incidence has been shown to be higher in patients who receive infusion rates >50 mL/hour.[52] Contrary to the common perception, the impact of formula osmolality on the incidence of diarrhea remains uncertain. Liberal use of antibacterials predisposes ICU patients to diarrhea, which accounts for 20–50% of all cases of nosocomial diarrhea.[54] Broad-spectrum antibacterials alter colonic bacteria, thereby altering the fermentation of enterally administered carbohydrates to nonabsorbable metabolites, which cause a malabsorption syndrome and osmotic diarrhea. Almost 40% of patients receiving antibacterials develop antibiotic-associated diarrhea,[55] 15–25% of which is attributable to *Clostridium difficile* toxin. Unlike other forms of diarrhea, *C. difficile* is associated with significant morbidity and even mortality if toxic megacolon develops.[56] The number and duration of use of antibacterials are determinants for diarrhea associated with *C. difficile* infection. Diagnosis of *C. difficile* diarrhea requires a high index of suspicion and is typically made by detection of cytotoxins in the stool, although tissue culture toxin assays remain the gold standard. Newer rapid enzyme immunoassays can detect *C. difficile* with fair sensitivity (69–87%) and good specificity (99–100%).[57] While there are no guidelines as to how many assays are needed, the stool should be checked for toxin at least twice before *C. difficile* can be excluded. Importantly, subsequent episodes of diarrhea must be evaluated for *C. difficile*-associated diarrhea in the same manner and with the same vigilance as initial episodes.

Table II. Common causes of diarrhea in mechanically ventilated patients

Enteral nutrition
Hyperosmolar formulas
High infusion rates (>50 mL/h)
Dietary lipids
Medications
Antacids (Mg^{+3}-based)
Histamine H_2 receptor antagonists (with or without antacids)
Antibacterials
Infection with *Clostridium difficile*
Chronic severe hypoalbuminemia (<2.6 g/dL)
Prolonged starvation (>5 days)
Interference with bile acid homeostasis due to intestinal mucosal atrophy

Relative luminal excess of bile acids[58] as a result of decreased absorption related to atrophy of the terminal ileum following starvation (as early as 4 days)[59] and hypoalbuminemia also contribute to diarrhea in the ICU.[60,61] Although the precise role of hypoalbuminemia as a risk factor has been challenged,[58] it can lead to gut edema and impaired nutrient absorption. Albumin levels less than 2.6 g/dL have been associated with an increased risk of diarrhea[60] although chronicity, rather than severity, of hypoalbuminemia is a more important contributor to diarrhea.

2.2.3 Other Complications

Mechanical ventilation not only affects hollow organs of the GI tract, but can also impact on solid organs, such as the liver, pancreas and gallbladder. It is noteworthy that most available evidence regarding the effects of positive pressure ventilation on solid organs comes from animal studies and has been extrapolated to humans.

Pancreas

In animals, PEEP may decrease blood flow to the pancreas and stomach to a greater extent than to the intestines. Furthermore, hemodynamic consequences of PEEP in the pancreas can persist despite the maintenance of mean arterial pressure.[62] In animals, high levels of PEEP (>15cm H_2O) cause pancreatitis, particularly when the pancreas is stimulated.[63] Whether mechanical ventilation alone may cause elevation in pancreatic enzymes and pancreatitis in humans is unknown. However, these concerns, while theoretic, are worthy of consideration in critically ill patients with otherwise unexplained pancreatitis.

Liver

Positive pressure ventilation with PEEP may reduce both portal venous and hepatic arterial blood flow along with hepatic venous oxygen saturation.[64-67] These effects occur in parallel with changes in cardiac output. Improvement of cardiac output im-

proves hepatic blood flow[65,66] similar to that seen with enteral feeding.[68] PEEP also elevates both portal and hepatic venous pressures and causes hepatic congestion in animals.[66,69] This has been speculated to be due to increased portal transmural pressure as a result of a rise in hepatic venous pressure. Positive pressure ventilation also mediates its adverse effects on portal blood flow by raising intrathoracic venous pressure,[64] increasing hepatic sinusoidal resistance via mechanical compression of the liver by the descending diaphragm[65,67] and diminishing mesenteric blood flow.[64]

Collectively, a mismatch between hepatic metabolic demand and PEEP-induced impairment in blood and oxygen supply can result in abnormal liver function. In patients with septic shock, PEEP impairs gluconeogenesis (a marker for hepatic metabolic performance) in parallel to reductions in cardiac output and hepatic venous oxygen saturation.[70] Conceivably, high PEEP may impair the clearance of drugs that are hepatically metabolized. In view of current evidence, it is reasonable to hypothesize that PEEP contributes to liver dysfunction, especially in the presence of hypoxemia, hypotension or any other condition that compromises hepatic oxygen supply.

Gallbladder

Acute acalculous cholecystitis is an insidious complication that affects ~1% (0.2–3%) of ICU patients.[71,72] The pathogenesis is most likely multifactorial, involving both ischemic and chemical (biliary) injuries to the gallbladder epithelium. Mechanical ventilation as well as shock, sepsis, multiple transfusions, dehydration, prolonged enteral fasting, total parenteral nutrition and medications (e.g. sedatives and opiates) have been implicated in the pathogenesis of acute acalculous cholecystitis. Prolonged fasting and resultant biliary sludge are known risk factors for acalculous cholecystitis,[73] and are frequently encountered in critically ill patients. Biliary sludge occurs as a result of decreased cholecystokinin (CCK)-mediated gallbladder emptying (which normally occurs several times a day) and stagnation of concentrated bile.[74]

Mechanical ventilation may affect the gallbladder epithelium both directly, by causing hypoperfusion and ischemia of the wall, and indirectly, by leading to poor contractility with consequent biliary stasis and sludge formation similar to prolonged fasting.[75] Motility changes can be detected as early as 24 hours after admission to the ICU. For the same duration of starvation following major abdominal surgery, patients requiring mechanical ventilation had a higher degree of gallbladder atony compared with those who were spontaneously breathing. Early diagnosis of acalculous cholecystitis is crucial because of the high morbidity and mortality (up to 50%) associated with this condition.[76]

3. Prevention and Treatment

Splanchnic hypoperfusion appears to play a key role in the pathogenesis of many GI complications associated with mechanical ventilation. Thus, maintenance of normal hemodynamics, and splanchnic blood flow and oxygen delivery are crucial in the prevention of these complications. In fact, early aggressive hemodynamic support decreases the incidence of bleeding from stress-related mucosal damage to negligible levels.[39] In addition to early hemodynamic stabilization, advances in ICU care and use of prophylaxis for SRMD have resulted in a decline in the incidence of SRMD-associated bleeding in the last decade.[77,78]

The impact on the GI tract of protective ventilatory strategies with low tidal volume ventilation has yet to be reported. However, in light of current knowledge regarding the probable association between 'injurious' ventilatory strategies (causing volutrauma and biotrauma) and SIRS/MODS, the avoidance of high tidal volumes and the use of optimal PEEP levels to minimize repetitive opening and collapse of alveoli may prove beneficial and should be part of a strategy for the prevention of GI complications.

3.1 GI Hemorrhage

3.1.1 Stress ulcer prophylaxis

SRMD occurs when the injurious effects of gastric acid overwhelm the protective and reparative mucosal defense mechanisms that are impaired by the ischemia that frequently occurs during critical illness and mechanical ventilation[37,79,80] (figure 4). Mucosal ischemia decreases the capacity to neutralize hydrogen ions and contributes to intramural acidosis, cell death and ulceration.[81,82] Ischemia also compromises gastric energy utilization and impairs protective processes (e.g. mucus production), especially in the fundus, where most SRMD develops.[37,82] Although luminal hyperacidity is not required, gastric acid is an essential factor in the pathogenesis of SRMD.[30,83] Therefore, it is not surprising that therapies targeting gastric acid or improving mucosal defense have become the mainstay of prevention (table III).

Pharmacologic Approaches

Medications that target gastric acid secretion, such as histamine H_2-receptor antagonists and proton pump inhibitors, prevent SRMD by raising the gastric fluid pH (ideally above 4.0) and reducing the diffusion of hydrogen ions back into the mucosa. Histamine H_2 receptor antagonists provide prophylaxis against SRMD by inhibiting gastric acid secretion. The major concern with the use of histamine H_2 receptor antagonists is tolerance or tachyphylaxis. Continuous administration of these agents may provide more effective acid inhibition compared with intermittent dosing, but the relevance of this practice remains unclear.[84]

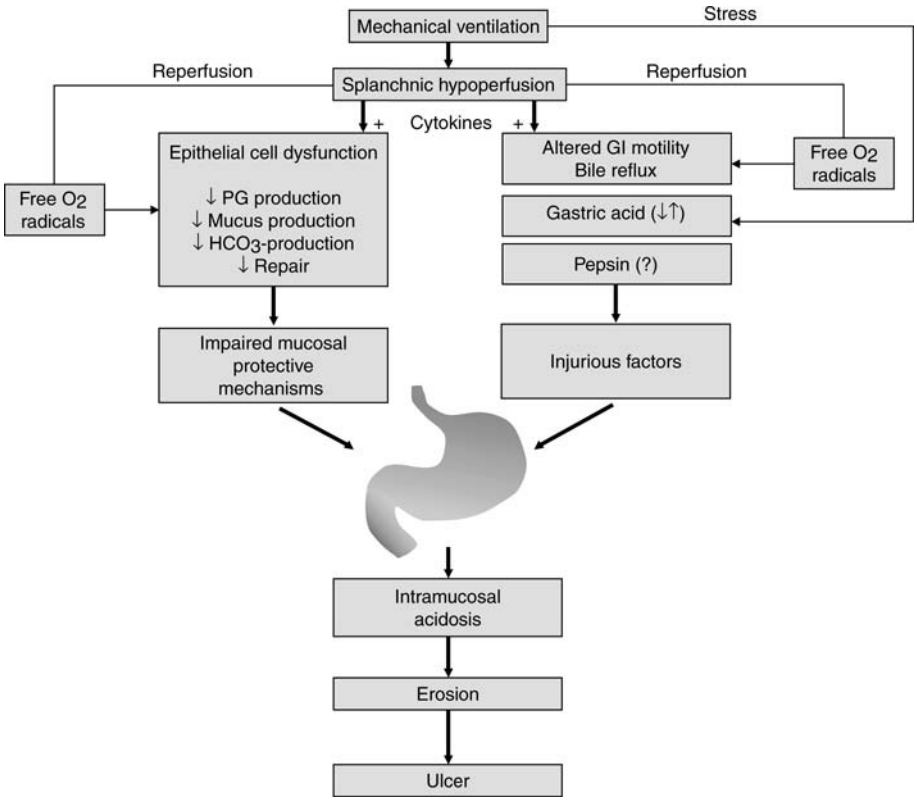

Fig. 4. Proposed mechanisms for the development of stress-related mucosal damage (SRMD) in mechanically ventilated patients. SRMD occurs when the harmful effects of gastric acid overwhelm the protective and reparative mechanisms of the mucosal defense mechanisms which are impaired due to local mucosal ischemia that frequently occurs during critical illness and mechanical ventilation. **GI** = gastrointestinal; **PG** = prostaglandin; ↓ = decrease; ↑ = increase.

Although routine measurements of gastric pH (especially within the first 24 hours) have been recommended when histamine H_2 receptor antagonists are used, until now no studies have proved the superiority of pH-adjusted dosing over standard regimens.

Proton pump inhibitors provide more consistent pH control than histamine H_2 receptor antagonists. Compared with oral proton pump inhibitors, intravenous (IV) forms have the advantages of ease of administration, increased drug delivery to parietal cells and more rapid onset of action. Newer proton pump inhibitors are also devoid of the unwanted adverse effects on cytochrome P450, making them attractive alternatives for stress ulcer prophylaxis. In critically ill patients, IV administration of proton pump inhibitors, achieves and maintains gastric pH ≥4 within hours of initiation of therapy, with a progressive increase of pH within the first 48 hours.[85,86] On the other hand, continuous IV administration of histamine H_2-receptor antagonists is unable to maintain pH control by day two, despite achieving a gastric pH ≥4 initially. Until now, no large-scale study has specifically investigated the role of IV proton pump inhibitors in SRMD prophylaxis or whether more consistent increases in pH translate into better outcomes. Thus, the growing use of proton pump inhibitors in the ICU is without strong clinical data to support this practice in every critically ill patient.

As in the case with histamine H_2 receptor antagonists, antacids neutralize gastric acid in a dose-dependent fashion. Other beneficial effects include bile acid binding and increased mucosal prostaglandin production (particularly with antacids containing aluminum hydroxide). Frequent administration and pH monitoring render the use of antacids cumbersome and, consequently, antacids have become historical footnotes in stress ulcer prophylaxis in most ICUs.

Pirenzepine is another pH-altering drug that acts via activation of muscarinic (M_1) receptors and has been successfully used for stress ulcer prophylaxis in Europe. Other preventive strategies (e.g. sucralfate, misoprostol) provide cytoprotection via augmentation of mucosal defensive mechanisms and normalization of gastric mucosal microcirculation.[87]

Concerns About Prophylactic Therapy

Short-term use of either pH-altering or cytoprotective medications is relatively safe (incidence of adverse effects <1%).[88] The major concern with the use of pH-altering medications is their association with gastric colonization with *Enterobacteriacea* (due

Table III. Medications used for stress ulcer prophylaxis in mechanically ventilated patients (reproduced from Mutlu et al.,[2] with permission)

Medication	Mechanism of action	Other protective mechanisms	Complications/concerns
Antacids	Direct neutralization of gastric acid in a dose-dependent fashion; gastric pH is kept above 3.5–4.0	Bind to bile acids (Al^{+3}-based); increase local prostaglandin (PG) production; stimulate epithelial regeneration	Inconvenient and time consuming; increased nursing costs; hypermagnesemia (Mg^{+2}-based); hypophosphatemia (Al^{+3}-based); constipation (Al^{+3}-based); diarrhea (Mg^{+2}-based); interferes with absorption of certain drugs (e.g. tetracycline, quinolones)
Histamine H_2 receptor antagonists	Increase gastric pH by blocking histamine type 2 receptors	No cytoprotective effects	Tachyphylaxis; interstitial nephritis; confusion (especially elderly); thrombocytopenia; hypotension, sinus bradycardia (rapid IV infusion); cytochrome P450 enzyme-mediated effects (particularly cimetidine)
Proton pump inhibitors	Inhibit parietal cell H^+-K^+-ATPase and block the final step of H^+ ion production	No beneficial cytoprotective effects	Lack of data with IV formulations; diarrhea; cytochrome P450 enzyme-mediated effects
Sucralfate	No effect on luminal pH; cytoprotective; acts via coating and protection of gastric mucosa	Increases local production of PGs; stimulates mucus/HCO_3 production (independently of PG); stimulates epidermal growth factor	Antibacterial effects; constipation; interferes with the absorption of certain drugs (e.g. tetracycline, quinolones)
Prostaglandin analogs	Antisecretory and cytoprotective effects on the gastric mucosa	Inhibit acid secretion at high doses	Diarrhea; abdominal pain
Pirenzepine	Anticholinergic; inhibits acid secretion via M_1 muscarinic receptors	Increases local PG production; stimulates mucus/HCO_3 production (can occur independently of PG); improves mucosal blood flow (can occur independently of PG)	Not available in North America

IV = intravenous.

to increased gastric pH) and subsequent retrograde gastro-oropharyngeal contamination leading to an increased risk of ventilator-associated pneumonia (VAP).[89-91] When all studies that evaluated sequential colonization from stomach to trachea were considered, gastric colonization preceded tracheal colonization in 4–24% and VAP in 0–15% of patients.[92] Acidification of enteral feeding reduces the incidence of gastric colonization significantly, but not VAP.[93] Earlier reports[94-96] showing a lower incidence of VAP with sucralfate have been challenged by studies that reported only a trend[34,38] or no difference.[97-100] This lack of consensus can be attributed to the differences in study design, gastric pH measurement methods, medication dosage, timing of VAP (early vs late), gastric volume, simultaneous administration of enteral feeding and, more importantly, body position (supine vs semirecumbent), which may predispose an individual to gastro-oropharyngeal colonization. Based on available data, the risk of VAP attributable to pH-altering drugs can be minimized if clinicians carry out preventive measures, including keeping the patient in a semi-recumbent position, avoiding high gastric residuals and administering the enteral feeds into the small bowel whenever possible.

Supine positioning is an independent predictor of VAP, thus proper positioning may be more important than gastric pH.[101,102] Semi-recumbent positioning has been strongly recommended for the prevention of nosocomial pneumonia.[103] Thus, until the contribution of positional effects on reflux is determined, no firm conclusions can be made regarding whether gastric colonization leads to VAP.

Choice of Medication

There is no consensus on the drug of choice for stress ulcer prophylaxis. Several meta-analyses provide conflicting results on the superiority of any medication.[34,104-108] Discrepancies result from methodological problems in trials, inclusion of non-randomized studies, and differences in evaluated endpoints

(asymptomatic versus clinically evident versus important bleeding). Nevertheless, both pH-altering agents (histamine H_2 receptor antagonists, proton pump inhibitors [enteral form] and antacids) and sucralfate decrease the incidence of clinically significant bleeding by approximately 50% (from ~4% to 1.7–2%) and are effective in the prevention of clinically evident as well as significant stress ulcer bleeding.[34,107] Limited studies on combination therapy suggest better pH control, but no additional benefit in clinical outcomes compared with single agent therapy.[109,110]

Most deaths in patients with stress ulcer bleeding do not result from GI hemorrhage. Thus, the contribution of stress ulcer bleeding to overall ICU mortality does not appear to be significant in unselected ICU populations and routine prophylaxis in all patients is not warranted. Identification of patients at risk of stress ulcer bleeding appears to be more important than the particular medication used and can reduce unnecessary medication use and cost. Respiratory failure requiring mechanical ventilation for more than 48 hours and coagulopathy (defined as a platelet count of <50 000mm^3, an international normalized ratio of >1.5, or a partial thromboplastin time of more than twice the control value) are the two most important risk factors for stress ulcer bleeding. On the contrary, when neither of these risk factors are present, the incidence of clinically significant stress ulcer bleeding is negligible (0.1%).[28] Among mechanically ventilated patients, those who develop organ dysfunction (particularly renal failure) at any time during the ICU stay appear to be especially at high risk of stress ulcer bleeding.[35] Additional risk factors for which stress ulcer prophylaxis should be considered include sepsis, hypotension, hepatic failure, renal failure, major trauma, extensive burns and intracranial hypertension.

A functional GI tract is important in choosing regimens for ulcer prophylaxis (figure 5). When the enteral route is available, histamine H_2 receptor antagonists or sucralfate can be administered for the prevention of SRMD. Oral proton pump inhibitors should be considered as a second-line agent because of their lack of superiority over histamine H_2 receptor antagonists and difficulties encountered with their administration (i.e. clogging of enteral tubes). When the GI tract is not an option, intravenous histamine H_2 receptor antagonists should be used as a first-line agent. Routine use of proton pump inhibitors administered IV is not justified because there is a lack of evidence showing their superiority over histamine H_2 receptor antagonists in stress ulcer prophylaxis, and also because of their higher costs and the low incidence of clinically significant bleeding with aggressive hemodynamic support. Therefore, their use should be reserved for patients who have active GI bleeding prior to the development of critical illness. Proton pump inhibitors may also be used in patients in whom histamine H_2 receptor antagonists are contraindicated

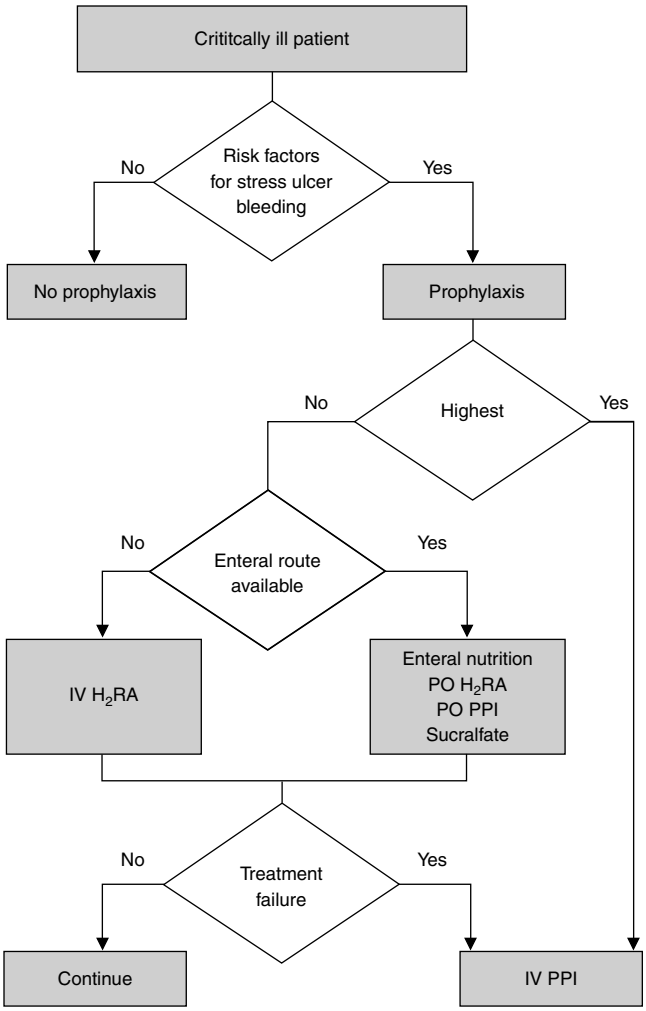

Fig. 5. Stress ulcer prophylaxis in mechanically ventilated patients. Choice of medication depends on the availability of the enteral route. When IV medications are considered, PPIs should be reserved for patients with active gastrointestinal bleeding and for those with the highest risk for hemorrhage. **H_2RA** = histamine H_2 receptor antagonist; **IV** = intravenous; **PO** = oral; **PPI** = proton pump inhibitor.

(e.g. severe thrombocytopenia, undesired drug interactions) or are ineffective (e.g. history of GI bleeding with histamine H_2-receptor antagonists or sucralfate). We believe that proton pump inhibitors administered IV should also be considered for patients with multiple risk factors for stress ulcer bleeding, such as coagulopathy, renal failure, or prolonged shock in addition to respiratory failure requiring mechanical ventilation. Patients with high gastric acid production (i.e. head trauma patients) may also potentially benefit from IV proton pump inhibitors. Among patients with visible vessels that are nonbleeding or adherent clots, who do not undergo endoscopic therapy, acid inhibition with proton pump inhibitors significantly reduces the rebleeding rate and the need for sur-

gery.[111] Similarly, even after endoscopic therapy, proton pump inhibitors provide a beneficial effect on hemostasis, which is a pH-dependent process.[112] Platelet aggregation and plasma coagulation are nearly abolished below a pH of 5.4 and fibrin clots may dissolve when the pH falls below 4.0. Therefore, in clinically evident or significant stress ulcer bleeding, proton pump inhibitors administered IV are preferable to histamine H_2-receptor antagonists as they maintain a more reliable pH control, which is essential for local hemostatic mechanisms.

Enteral Feeding

Enteral feeding may also decrease the risk of clinically evident GI bleeding.[35,48,49] The beneficial effects of enteral feeding are probably multifactorial, including dilutional alkalinization of gastric fluid and mucosal cytoprotection (by restoration of gastric epithelial energy stores).[35,113] The latter is a more likely, but unproven, explanation since the alkalizing effects of enteral feeding are variable and parenteral nutrition is also associated with reduced stress ulcer bleeding.[113] In a multicenter trial, histamine H_2 receptor antagonists provided stress ulcer prophylaxis regardless of whether or not patients were receiving enteral nutrition.[35] Furthermore, in another study, patients who were receiving only enteral nutrition for stress ulcer prophylaxis had a higher incidence of stress ulcer bleeding compared with those who were receiving prophylaxis with histamine H_2 receptor antagonists and/or antacids.[36] All studies that investigated the impact of enteral nutrition on stress ulcer prophylaxis were limited in several aspects, including differences in study designs, patient populations, type and amount of enteral formula administered, and lack of definition of stress ulcer bleeding. Therefore, in view of the limited data, the use of enteral nutrition as the only therapy for stress ulcer prophylaxis should be discouraged until more definitive studies comparing enteral nutrition with pharmacologic prevention are available. Initiation and discontinuation of pharmacologic prophylaxis should be independent of enteral nutrition.

3.1.2 Erosive Esophagitis

Prevention of erosive esophagitis requires maintenance of semi-recumbent positioning, judicious use of nasogastric tubes and the institution of strategies that improve gastric emptying and prevent gastroesophageal and duodenogastric reflux (e.g. metoclopramide).

3.2 Non-Hemorrhagic Complications

3.2.1 GI Hypomotility

Treatment options for GI hypomotility are limited; thus, preventive measures such as correction of electrolyte abnormalities (e.g. hypokalemia) and avoidance of medications that impair GI motility (i.e. opiates) are crucial.[22] β-Adrenoceptor stimulation with catecholamines delays orocecal and duodenocecal transit time.[114] A β-adrenoceptor agonist, isoproterenol (isoprenaline), inhibits contractility in the antrum and small intestine.[115] On the contrary, β-adrenoceptor blockade with atenonol or propranolol hastens both transit times.[114] In addition to β-adrenergic agonists and dopamine that may cause GI hypomotility at doses as low as 5 μg/kg/min, phenothiazines, diltiazem, verapamil, and drugs with anticholinergic adverse effects should also be avoided if possible.[116] If necessary, nasogastric suction and/or rectal tubes and, in intractable cases, colonoscopy, can be used to decompress the GI tract if significant dilation develops. Rectal tubes have been associated with complications, including discomfort, local ulceration, infection and perforation of the rectum, and should not be used unless necessary.

Prokinetic agents can be considered once mechanical obstruction is excluded (table IV). Withdrawal of cisapride from the US market two years ago has limited the treatment options to metoclopramide and erythromycin. The precise mechanism of action of metoclopramide is unclear, but it improves antroduodenal coordination and reverses the inhibitory effects of dopamine on GI motility. Similar improvement is achieved with erythromycin 200mg once daily via its action on motilin receptors.[117,118] It is noteworthy that an intact vagal pathway is necessary for erythromycin's beneficial effects on the GI tract.[119] Although not proven, the use of erythromycin could conceivably contribute to overgrowth of resistant bacteria (due to subinhibitory concentrations of antibacterials that may promote bacterial resistance). Prucalopride is a novel enterokinetic that enhances gastric, small bowel and colonic motility via its excitatory effect on serotonin 5-HT_4 receptors. It may prove useful in improving GI hypomotility in critically ill patients.[120]

Domperidone, a peripheral type 2 dopamine receptor antagonist, regulates the motility of gastric and small intestinal smooth muscle with some effects on the motor function of the esophagus.[121] It has been shown to increase the duration of antral and duodenal contractions and increase gastric emptying. It also has antiemetic activity as a result of blockade of dopamine D_2 receptors in the chemoreceptor trigger zone of the brainstem. Because only a small amount of domperidone crosses the blood-brain barrier, adverse effects in the CNS (i.e. extrapyramidal adverse effects) are rare. Domperidone is not available in the US, but can be obtained in Canada or Mexico.

Bethanechol is a synthetic parasympathomimetic that acts directly on muscarinic acetylcholinergic receptors. Stimulation of muscarinic receptors restores GI peristalsis, increases motility, and increases the resting lower esophageal sphincter pressure. How-

Table IV. Treatment options for gastrointestinal hypomotility in mechanically ventilated patients

Medication	Mechanism of action	Dosage	Concerns/comments/adverse effects
For upper GI hypomotility			
Metoclopramide	Unclear	10mg every 6–8h given orally; 10mg every 6–8h given IV	Restlessness, dizziness, anxiety, drowsiness, extrapyramidal effects, diarrhea, confusion, irritability, dose needs to be adjusted in renal failure
Erythromycin	Acts via motilin receptors	3 mg/kg once daily (IV, in 1 hour; ~200mg in 70kg patient)	Emergence of bacterial resistance (major concern), nausea, vomiting, abdominal pain, cramps, hepatotoxicity, elevated transaminases, erythema multiforme
Domperidone (not commercially available in the US)	Dopamine D_2 receptor antagonist	10–20mg every 6–8h given orally	Hyperprolactinemia
Bethanechol	Cholinergic receptor agonist	25–50mg every 6–8h given orally; 5mg every 6–8h given IV	Cholinergic effects (bronchospasm, flushing, diarrhea, abdominal pain, nausea, tachycardia, negative inotropy, hypotension, lacrimation, diaphoresis, increased gastric acid secretion)
CIRC or Ogilvie's syndrome			
Neostigmine	Cholinergic effects; inhibits acetylcholine-esterase	2mg over 3–5 min or 0.4–0.8 mg/h over 24h (IV)	Bradycardia, increased airway secretions, bronchospasm, cardiac arrest, dose needs to be adjusted in renal failure (glycopyrrolate diminishes central cholinergic effects)

CIRC = critical illness-related colonic hypomotility; **GI** = gastrointestinal; **IV** = intravenous.

ever, its use is significantly limited by cholinergic adverse effects.[1]

Neostigmine has been successfully used as a therapeutic tool for CIRC and Ogilvie's syndrome.[50,122] Major concerns regarding the use of neostigmine include bradycardia, increased airway secretions and bronchial reactivity. Concomitant treatment with neostigmine and the anticholinergic agent glycopyrrolate has been reported to diminish the central cholinergic effects of neostigmine without diminishing its effect on colonic motility.[123]

3.2.2 Diarrhea

Treatment of diarrhea depends on the underlying cause. The inability to identify the exact cause often complicates the picture and limits care. *Clostridium difficile* should always be considered in the differential diagnosis. When diarrhea is present, antibacterial therapy should be discontinued, if possible, otherwise oral metronidazole should be initiated. Oral vancomycin is effective, but should be reserved for patients who cannot tolerate or do not respond to metronidazole or for those who are in the first 20 weeks of pregnancy. Diarrhea associated with enteral feeding is generally self-limited and subsides with a reduction in feeding rate. If possible, hyperosmolar formulas should be replaced with isotonic tube feedings. Neither routine use of peptide-based enteral formulas nor the addition of fiber offer any benefit over standard formulas (with whole protein) in terms of reducing the incidence of diarrhea.[124-128] Nonetheless, peptide-based enteral formulas may be considered in patients with severe hypoalbuminemia (albumin <2.6 g/dL) and diarrhea.[124-126]

3.2.3 Acalculous Cholecystitis

The only strategy that has been proposed in prevention of acalculous cholecystitis is daily stimulation of gallbladder contraction with IV CCK, which has been shown to be effective in patients receiving total parenteral nutrition.[129] Because prolonged fasting and resultant biliary sludge are known risk factors for acalculous cholecystitis,[73] we believe that early enteral nutrition and maintenance of normal hemodynamics are important in the prevention of acalculous cholecystitis. Although CCK may potentially be beneficial in critically ill patients, particularly those who cannot be fed enterally, its efficacy and cost effectiveness have not been well established.

Early diagnosis is critical in preventing the high morbidity and mortality (up to 50%) associated with acalculous cholecystitis.[76] The diagnosis may often be unrecognized due to the complexity of underlying medical and surgical problems and the lack of reproducible signs and biochemical parameters. Aspiration of the gallbladder has a limited role in the diagnosis of acalculous cholecystitis because of its low sensitivity.[130] Diagnosis relies on imaging studies, particularly ultrasonography, which has become the modality of choice. While lacking specificity, major ultrasonographic criteria include biliary sludge, gallbladder distention (hydrops) and gallbladder wall thickening in the absence of ascites and hypoalbuminemia. Because of high false-positive rates in critically ill patients, who frequently are fasting and have viscous bile, hepatobiliary scintigraphy is better at excluding than confirming the diagnosis of acalculous cholecystitis.[131]

Although cholecystectomy has been the traditional approach, it is not always feasible because of the severity of underlying disease in ICU patients. In high-risk patients, percutaneous cholecystostomy is an acceptable option with a low procedure-related risk and a success rate >60%.[76,132] Transpapillary endoscopic cholecystostomy is another treatment modality for those who are poor candidates for the percutaneous approach.

4. Conclusions

Mechanically ventilated patients frequently develop GI complications, some of which can be seen in up to 50% of patients. While it remains unclear to what extent these complications influence mortality, they are undoubtedly associated with significant morbidity, rendering the care of critically ill patients more difficult and increasing the length of ICU stay and costs. The properties of splanchnic vasculature put mechanically ventilated patients at risk of a variety of GI complications that can impact on the outcome of critically ill patients. Maintenance of splanchnic perfusion appears to be important in the prevention of these complications. Since normal hemodynamics cannot always be achieved, pharmacologic prophylaxis remains the mainstay of preventive strategies.

Improved understanding of the systemic effects of mechanical ventilation and greater application of lung-protective ventilatory strategies may potentially minimize positive pressure-induced reductions in splanchnic perfusion, and systemic cytokine release, and consequently reduce the incidence of GI complications associated with mechanical ventilation. Unquestionably, more studies are warranted to better understand the systemic effects of mechanical ventilation on the GI tract and to investigate the impact of lung-protective ventilatory strategies on GI complications. In the meantime, preventive, evidence-based strategies remain important in reducing the impact of these complications and improving outcomes in critical illness.

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