Mechanical ventilation (MV) is a lifesaving therapy with a myriad of organ-system complications that can significantly affect the outcome of critically ill patients. Like other organ systems, GI complications may be directly attributable to MV, but most are a reflection of the disease process that required intensive care. Incorporated in this review are discussions of the most prevalent GI complications associated with MV, such as stress ulcer and GI hypomotility (Table 1). The current diagnosis and management of these conditions and other less common complications are also included.

**For editorial comment see page 996**

INTERACTIONS BETWEEN MV AND CRITICAL ILLNESS

The interactions between critical illness and MV and their effect on the GI tract are complex. MV can contribute to the pathogenesis of GI problems in much the same way as critical illness. Unfortunately, the coexistence of critical illness makes it impossible to determine if MV is directly responsible for the GI complications seen in patients receiving MV. Thus, while the association exists, it is not clear whether there is a direct causal relationship between MV and GI complications. Table 2 summarizes these complications on an organ basis. Nevertheless, in view of experimental and human data, it is reasonable to conclude that in many instances, MV may potentiate the adverse effects of an underlying critical illness and worsen GI pathophysiology.

Among several mechanisms suggested to explain how MV unfavorably affects the GI tract, splanchnic hypoperfusion appears to be particularly important (Fig 1). Conceptually, this is exemplified by the critical role that gastric mucosal hypoperfusion plays in the pathogenesis of stress-related mucosal damage (SRMD), which is discussed in detail below. Splanchnic hypoperfusion during MV can occur as a consequence of (1) decreased mean arterial pressure and/or (2) increased resistance in the GI vascular bed.
Moreover, these patients frequently have elevated catecholamines because of sympathetic activation.13–15 These neurohormonal alterations can contribute significantly to splanchnic hypoperfusion by leading to vasoconstriction and redistribution of blood away from the splanchnic vascular bed.16,17 Whether because of decreased cardiac output and/or increased vascular resistance, splanchnic hypoperfusion produces an imbalance between oxygen supply and demand (a relative oxygen shortage) that may contribute to the development of GI complications, such as mucosal damage (eg, stress ulcer) and/or altered GI motility (eg, ileus).16–18 Perhaps more concerning than splanchnic hypoperfusion itself is reperfusion injury and further damage to GI epithelial cells that may occur after restoration of blood flow after prolonged periods of hypoperfusion.19 Repetitive episodes of hypoperfusion followed by reperfusion may be responsible for acute nonocclusive mesenteric ischemia in the critical-care setting.20 Recent advances in our understanding of the adverse effects of MV suggest an important role for cytokines in the pathogenesis of GI complications. Cytokines (eg, tumor necrosis factor-α, interleukin [IL]-1, and IL-8) are inflammatory mediators that can affect many organs and elicit a variety of physiologic and biochemical responses to critical illness.21 They cause a series of intracellular signaling events via highly specific cell surface receptors that typically result in elaboration of other cytokines within the target cell. If these processes are not attenuated, excessive amplification of the inflammatory cascade and overproduction of proinflammatory mediators can occur with the consequent uncontrolled activation of the immune system.21,22 These processes can lead to a number of clinical sequelae in the GI tract as a part of multiple organ dysfunction syndrome (MODS).23,24 Cytokines may contribute to splanchnic hypoperfusion as well, and may also impair intestinal smooth muscle function.16,25–27 In animals, MV with “injurious” (large tidal volume, high end-inspiratory pressures) ventilatory strategies has been shown to cause an increase in production of pulmo-

### Table 1—GI Complications Seen in Patients Receiving MV

<table>
<thead>
<tr>
<th>Complications</th>
<th>Incidence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erosive esophagitis</td>
<td>48</td>
</tr>
<tr>
<td>SRMD</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic, endoscopically</td>
<td>74–100</td>
</tr>
<tr>
<td>Clinically evident bleeding</td>
<td>5–25</td>
</tr>
<tr>
<td>Clinically significant bleeding</td>
<td>3–4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15–51</td>
</tr>
<tr>
<td>Decreased bowel sounds</td>
<td>50</td>
</tr>
<tr>
<td>High gastric residuals</td>
<td>39</td>
</tr>
<tr>
<td>Constipation</td>
<td>15</td>
</tr>
<tr>
<td>Ileus</td>
<td>4–10</td>
</tr>
<tr>
<td>AAC</td>
<td>0.2–3</td>
</tr>
</tbody>
</table>

### Table 2—Organ-Specific GI Complications During MV

<table>
<thead>
<tr>
<th>Organs</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus and stomach</td>
<td>Erosive esophagitis</td>
</tr>
<tr>
<td>GER</td>
<td>Stress ulcer</td>
</tr>
<tr>
<td>Stress ulcer</td>
<td>Impaired gastric emptying</td>
</tr>
<tr>
<td>Intolerance to enteral nutrition</td>
<td></td>
</tr>
<tr>
<td>Small intestines and colon</td>
<td>Stress ulcer</td>
</tr>
<tr>
<td>Ileus</td>
<td>Colonic pseudo-obstruction</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Altered intestinal microflora</td>
</tr>
<tr>
<td>Bacterial overgrowth</td>
<td>Intestinal luminal toxins</td>
</tr>
<tr>
<td>Possibility of acute nonocclusive mesenteric ischemia</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>Increased transaminase and/or bilirubin levels</td>
</tr>
<tr>
<td>Impaired hepatic function</td>
<td>Impaired drug metabolism</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>Atonic gallbladder</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Possibility of acalculous cholecystitis</td>
</tr>
<tr>
<td>Possibility of acute pancreatitis</td>
<td></td>
</tr>
<tr>
<td>Impaired hepatic function</td>
<td>Impaired drug metabolism</td>
</tr>
<tr>
<td>Impaired hepatic function</td>
<td>Impaired drug metabolism</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Asymptomatic rise in amylase and lipase levels</td>
</tr>
<tr>
<td>Possibility of acute pancreatitis</td>
<td></td>
</tr>
</tbody>
</table>
nary cytokines, as well as increasing alveolar capillary permeability that would increase the transfer of intrapulmonary cytokines from lungs to the systemic circulation. Recently, these data were confirmed in humans by Ranieri and colleagues, who demonstrated that injurious ventilatory strategies (high end-inspiratory pressures) are associated with greater increases in cytokine levels in both BAL and serum than a lung “protective” ventilatory strategy (low end-inspiratory pressures). Moreover, both high peak pressures as well as the absence of PEEP have been shown to increase bacterial translocation from the lung into the bloodstream in animal models of intratracheal instillation of bacteria, providing another mechanism by which MV can produce systemic manifestations. Growing evidence in regards to increased cytokines during MV (particularly with injurious strategies) suggests a potentially critical role for MV in the initiation and propagation of a systemic inflammatory response that may include dysfunction and damage to the GI tract.

The potential contribution of MV to the development of GI complications is not limited to its indirect effects on the GI tract. Medications that are frequently used to facilitate MV such as opiates and sedatives, particularly benzodiazepines, may decrease GI motility and impair venous return via venodilation and/or diminution of responsiveness to vasoressor agents. Other commonly used medications that are frequently associated with GI complications in patients receiving MV include vasoressors (as discussed above), antibiotics, and additives in oral medications (e.g., sorbitol).

Critical illness may promote GI complications via adverse effects on splanchnic blood flow and increased levels of proinflammatory mediators. In the last decade, alterations at the cellular level have become a focus of study as several investigators have suggested a role for altered gut barrier function in the pathogenesis of MODS. Decreased mucosal perfusion appears to play a pivotal role in intestinal mucosal injury; however, other consequences of critical illness such as malnutrition and altered intestinal microflora may also threaten GI epithelial cells. As a result of these unfavorable changes, gut barrier function can be compromised during critical illness. Gut barrier function is dependent on integrity of mucosal cells and intracellular junctions, mucus production, gut-associated lymphoid tissue, and secretory IgA production, all of which may be impaired during stressful events. Although not clearly established in humans, it is reasonable to presume that alterations in barrier function may allow the passage of proinflammatory mediators (e.g., endotoxin) and possibly microorganisms from intestinal lumen to the bloodstream. This process can become self-sustaining if the underlying disease that initiates the cascade is not abbreviated.

As described above, the complexity of interactions between critical illness and MV on the GI tract necessitates that intensivists understand the pathogenesis of GI complications to allow appropriate management as well as prospective use of preventive practices. Conceivably, critical illness may serve as a “priming” factor that allows MV to affect the GI tract. Thus, the combination of effects of critical illness and MV may create an ideal environment for the development of these complications.
GI Hemorrhage

Critically ill patients, especially those who are receiving MV, are prone to a spectrum of GI mucosal lesions that may result in GI hemorrhage. Acute respiratory failure requiring MV for > 48 h has been shown to be one of the two strongest independent risk factors for clinically important GI bleeding in the ICU. It is not clear, however, whether MV contributes to the pathophysiology of GI bleeding or if it is simply a marker of severity of critical illness.

SRMD

Background and Clinical Significance: SRMD is the most common cause of GI bleeding in patients receiving MV. Within a few hours of critical illness, macroscopic damage becomes evident as subepithelial petechiae progress to lesions ranging from superficial erosions to true gastric ulcers. These mucosal lesions tend to be multiple and occur predominantly in the fundus of the stomach, typically sparing the antrum. Distal (antral and duodenal) mucosal erosions and/or ulcers can also develop, although they typically appear later, tend to be deeper, and may be associated with a higher incidence of bleeding.

Most (74 to 100%) critically ill patients have endoscopically detectable mucosal erosions and subepithelial hemorrhage within 24 h of admission to the ICU. These lesions are generally asymptomatic and may or may not produce occult fecal blood. Symptomatic lesions have a wide spectrum of clinical presentations including occult, overt, or clinically significant bleeding. Overt bleeding includes frank hemorrhage, which is generally easy to detect based on the appearance of hematemesis, melena, coffee-ground–like material in nasogastric tube aspirates, or hematochezia. Clinically significant or life-threatening bleeding is defined as bleeding that causes hemodynamic changes or necessitates transfusion. Patients receiving MV who develop clinically significant bleeding generally do so within the first 2 weeks of their ICU stay.

Because erosions are strictly mucosal lesions and therefore involve only small vessels, clinically detectable bleeding typically does not occur unless true ulcer develops. By definition, ulcers extend beyond the mucosa and into the submucosa and muscularis propria where they can erode into larger arteries (Fig 2). Overt bleeding because of SRMD occurs in up to 25% of critically ill patients who do not receive prophylactic therapy. Approximately 20% of clinically evident hemorrhages (ie, 5% of all critically ill patients) are also clinically significant, such that they cause hemodynamic changes or necessitate transfusion. Thus, the overall incidence of clinically significant GI bleeding in patients not given prophylactic treatment for SRMD is approximately 3 to 4%, ranging from 0.6 to 5%. Clinically significant stress ulcer bleeding is associated with increased morbidity and has been shown to increase ICU length of stay (and cost) by as much as 11 days. Similarly, mortality has also been shown to be several-fold higher in patients who develop stress ulcer bleeding compared with those...
who do not; importantly, these patients generally die of their primary disease process, not GI hemorrhage.34,35

Pathophysiology of SRMD: SRMD occurs because of complex interactions of injurious gastric luminal factors (eg, gastric acid, pepsin), reduced mucosal blood flow, reduced intramucosal pH, and impaired gastric defense mechanisms (Fig 3).44–46 Gastric acid appears to be essential for stress ulceration, but it is not the only pathogenetic factor. In most clinical situations associated with SRMD, luminal hyperacidity is not identified and, indeed, gastric fluid pH is not different from normal (24-h mean gastric pH of approximately 2; range, 1 to 3).2,47 Nevertheless, gastric fluid is still acidic and provides enough hydrogen ions to keep the gastric mucosa under constant attack. Interestingly, some critically ill patients, particularly the elderly, and those with severe underlying illness may have increased gastric pH (> 4) even without prophylactic therapy.48,49 However, hyperacidity has been suggested to be important in some patients with head trauma and thermal injuries.50,51 Other injurious luminal factors include pepsin and bile (because of duodenogastric reflux), but their precise roles in the pathogenesis of SRMD are not completely established. Better understood is how mucosal ischemia because of decreased splanchnic blood flow contributes to the development of SRMD.41,52 Mucosal ischemia decreases the capacity to neutralize hydrogen ions and contributes to intramural acidosis, cell death, and ulceration.53,54 Ischemia also may compromise gastric energy metabolism and impair protective processes (eg, mucus production), especially in the fundus where most stress-related injury develops.41,54 Collectively, the imbalance between the injurious effects of gastric acid and the protective and “reparative” mechanisms that are impaired because of local mucosal ischemia predispose patients receiving MV to stress-related mucosal erosions and ulcers.

Prophylactic Treatment: The incidence of bleeding from SRMD appears to be decreasing, probably because of better care of ICU patients and prevention of mucosal hypoperfusion and acidosis.55,56 In a study of 167 patients receiving MV without stress ulcer prophylaxis, Zandstra and Stoutenbeek43 showed that aggressive hemodynamic support to ensure adequate tissue perfusion resulted in near complete lack of GI bleeding (only one patient, 0.6%). As it is not always possible to maintain mucosal blood flow, other prophylactic measures have gained importance. Because at least some acid is essential for the development of stress ulceration, therapies that target gastric acid not surprisingly decrease the incidence of SRMD and thus have become mainstays of prevention. Table 3 summarizes the mechanisms of actions of the currently available treatment modalities that are effective in providing stress ulcer protection.37,57–61 Among pH-altering drugs, while some inhibit acid secretion (eg, histamine type-2 [H2]-receptor antagonists, proton pump inhibitors), others neutralize luminal acid (antacids) with no impact on production or secretion. Medications in this class prevent stress ulcer formation by raising the gastric fluid pH (ideally > 4.0) in a dose-dependent fashion, which results in a significant reduction of diffusion of hydrogen ions back across the mucosa. While continuous administration of H2-receptor antagonists may provide more effective acid inhibition compared to intermittent dosing, the relevance of this practice is not known.62,63 A continuous rise in pH value > 4 is not guaranteed even with high doses of H2-receptor antagonists.58 Although routine measurements of gastric pH (especially within the first 24 h) are recommended when H2-receptor antagonists are used, until now (to our knowledge) no studies have proven the superiority of pH-adjusted dosing over the standard regimen. Like H2-receptor antagonists, antacids neutralize gastric acid

![Figure 3. Proposed mechanisms for development of stress ulceration. SRMD results from the complex interaction of multiple systems. The specific relationships depicted remain somewhat speculative. Reprinted with permission from Bresalier.44](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21961/)
in a dose-dependent fashion. Frequent pH monitoring has been widely recommended when antacids are used in prevention of SRMD. This recommendation is intended to achieve effective (pH 3.5–4.0), continuous increases in gastric pH.64 This practice typically requires that antacids should be administered at 1- to 2-h intervals. However, controversies about pH-adjusted and “unguided” low-dose and high-dose antacid therapy in the treatment of peptic ulcer disease also raise questions about the validity of frequent pH monitoring in prevention of SRMD.65–68 The knowledge that beneficial effects of antacids are not limited to their acid neutralizing properties, but also include bile acid binding69 and increased mucosal prostaglandin production70 (particularly with antacids containing aluminum hydroxide) may explain the successful prevention of SRMD even when antacid administration is not based on pH measurements. Another pH-altering drug is pirenzepine, which is an anticholinergic that acts via muscarinic (M1) receptors. It has been successfully used for stress ulcer prophylaxis but is not available in North America.60 Other preventive strategies (eg, sucralfate, misoprostol) provide cytoprotection via augmentation of mucosal defensive mechanisms and normalization of gastric mucosal microcirculation.71–73 These prophylactic measures reduce clinically important bleeding rates by 50%. Although a national survey has shown that two thirds of physicians prefer H₂-blockers as prophylactic therapy, the optimal treatment regimen continues to be the subject of debate.74 Respondents to this recent survey selected ranitidine (31%) mostly because of ease of administration, famotidine (24%) because of formulary availability, sucralfate (24%) for a better side-effects profile, and cimetidine (12%) for cost-effectiveness.

Table 3—Properties of Medications Used for Stress Ulcer Prophylaxis*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mode of Action</th>
<th>Other Protective Mechanisms</th>
<th>Comments/Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antacids</td>
<td>Direct neutralization of gastric acid in a dose-dependent fashion</td>
<td>Binds to bile acids (Al⁺³ based)</td>
<td>Increased nursing costs</td>
</tr>
<tr>
<td></td>
<td>Gastric pH is kept &gt; 3.5–4.0</td>
<td>Increases local PG production</td>
<td>Hypermagnesemia (Mg⁺² based)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>improved mucosal blood flow</td>
<td>Hypophosphatemia (Al⁺³ based)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>increased mucus/HCO₃ production</td>
<td>Constipation (Al⁺³ based)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stimulates epithelial regeneration</td>
<td>Diarrhea (Mg⁺² based)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Interferes with absorption of certain drugs (eg, tetracycline, quinolones)</td>
</tr>
<tr>
<td>H₂-Blockers</td>
<td>Increase gastric pH by blocking H₂-receptors</td>
<td>No beneficial cytoprotective effects</td>
<td>Continuous provides better pH control for intermittent, but is not more effective as a preventive therapy</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>Inhibits parietal cell H⁺-K⁺-adenosine triphosphatase and blocks the final step of H⁺ ion production</td>
<td>No beneficial cytoprotective effects</td>
<td>Interstitial nephritis</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>Aluminum sucrose sulfate</td>
<td>Increases local PG production</td>
<td>Confusion (especially elderly)</td>
</tr>
<tr>
<td></td>
<td>Does not affect the luminal pH</td>
<td>Stimulates mucus/HCO₃ production (independently of PG)</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Acts via coating and protection of gastric mucosa</td>
<td>Stimulates epidermal growth factor</td>
<td>Hypotension, sinus bradycardia (rapid IV infusion)</td>
</tr>
<tr>
<td>Prostaglandin analogs</td>
<td>Antisecretory and cytoprotective effects on the gastric mucosa</td>
<td>Inhibits acid secretion at high doses</td>
<td>P450-mediated effects (particularly cinetidine)</td>
</tr>
<tr>
<td>Pirenzepine</td>
<td>Anticholinergic</td>
<td>Increases local PG production</td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td>Inhibits acid secretion via M₁ muscarinic receptors</td>
<td>Stimulates mucus/HCO₃ production</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improves mucosal blood flow (2 and 3 can occur independently of PG)</td>
<td></td>
</tr>
</tbody>
</table>

*PG = prostaglandin.
meta-analyses of preventive therapies have been conflicting. Disagreements result from methodologic problems in evaluated trials, inclusion of nonrandomized studies, and differences in evaluated end points. In two earlier meta-analyses, Shuman et al and Lacroix et al found that H2-blockers and antacids were equally effective in reducing overt bleeding as compared to no prophylaxis. In a subsequent overview in which both overt and clinically important bleeding were combined, Tryba confirmed these findings, and even suggested a tendency in favor of antacids. Contradicting these results, Cook and colleagues found that antacids were less efficacious than H2-blockers and had only a nonsignificant trend toward decreased overt bleeding when compared with no prophylaxis.

Similarly, differences among meta-analyses of sucralfate vs H2-blockers exist. Although both initial meta-analyses suggested that sucralfate was associated with a lower rate of overt bleeding than H2-blockers, this reduction reached statistical significance in only one study. A more recent meta-analysis by Cook et al showed a trend that favored sucralfate with respect to preventing overt bleeding with an odds ratio of 0.89 (95% confidence interval, 0.63 to 1.27). More importantly, there was no evidence that sucralfate, antacids, and H2-blockers differ with respect to the prevention of clinically important bleeding. Complicating these previous results, a more recent randomized trial demonstrated a significantly lower risk of clinically important GI hemorrhage in patients receiving H2-receptor antagonists compared to sucralfate (1.7% vs 3.8). Surprisingly, when compared to the risk in historical control subjects (3.7%), sucralfate (3.8%) had no effect on overt bleeding in this study. More importantly, there was no difference between treatments in terms of overall mortality or length of ICU stay. Despite the emergence of conflicting data from this most recent large study by Cook et al, both sucralfate and H2-blockers appear to be effective in prevention of clinically important stress ulcer bleeding. Finally, studies that have examined the efficacy of various combination therapies, including H2-blockers with antacids and H2-blockers with pirenzepine, have not shown any superiority in clinical outcomes compared to single-agent therapy, despite better control of gastric pH with combination therapy.
Another preventive strategy that seems to decrease the risk of overt GI bleeding in patients receiving MV is enteral feeding. The precise mechanism of this beneficial effect is not known and is probably multifactorial. Enteral feeding may prevent SRMD by providing cytoprotection by restoration of gastric epithelial energy stores and dilutional alkalization of gastric fluid. Because its effects on gastric pH are variable, cytoprotection remains to be a more likely explanation (however not proven) for reduction in stress ulcer bleeding. Interestingly, parenteral nutrition alone has been reported to provide stress ulcer prophylaxis comparable to standard preventive therapy. While a recent randomized multicenter trial reported that H2-blockers offer stress ulcer prophylaxis regardless of whether the patients receive enteral nutrition, to our knowledge, there has been no direct comparison of enteral feeding and stress ulcer prophylaxis. Further studies investigating relative effectiveness of enteral nutrition vs stress ulcer prophylaxis on GI bleeding outcomes are warranted.

Concerns About Prophylactic Therapy: Side effects ascribed to antacids, H2-receptor antagonists, and sucralfate are uncommon and occur in <1% of patients, particularly when administered on a short-term basis. However, concerns regarding the possibility of increased risk of pneumonia because of gastric colonization have led to numerous investigations regarding the use of antacids and H2-blockers in critically ill patients. Stress ulcer prophylaxis with antacids and/or H2-blockers raises gastric pH and increases colonization of the stomach with Enterobacteriaceae. Retrograde oropharyngeal contamination by colonized gastric contents and subsequent aspiration to the lower airways have been suggested to cause nosocomial pneumonia. Studies showing that supine positioning is an independent predictor of ventilator-associated pneumonia (VAP) support the importance of gastro-oropharyngeal colonization. In view of available evidence, the Centers for Disease Control and Prevention has recommended semirecumbent positioning to prevent nosocomial pneumonia.

While there is a wealth of data implicating the stomach as a reservoir for microorganisms causing VAP, there is an ongoing controversy about the contributory roles of gastric pH and colonization and subsequent aspiration. Confirming the role of gastric acidity and the importance of gastro-oropharyngeal route are studies reporting lower incidences of nosocomial pneumonia in patients who received sucralfate than patients who received pH-altering drugs. Gastric colonization may be particularly important in the pathogenesis of late-onset VAP (>4 days of MV). A recent meta-analysis and a large randomized controlled trial by Cook et al. corroborate these previous investigations by showing a "trend" toward a lower incidence of pneumonia in patients who received sucralfate compared to other prophylactic measures that alter gastric pH. Other investigators have challenged the importance of the gastro-oropharyngeal route. In a randomized trial of 141 patients receiving MV, Bonten et al. found that antacids and sucralfate had similar effects on gastric acidity, colonization rates, and incidence of VAP. High gastric pH influenced colonization of the stomach but not of the upper respiratory tract or the incidence of VAP. When all studies that evaluated the sequential colonization from the stomach to the trachea were considered, gastric colonization preceded tracheal colonization in 4 to 24% and VAP in 0 to 15% of patients. A recent small prospective trial of acidification of enteral feeding reduced the incidence of gastric colonization (2% vs 43%) but failed to show any beneficial effects on the incidence of VAP.

Although the gastro-oropharyngeal route may not be the predominant mechanism for nosocomial pneumonia, there is some evidence that supports its importance if certain precautions (eg, recumbent body position) are not undertaken. The variability of published data and the resulting controversy are most likely because of the differences in study design, measurement of gastric pH, dose of drugs administered, definition of VAP, body position (supine vs semirecumbent), gastric volume, and whether patients received simultaneous enteral feeding. More studies, particularly those controlled for the body position, are warranted to clarify the relative contribution that gastric colonization makes to the development of VAP. Until then, the risk of VAP attributable to stress ulcer prophylaxis with pH-altering drugs can be minimized if clinicians carry out preventive measures, including keeping the patient in a semirecumbent position, avoiding high gastric residuals, and administering the enteral feedings into the small bowel as opposed to the stomach. While placing the feeding tube beyond the stomach may prevent the undesirable effects of enteral feeding, such as gastric colonization and distention, it may hinder the beneficial effects of dilutional alkalization on stress ulcer. At this time, to our knowledge, there is no study comparing the relative risks and benefits of such practice.

Currently, there is no consensus on the drug of choice for stress ulcer prophylaxis. Despite recent conflicting evidence, both pH-altering medications and sucralfate appear to effectively prevent overt stress ulcer bleeding. The choice of drug depends on the availability of enteral route for drug administration. Until parenteral proton pump inhibitors become available, H2 antagonists remain the only option for IV use in North America. When enteral
administration is feasible, both H₂ antagonists and sucralfate can be administered for prophylaxis. Increasing use of duodenal tubes limits the use of sucralfate because it needs to be administered into the stomach in order to be effective. Antacids remain an alternative, but frequent administration makes their use cumbersome. Proton pump inhibitors are reasonable options; however, they are expensive, lack well-designed controlled studies, and are therefore second-line agents. Nevertheless, it is important to mention that a small, double-blind, placebo-controlled study showed that omeprazole may decrease the rate of further bleeding and the need for surgery in patients with recent ulcer-related upper-GI tract bleeding, particularly in those with visible vessels or adherent clots. Because of the small study size and the lack of therapeutic endoscopy, which is contrary to the current practice, these findings cannot be easily applied to the current management of ulcer-related hemorrhage in Western countries. More importantly, the study failed to show a significant difference in mortality between the omeprazole-treated group and the placebo-treated group. It is also noteworthy that in an earlier study, when all patients, not only those with evidence for recent bleeding, were evaluated, omeprazole therapy provided no advantage with respect to rates of rebleeding, transfusion requirements, need for surgery, or mortality.

The identification of patients who might benefit from prophylactic therapy appears to be more important than the particular medication used. Although it is widely practiced, not all critically ill patients need prophylaxis for SRMD. Moreover, no evidence is available (to our knowledge) to suggest that stress ulcer prophylaxis improves mortality in critically ill patients. This is probably because most deaths in patients with stress ulcer bleeding are not because of GI hemorrhage. In unselected ICU populations, the contribution of stress ulcer bleeding to overall ICU mortality does not appear to be significant; however, this may not be the case in high-risk patients. In a study that evaluated the cost-effectiveness of stress ulcer prophylaxis, Ben-Menachem et al. concluded that “the cost of prophylaxis is substantial, and may be prohibitive in ICU patients at low-risk of developing stress-related hemorrhage.” Current evidence suggests that patients with respiratory failure requiring MV for >48 h and those with coagulopathy (defined as a platelet count of < 50,000/µL, an international normalized ratio of > 1.5, or a partial thromboplastin time more than twice the control value) are at the highest risk and should receive prophylactic therapy. The incidence of clinically significant stress ulcer bleeding in patients without respiratory failure or coagulopathy appears to be negligible (0.1%). Among patients receiving MV, those who develop organ dysfunction, particularly renal failure, at any time during their ICU stay appear to be at especially high risk for stress ulcer bleeding. 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 (Table 5).

**Esophagitis**: Esophageal mucosal injury or erosive esophagitis occurs in nearly 50% of patients receiving MV and accounts for one fourth of all upper-GI bleedings in ICU patients. Potential mechanisms of esophageal injury in critically ill patients are nasogastric tubes, gastroesophageal reflux (GER), and duodenogastroesophageal (bile) reflux. Nasogastric tubes cause mechanical irritation and interfere with normal esophageal motility and sphincter function. Patients with nasogastric tubes also have a higher incidence of GER compared to those without it. Although supine body position contributes to the increased incidence of GER in patients receiving MV, restoration to semirecumbent position does not provide complete protection. In a prospective study of 15 patients who had both intratracheal and nasogastric intubations, Orozco-Levi et al. showed the presence of GER irrespective of body position. This study emphasized a pivotal role of the nasogastric tube in the development of GER. In another recent prospective study, the use of smaller-sized nasogastric tubes (external size, 2.85 mm vs 6 mm) did not affect the incidence of GER in ICU patients receiving MV. These results corroborate studies from healthy volunteers, which also show that the size of a nasogastric tube is not an important determinant of GER in normal subjects during short-term nasogastric intubation. While GER is common in patients receiving MV, the standard use of stress ulcer prophylaxis makes acid-
induced mucosal damage a less likely explanation for esophagitis.113,117 In a study111 of 25 patients receiving MV, only 1 of 12 patients (8%) with esophagitis was found to have pathological acid reflux, whereas 9 patients (75%) had evidence of bile reflux, suggesting that chemical injury induced by duodenogastroesophageal reflux and direct trauma caused by nasogastric tubes are the most important factors in the pathogenesis of esophageal mucosal injury. The severity of esophagitis correlates with the volume of residual gastric contents. Gastric colonization of bacteria, which alters bile composition and increases the percentage of injurious unconjugated bile, may contribute to esophageal damage.55,118

To minimize the occurrence and severity of esophageal injury, patients should be kept in a semirecumbent position, nasogastric tubes should be used judiciously, and strategies that improve gastric emptying and prevent both GER and duodenogastric reflux (eg, metoclopramide) should be instituted. Until the controversy about the role of gastric colonization in nosocomial pneumonia resolves, measures that minimize GER and hence microaspiration of contaminated gastric contents remain reasonable approaches to minimize VAP.92,95

NONHEMORRHAGIC COMPLICATIONS

Hypomotility

GI hypomotility manifesting as decreased bowel sounds or abdominal distention is common and has been reported in up to half of patients with respiratory failure.6 In a recent multicenter study, Montejo119 prospectively investigated the frequency of nonhemorrhagic GI complications in 400 ICU patients receiving enteral feeding. Almost two thirds of subjects developed one or more GI complications; high gastric residuals (39%) and constipation (15.7%) were most common. Patients with GI complications had longer ICU stays (20.6 [15.7%] were most common. Patients with GI complications had longer ICU stays (20.6 ± 1.2 days vs 15.2 ± 1.3 days) and higher mortality (31% vs 16%) compared to the group without GI complications.

Using manometric evaluation, it has been reported that the motility of the upper GI tract in patients receiving MV is severely impaired.5 Contractile activity was completely lost in the stomach and diminished to a lesser degree in the duodenum. Subsequently, Heyland et al120 and Bosscha et al121 confirmed the presence of impaired gastric emptying with reduced but persistent duodenal activity during MV. These abnormalities may be related to dysfunction of interstitial cells of Cajal that are concentrated in the antrum and act as the pacemaker and controller of GI motor activity.122 Clinically, most patients with hypomotility present with intolerance to enteral nutrition and high gastric residuals. This contraction abnormality may also favor duodenogastroesophageal reflux and colonization of the stomach by enteric Gram-negative pathogens.123 In a recent study, Dive and colleagues124 showed the presence of duodenogastroesophageal reflux in 10 of 11 patients receiving MV who were receiving nasojejunal tube feedings.

Correction of electrolyte abnormalities (eg, hypokalemia, hypomagnesemia) and avoidance of medications (particularly opiates) that impair GI motility are important for the prevention of ileus and bowel dilatation.120 Like opiates, dopamine has been shown to impair GI motility. This negative effect can be seen at doses as low as 5 μg/kg/min and worsens with increasing rates of infusion.125,126 Other commonly used medications that cause GI hypomotility are phenothiazines, diltiazem, verapamil, and drugs with anticholinergic side effects. If necessary, nasogastric suction and/or rectal tubes and, in intractable cases, colonoscopy can be used to decompress the GI tract.127 Rectal tubes have been associated with complications including discomfort, local ulceration, infection, and perforation of rectum.128 Prokinetic agents, such as erythromycin, have been shown to promote gastric emptying in patients receiving MV and should be considered once mechanical obstruction is excluded. Erythromycin, 200 mg once daily, can improve gastric motility in these patients by increasing the amplitude of antral contractions and improving antroduodenal coordination.129–131 While erythromycin acts via motilin receptors, an intact vagal pathway has been shown to be necessary for its GI effects.132,133 Metoclopramide is another prokinetic agent that is useful in the treatment of gastroduodenal hypomotility.134,135 The precise mechanism of action is unclear, but metoclopramide improves antroduodenal coordination and reverses the inhibitory effects of dopamine on GI motility.125,136,137 Similarly, cisapride stimulates myenteric cholinergic nerves with consequent increase of acetylcholine release and has been used extensively in ICU patients to promote motility.138,139 However, > 300 reports showing its association with cardiac arrhythmia, including 80 deaths, have led to withdrawal of cisapride from the US market, although it will remain available through a limited-access program to patients for whom other therapies are not effective. There are insufficient data directly comparing the relative potency of prokinetics in critically ill patients with GI hypomotility.140 The only relevant study,141 in critically ill patients looked at the effects of single doses of cisapride (10 mg), erythromycin (200 mg), and metoclopramide (10 mg) administered sequentially q12h to critically ill patients intolerant to enteral nutrition. Metoclopramide and cisapride were more effective in accelerating gastric...
emptying compared to erythromycin. In addition, metoclopramide had a faster onset of action than cisapride. Limitations of this work include small study size (10 patients) and results that are in contrast to meta-analysis data\textsuperscript{140} from patients with chronic gastroparesis (eg, diabetic gastroparesis), which suggested faster gastric emptying and improvement in GI symptoms with erythromycin compared to metoclopramide. Further investigation in larger populations for longer durations is required to define the precise roles of these agents in critical illness. Interestingly, to our knowledge, there are no studies comparing promotility agents with correctly positioned postpyloric (ie, duodenal) feeding tubes, which might obviate the need for these agents.

A recent study\textsuperscript{142} has suggested that neostigmine may be effective in patients with intestinal pseudo-obstruction; although not tested in patients with respiratory failure, it may become a therapeutic tool for colonic hypomotility in critical illness. Major concerns with the use of neostigmine are 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 the improvement in colonic motility.\textsuperscript{143} Further studies that examine the effects of combination therapy with neostigmine and glycopyrrolate are warranted.

**Diarrhea**

Among nonhemorrhagic complications, diarrhea is the most distressing to patients and nursing staff. Up to 50% of critically ill patients develop diarrhea during their ICU stay, and those with acute respiratory failure appear to be particularly at risk.\textsuperscript{6,144–146} Although many factors have been implicated, the etiology of diarrhea in ICU is unknown and probably multifactorial (Table 6.\textsuperscript{144,146–149})\textsuperscript{.145} While controversy about the role of each risk factor continues, it has also been suggested that diarrhea may be a reflection of the severity of underlying illness that leads to gut dysmotility.\textsuperscript{150}

Diarrhea is a frequently reported complication of enteral feeding, affecting up to 12 to 25% of patients even in the absence of GI dysfunction.\textsuperscript{147,151–153} Smith and colleagues\textsuperscript{147} found that patients receiving MV who had higher infusion rates (>50 mL/h) and those who were receiving hyperosmolar formulas have diarrhea more frequently and for a longer duration. Contradicting these findings, Heimbürger et al\textsuperscript{154} found no association between the osmolality of tube feedings and diarrhea. His curious finding may be the result of impaired fermentation (because of eradication of colonic bacteria by antibiotics) and subsequent malabsorption of carbohydrates that causes an osmotic diarrhea.\textsuperscript{155,156} Reducing the rate of tube feeds generally improves diarrhea, probably by reducing the carbohydrate load to the gut. Thus, dilution of enteral formulas may not be helpful, especially if the patient is receiving an iso-osmolar tube feeding. Interestingly, there exist no data (to our knowledge) to suggest that dilution of enteral formulas reduces the incidence of diarrhea. This practice is a misconception that resulted from previous experience with hyperosmolar formulas and should not be expected to decrease the diarrhea seen with iso-osmolar feedings. Interestingly, diluting iso-osmolar tube feedings may be associated with decreased absorption of nutrients. In view of current evidence, there is no need to start enteral nutrition by diluting iso-osmolar tube feeds in an attempt to improve tolerance or prevent diarrhea.

Recently, relative luminal excess of bile acids has been offered as a cause of diarrhea in ICU patients.\textsuperscript{149} Animal studies have shown that prolonged starvation causes diffuse atrophy of the gut, including the terminal ileum.\textsuperscript{157,158} Hernandez et al\textsuperscript{159} performed duodenal biopsies in 15 critically ill patients after at least 4 days of fasting (mean, 7.8 days) and confirmed the presence of mucosal atrophy. Theoretically, if mucosal damage extends to the terminal ileum, abnormal bile acid homeostasis can occur. To test this hypothesis, DeMeo and colleagues\textsuperscript{149} measured stool bile acid concentrations in critically ill patients who underwent fasting for at least 5 days. Eighteen of 19 critically ill patients (95%) developed diarrhea when enteral feedings were instituted after 5 days of fasting. Eighty-five percent of the subjects had fivefold to 10-fold increases in stool bile acid as compared to normal volunteers.\textsuperscript{160} The administration of bile acid-binding agents improved diarrhea in this study.

### Table 6—Causes of Diarrhea in Patient Receiving MV

<table>
<thead>
<tr>
<th>Cause</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteral nutrition</td>
<td>Hyperosmolar formulas\textsuperscript{147}</td>
</tr>
<tr>
<td>High infusion rates (&gt;50 mL/h)\textsuperscript{147}</td>
<td>Hyperosmolar formulas\textsuperscript{147}</td>
</tr>
<tr>
<td>Dietary lipids\textsuperscript{146}</td>
<td>Hyperosmolar formulas\textsuperscript{147}</td>
</tr>
<tr>
<td>Infection</td>
<td>Hyperosmolar formulas\textsuperscript{147}</td>
</tr>
<tr>
<td>C difficile</td>
<td>Hyperosmolar formulas\textsuperscript{147}</td>
</tr>
<tr>
<td>Medications</td>
<td>Hyperosmolar formulas\textsuperscript{147}</td>
</tr>
<tr>
<td>Antacids (Mg\textsuperscript{2+} based)\textsuperscript{9}</td>
<td>Antacids (Mg\textsuperscript{2+} based)\textsuperscript{9}</td>
</tr>
<tr>
<td>H\textsubscript{2}-Receptor antagonists (with or without antacids)\textsuperscript{9,144}</td>
<td>Antacids (Mg\textsuperscript{2+} based)\textsuperscript{9}</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Hyperosmolar formulas\textsuperscript{147}</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>Hyperosmolar formulas\textsuperscript{147}</td>
</tr>
<tr>
<td>Prolonged fasting (&gt;5 d)\textsuperscript{149}</td>
<td>Hyperosmolar formulas\textsuperscript{147}</td>
</tr>
<tr>
<td>Interfering with bile acid homeostasis due to intestinal mucosal atrophy</td>
<td>Hyperosmolar formulas\textsuperscript{147}</td>
</tr>
</tbody>
</table>

\textsuperscript{1}References [144–146].
Liberal use of antibiotics in ICU patients predisposes patients to antibiotic-associated diarrhea, which accounts for 20 to 50% of all cases of nosocomial diarrhea. Five to 38% of patients receiving antibiotics develop antibiotic-associated diarrhea. The incidence has increased fivefold over 10 years, probably because of increasing use of cephalosporins in the early 1990s. Fifteen to 25% of antibiotic-associated diarrhea is caused by *Clostridium difficile* infection. Antibiotic-associated diarrhea that is not due to *C. difficile* is probably caused by the direct effect of the antibiotic on intestinal motility and by a reduction of intestinal carbohydrate fermentation.

It is usually self-limited and resolves with the discontinuation of antibiotic therapy. *C. difficile*, however, is associated with significant morbidity and even mortality if fulminant colitis or toxic megacolon develops because of delay in diagnosis. The clinical presentations of *C. difficile* infection include—in increasing order of severity—asymptomatic carriage, antibiotic-associated colitis without pseudomembrane formation, pseudomembranous colitis, and fulminant colitis. Fortunately, the most severe forms are also the least common. *C. difficile* diarrhea increases hospital length of stay by an average of 3 weeks. The number and duration of the antibiotics seem to be determinant for *C. difficile* diarrhea. In addition to frequent antibiotic use, patients receiving MV have other risk factors for *C. difficile* diarrhea, including advanced age, prolonged hospitalization, and severe underlying illness. Diagnosis of *C. difficile* diarrhea requires a high index of suspicion and is frequently made by detection of cytotoxins in the stool. The tissue culture assay remains the “gold standard,” but it is expensive and requires overnight incubation of samples. The new rapid enzyme immunoassays (EIAs) can detect *C. difficile* with fair sensitivity (69 to 87%) and good specificity (99 to 100%). The major advantages of EIAs are that they are less expensive and quicker to perform than tissue culture assay, do not require specialized training of laboratory personnel, and provide reasonable sensitivity and specificity particularly compared to the initial assays, which were based on latex particle agglutination. Owing to the lack of sensitivity, it may be necessary to repeat the EIA. While there are no guidelines as to how many assays should be performed before *C. difficile* can be excluded, repeat testing may be helpful when clinical suspicion is high. Clinical and laboratory features that predict a positive assay are the onset of diarrhea 6 days after the administration of antibiotics, hospital stay > 15 days, the presence of fecal leukocytes, the presence of semifomed (as opposed to watery) stools, and cephalosporin use. Interestingly, a commonly used drug, sucralfate, has been suggested to interfere with *C. difficile* cytotoxin-B assays, by either direct binding to the toxin itself or through its antibacterial effects.

Hypoalbuminemia has been implicated as a predisposing factor for diarrhea in critically ill patients. However, another study has questioned its precise role as a risk factor. Earlier investigations have suggested that low albumin levels can lead to gut edema and impaired nutrient absorption. Brinson and Kolts reported that all patients with a serum albumin level < 2.6 g/dL developed diarrhea, while no diarrhea was seen in those with a level > 2.6 g/dL. Subsequently, Hwang et al confirmed the association between hypoalbuminemia (albumin < 2 g/dL) and diarrhea. For the same degree of hypoalbuminemia, subjects with chronic malnutrition had a higher incidence of diarrhea compared to those with acute hypoalbuminemia (eg, burn patients). These results suggested that it is not the severity, but rather the chronicity of malnutrition, that is more important in the development of diarrhea.

Treatment of diarrhea depends on the underlying cause. The inability to identify the exact cause often complicates the picture and limits optimal care. *C. difficile* should always be considered in the differential diagnosis and therefore initial workup should include stool cytotoxin assays. The first step in managing diarrhea in association with confirmed or suspected *C. difficile* infection is to discontinue antibiotic therapy, if possible. Patients should be placed on regimens of enteral precautions and empiric antibiotic therapy while the laboratory tests are pending. Oral metronidazole remains the drug of choice, with oral vancomycin being reserved for patients who cannot tolerate or do not respond to metronidazole or for those who are pregnant. Isotonic tube feedings can minimize diarrhea because of hyperosmolar formulas, but there is no evidence to support enteral nutrition with a hypotonic formula (by diluting isotonic tube feedings) to decrease diarrhea in critically ill patients. Studies that evaluated the effects of peptide-based enteral formulas with standard tube feedings that contain whole protein do not show any difference in incidence of diarrhea. Similarly, the addition of fiber to promote the development of colonic flora does not offer any benefit over standard formulas in terms of reducing diarrhea. Although not shown to be beneficial in all patients, formulas composed of small peptides (eg, Peptamine; Nestle; Deerfield, IL) may be better tolerated in patients with severe hypoalbuminemia (albumin < 2.6 g/dL) and diarrhea.

**Effects on GI Hemodynamics**

MV has a number of adverse effects on splanchnic hemodynamics, particularly when PEEP is used (Table 7). It is noteworthy that most of the available
evidence regarding how MV affects hemodynamics in the different vascular beds of the GI tract comes from animal studies. While MV may compromise GI hemodynamics in humans in a similar fashion, there are insufficient data to indicate how clinically relevant this problem is. Evidence from experimental studies suggests that PEEP decreases mesenteric blood flow in parallel with reductions in cardiac output. Love and colleagues\textsuperscript{12} studied the effects of increasing levels of PEEP on mesenteric perfusion in rats. Addition of 10 cm H\textsubscript{2}O of PEEP resulted in reductions in cardiac output and mesenteric blood flow by 31\% and 75\%, respectively. Although IV fluids improved cardiac output, mesenteric blood flow remained 45\% below baseline. These authors\textsuperscript{12} noted that decreased arteriolar diameter suggested reflex vasoconstriction. Supporting this hypothesis, dopexamine, a potent \textbeta\textsubscript{2}-adrenoceptor and dopaminergic agonist, has been shown to selectively improve mesenteric blood flow during MV.\textsuperscript{179,180} Results from the studies of the effects of dopamine on PEEP-induced mesenteric hypoperfusion have been controversial. Two studies\textsuperscript{181,182} report that dopamine and dobutamine at low and high doses (2.5 \textmu g/kg/min and 12.5 \textmu g/kg/min, respectively) failed to improve PEEP-induced mesenteric hypoperfusion. Within the splanchnic bed, PEEP may decrease blood flow to the pancreas and stomach to a greater extent than intestinal perfusion.\textsuperscript{183} Hemodynamic consequences of PEEP in the pancreas parallel reductions in cardiac output, but occur even when mean arterial pressure is maintained.\textsuperscript{184} In animals, high levels of PEEP (15 cm H\textsubscript{2}O) have been shown to cause pancreatitis, evidenced by inflammation, vascularization, necrosis, and hemorrhage on histology and increased serum amylase and lipase levels.\textsuperscript{185,186} Histopathologic changes were evident within the first 24 h of MV with PEEP and were more pronounced with simultaneous stimulation of the gland (using a cholecystokinin analog). Similar to animals, MV may lead to a rise in lipase and amylase levels in humans,\textsuperscript{186} but whether these findings represent clinically significant pancreatitis is unknown. An autopsy study\textsuperscript{187} has demonstrated major pancreatic injury in patients dying after shock. When patients were examined prospectively, only 4 of 13 patients (30\%) with elevated pancreatic amylase and lipase levels had clinical manifestations of acute pancreatitis.\textsuperscript{187} No histologic data from patients receiving MV without hemodynamic collapse are available (to our knowledge) to clearly indicate if MV is associated with clinically evident pancreatitis. Thus, concerns about detrimental effects of PEEP on the pancreas remain theoretic but worthy of consideration in critically ill patients with otherwise unexplained signs of pancreatitis.

Several investigators have demonstrated that portal venous and hepatic arterial blood flows and hepatic venous oxygen saturation (an indicator of the adequacy of hepatic oxygen supply) are reduced in animals treated with PEEP.\textsuperscript{188–193} Volume expansion restores cardiac output to pre-PEEP levels and improves hepatic blood flow in these studies.\textsuperscript{189,190} Interestingly, institution of enteral feeding may improve PEEP-associated changes in hepatic blood flow and oxygen delivery.\textsuperscript{194} In animals, positive-pressure ventilation with PEEP has been shown to elevate portal and hepatic venous pressures\textsuperscript{195} and cause hepatic congestion.\textsuperscript{190} The precise mechanism is not known, but increased portal transmural pressure owing to a greater increase in hepatic venous pressure in comparison to portal pressure has been speculated to be the explanation. Although elevation of intra-abdominal pressure during MV does not seem to play a role in PEEP-related splanchnic blood volume changes, it may interfere with flow in intra-abdominal shunts (eg, peritoneovenous).\textsuperscript{196}

Positive-pressure ventilation with PEEP mediates its adverse effects on portal blood flow by raising downstream pressure (right atrial, inferior vena cava),\textsuperscript{188,197} by increasing hepatic sinusoidal resistance via mechanical compression of the liver by the descending diaphragm,\textsuperscript{189,191} and by diminishing arterial inflow (mesenteric) into the gut.\textsuperscript{188} Conversely, alterations in hepatic arterial flow during PEEP are due, in part, to elevations of downstream pressure.\textsuperscript{191} While the pre-

Table 7—Effects of Positive-Pressure Ventilation With PEEP on Splanchnic Hemodynamics

<table>
<thead>
<tr>
<th>Blood Flow</th>
<th>Effects of PEEP on Regional Blood Flow</th>
<th>Effects of Restoration of Cardiac Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesenteric artery</td>
<td>↓ in parallel to reduction in cardiac output due to vasoconstriction in mesenteric bed</td>
<td>Improves, but does not normalize</td>
</tr>
<tr>
<td>Portal vein</td>
<td>↓ in parallel to reduction in cardiac output due to (1) elevation in downstream (right atrial) pressure</td>
<td>Returns to pre-PEEP levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2) increased hepatic sinusoidal resistance via mechanical compression by the diaphragm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3) diminished arterial inflow into the gut</td>
</tr>
<tr>
<td>Hepatic artery</td>
<td>↓ in parallel to reduction in cardiac output due to elevation in downstream pressure</td>
<td>Returns to pre-PEEP levels</td>
</tr>
</tbody>
</table>
cise role of arterial resistance is still controversial, the expected increase in the hepatic arterial resistance during PEEP has been shown to be counterbalanced by vasodilatation, described as “hepatic buffer response,” which compensates for reduced portal blood flow.

Studies addressing the clinical consequences of MV on portal hemodynamics have provided conflicting results. Nevertheless, a mismatch between the hepatic metabolic demand and the blood supply can result in abnormal liver function. Indeed, reduction in hepatic venous oxygen saturation has been associated with subsequent hyperbilirubinemia and elevation in transaminase levels in humans. In patients with septic shock, incremental rise in PEEP induces a drop in hepatic glucose production (a marker for hepatic metabolic performance) in parallel to reductions in cardiac output and hepatic venous oxygen saturation. Furthermore, hepatic clearance of drugs that are highly extracted at the hepatic level and therefore primarily depend on hepatic blood flow (e.g., lidocaine) can be impaired by positive-pressure ventilation. In view of current evidence, it is reasonable to hypothesize that PEEP causes liver dysfunction in the presence of hypoxemia, hypotension, or any other condition that further compromises hepatic oxygen supply and that abolishes the hepatic arterial buffer response.

**Acute Acalculous Cholecystitis**

Acute acalculous cholecystitis (AAC), defined as acute inflammation of the gallbladder in the absence of stones, is an insidious complication that has been increasingly recognized in the ICU. The incidence in critically ill patients ranges from 0.2 to 3%. MV (72 h) has been implicated among other risk factors, including shock, sepsis, multiple transfusions, dehydration, prolonged enteral fasting, total parenteral nutrition, and medications (e.g., sedatives and opiates; Table 8). The pathophysiology of ACC is probably multifactorial, involving both ischemic and chemical (bile) injuries to the gallbladder epithelium. Prolonged fasting interferes with normal emptying of the gallbladder and leads to stagnation of highly concentrated bile in its lumen. Redistribution of blood away from splanchnic because of critical illness, MV, and use of vasopressors may affect the gallbladder epithelium directly by causing hypoperfusion and ischemia of the gallbladder wall and indirectly by leading to poor contractility with consequent biliary stasis and sludge formation.

For the same duration of fasting after major abdominal surgery, subjects who remained intubated have been shown to have a higher degree of gallbladder atony compared to those who were spontaneously breathing. Motility changes were detected as early as 24 h after admission to the ICU. The abundance of risk factors that can impair mucosal resistance (visceral ischemia) against injurious effects of bile makes critical illness a perfect setup for ACC.

Early diagnosis is critical in prevention of the high morbidity and mortality (up to 50%) associated with ACC, which remains a major challenge to clinicians and radiologists. Diagnosis may often go unrecognized because of the complexity of underlying medical and surgical problems, and lack of reproducible signs and biochemical parameters. Aspiration of the gallbladder has a limited role in diagnosis of ACC owing to its low sensitivity. Therefore, diagnosis of ACC relies on imaging studies, particularly ultrasonography, which has become the modality of choice. Major ultrasonographic criteria for ACC include biliary sludge, gallbladder distention (hydrops), and gallbladder wall thickening in the absence of ascites and hypoalbuminemia. Unfortunately, these findings are not specific, but only suggestive. Other criteria are even less reliable and include stratified thickening of gallbladder wall and pericholecystic fluid collection, which is often associated with gallbladder perforation. In one study, 14 of 28 ICU patients (50%; 19 intubated) were found to have one of the three major ultrasonographic criteria for ACC, but none of these subjects needed any intervention.

To differentiate ACC from commonly seen gallbladder abnormalities in the ICU, scoring systems based on the combination of sonographic findings have been suggested. To overcome the limited sensitivity of these systems, other investigators have recommended serial ultrasonographic examinations. Although CT has the advantage of being more sensitive than ultrasonography in diagnosing ACC and superior at detecting other intra-abdominal abnormalities, ultrasonography can easily be performed at the bedside and therefore remains the screening procedure of choice. Because of high false-positive rates in critically ill patients who fre-

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**Table 8—Risk Factors for Acalculous Cholecystitis in Critically Ill Patients**

<table>
<thead>
<tr>
<th>Risk Factor</th>
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<tbody>
<tr>
<td>MV (≥ 72 h)</td>
</tr>
<tr>
<td>Shock</td>
</tr>
<tr>
<td>Systemic inflammatory response syndrome/sepsis</td>
</tr>
<tr>
<td>Multiple transfusions</td>
</tr>
<tr>
<td>Dehydration</td>
</tr>
<tr>
<td>Prolonged enteral fasting</td>
</tr>
<tr>
<td>Total parenteral nutrition</td>
</tr>
<tr>
<td>Medications (especially opiates, sedatives, and vasopressors)</td>
</tr>
</tbody>
</table>
quently have viscous bile, hepatobiliary scintigraphy is better at excluding than confirming the diagnosis of ACC.219,220

Although cholecystectomy has been the traditional approach, it is not always feasible because of the severity of underlying disease in ICU patients. In subjects who represent high risk for general anesthesia, drainage via percutaneous cholecystostomy has been shown to be an acceptable option with low procedure-related risk and success rates between 59% and 88%.215,221 Transpapillary endoscopic cholecystostomy is another treatment option suggested to be useful in those who are also poor candidates for a percutaneous approach.225

SUMMARY

MV is a lifesaving tool, but it is not without limitations. There are numerous GI complications seen in critically ill patients receiving MV. Although it remains unclear if these complications are the direct effect of MV, current knowledge suggests that MV may contribute to physiologic changes that may impair the function of the GI tract. These changes can lead to common complications, such as SRMD and associated GI hemorrhage and hypomotility, some of which can occur in up to 50% of patients receiving MV. It is unclear to what extent GI complications contribute to the mortality of critically ill patients, but undoubtedly they are associated with significant morbidity that impacts the care of these patients by increasing length of stay and costs. Nevertheless, it is quite likely that GI complications also lead to increased mortality in patients receiving MV. Currently, there exists a broad knowledge base to guide the application of preventive therapies to prevent SRMD, and new data are evolving that may prove helpful for disordered motility. As our understanding of the systemic effects of MV and lung protective ventilatory strategies improves, it can be expected that complications associated with MV will become less common. Our goal in patient care is to not only provide treatment, but to recognize the potential complications related to any given therapy. Better understanding of the limitations and consequences of MV will help us to identify and minimize these complications.

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