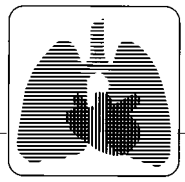

critical care review

GI Complications in Patients Receiving Mechanical Ventilation*

Gökhan M. Mutlu, MD; Ece A. Mutlu, MD; and Phillip Factor, DO, FCCP

Mechanical ventilation (MV) can be lifesaving by maintaining gas exchange until the underlying disorders are corrected, but it is associated with numerous organ-system complications, which 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 severity of the underlying disease that required intensive care. The interactions of the underlying critical illness and MV with the GI tract are complex and can manifest in a variety of clinical pictures. Incorporated in this review are discussions of the most prevalent GI complications associated with MV, and current diagnosis and management of these problems.

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Key words: complications; GI; mechanical ventilation; review; stress ulcer

Abbreviations: ACC = acute acalculous cholecystitis; EIA = enzyme immunoassay; GER = gastroesophageal reflux; H_2 = histamine type 2; IL = interleukin; MODS = multiple organ dysfunction syndrome; MV = mechanical ventilation; PEEP = positive end-expiratory pressure; SRMD = stress-related mucosal damage; VAP = ventilator-associated pneumonia

Mechanical ventilation (MV) is a lifesaving therapy with a myriad of organ-system complications that can significantly affect the outcome of critically ill patients.[1] 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[2–4] and GI hypomotility (Table 1).[5,6] The current diagnosis and management of these conditions and other less common complications are also included.

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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

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

Complications	Incidence, %
Erosive esophagitis	48
SRMD	
Asymptomatic, endoscopically evident damage	74–100
Clinically evident bleeding	5–25
Clinically significant bleeding	3–4
Diarrhea	15–51
Decreased bowel sounds	50
High gastric residuals	39
Constipation	15
Ileus	4–10
AAC	0.2–3

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

Organs	Complications
Esophagus and stomach	Erosive esophagitis
	GER
	Stress ulcer
	Impaired gastric emptying
	Intolerance to enteral nutrition
Small intestines and colon	Stress ulcer
	Ileus
	Colonic pseudo-obstruction
	Diarrhea
	Altered intestinal microflora
	Bacterial overgrowth
	Intestinal luminal toxins
	Possibility of acute nonocclusive mesenteric ischemia
Liver	Increased transaminase and/or bilirubin levels
	Impaired hepatic function
	Impaired drug metabolism
Gallbladder	Atonic gallbladder
	Possibility of acalculous cholecystitis
Pancreas	Asymptomatic rise in amylase and lipase levels
	Possibility of acute pancreatitis

bed. Several features of the splanchnic vascular bed put GI organs at particular risk for ischemic events.[7–9] First, the gut does not have the ability to autoregulate in order to compensate for reductions in BP. Second, splanchnic vasoconstriction may persist even after correction of hemodynamic instability. Third, the gut mucosa has a similar vascular architecture as renal medulla, permitting oxygen shunting and consequent distal hypoxia at the tips of villi, even under normal conditions.[9,10] Finally the oxygen content in gut mucosal vessels is significantly reduced because of dilutional effects of absorbed fluid and nutrients from intestinal lumen, resulting in a hematocrit of approximately 10%.[7]

MV, especially with high levels of positive end-expiratory pressure (PEEP), increases intrathoracic pressure, which decreases venous return by reducing the gradient between mean systemic venous pressure and right atrial pressure.[11] Reduced preload in return can result in decreased cardiac output and hypotension in those patients with predisposing factors for PEEP-induced hypotension, such as hypovolemia and impaired venoconstriction (*eg*, opiates). Splanchnic blood flow in these settings decreases in parallel with PEEP-induced reductions in cardiac output.[12]

MV with PEEP is also associated with increased plasma-renin-angiotensin–aldosterone activity and elevated catecholamines because of sympathetic activation.[13–15] Moreover, these patients frequently receive catecholamine therapy for BP support. 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-

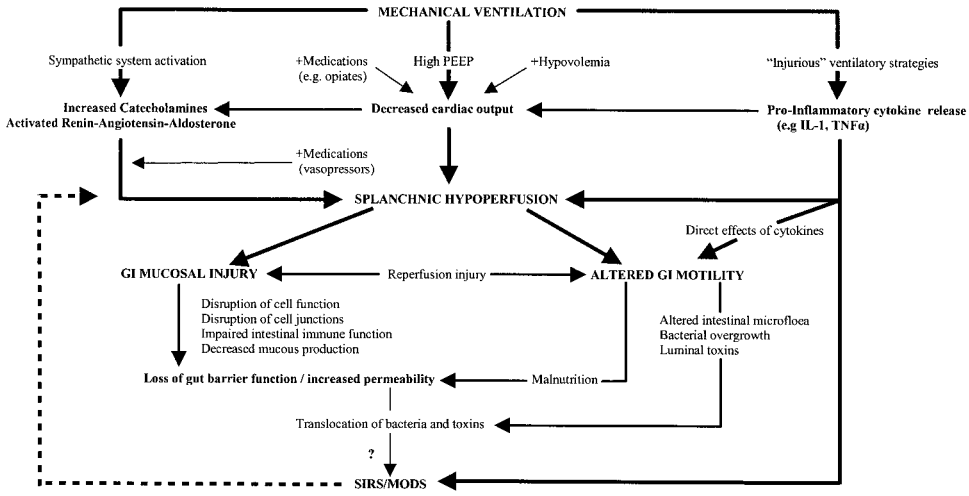

FIGURE 1. Proposed mechanisms for the development of GI complications during MV. MV can contribute to the pathogenesis of GI problems in much the same way as critical illness by affecting splanchnic blood flow and leading to increased release of proinflammatory mediators. SIRS = systemic inflammatory response syndrome; TNF-α = tumor necrosis factor-α.

nary cytokines, as well as increasing alveolar capillary permeability that would increase the transfer of intrapulmonary cytokines from lungs to the systemic circulation.[28–31] Recently, these data were confirmed in humans by Ranieri and colleagues,[32] 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.[33] 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 vasopressor agents. Other commonly used medications that are frequently associated with GI complications in patients receiving MV include vasopressors (as discussed above), antibiotics, and additives in oral medications (*eg*, 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[7] 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 (*eg*, endotoxin) and possibly microorganisms from intestinal lumen to the bloodstream.[19] 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.[34,35] It is not clear, however, whether MV contributes 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.[4] 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.[3,36]

Most (74 to 100%) critically ill patients have endoscopically detectable mucosal erosions and subepithelial hemorrhage within 24 h of admission to the ICU.[2–4] 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 nasogastic tube aspirates, or hematochezia. Clinically significant or life-threatening bleeding is defined as bleeding that causes hemodynamic changes or necessitates transfusion.[37] Patients receiving MV who develop clinically significant bleeding generally do so within the first 2 weeks of their ICU stay.[38]

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).[39] Overt bleeding because of SRMD occurs in up to 25% of critically ill patients who do not receive prophylactic therapy.[4,35,40] 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.[37] 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%.[35,41–43] Not surprisingly, 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.[38] Similarly, mortality has also been shown to be several-fold higher in patients who develop stress ulcer bleeding compared with those

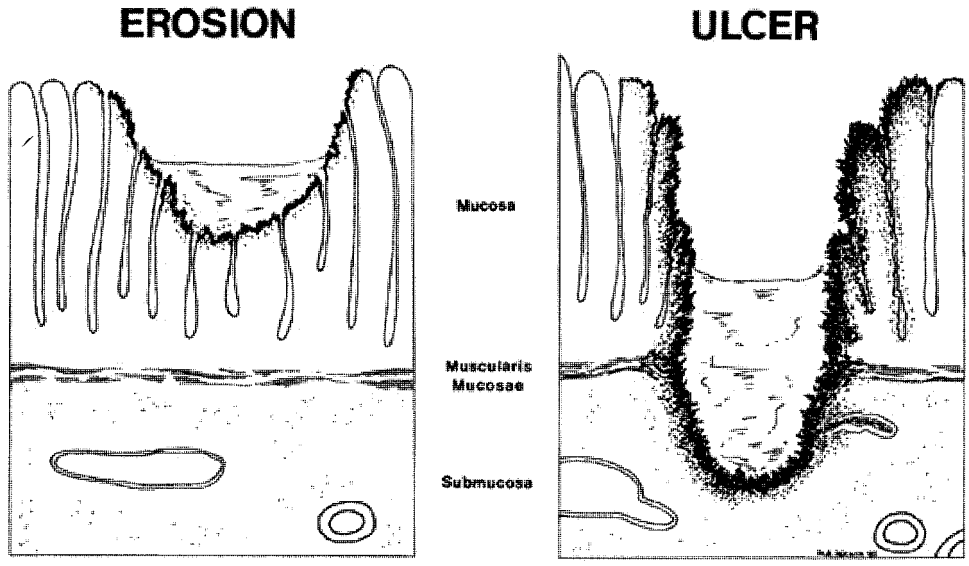

FIGURE 2. Illustration of the difference between an erosion and an ulcer. An erosion is a mucosal break that does not penetrate the muscularis mucosae, whereas an ulcer does penetrate the muscularis mucosae. Reprinted with permission from Weinstein.[39]

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.

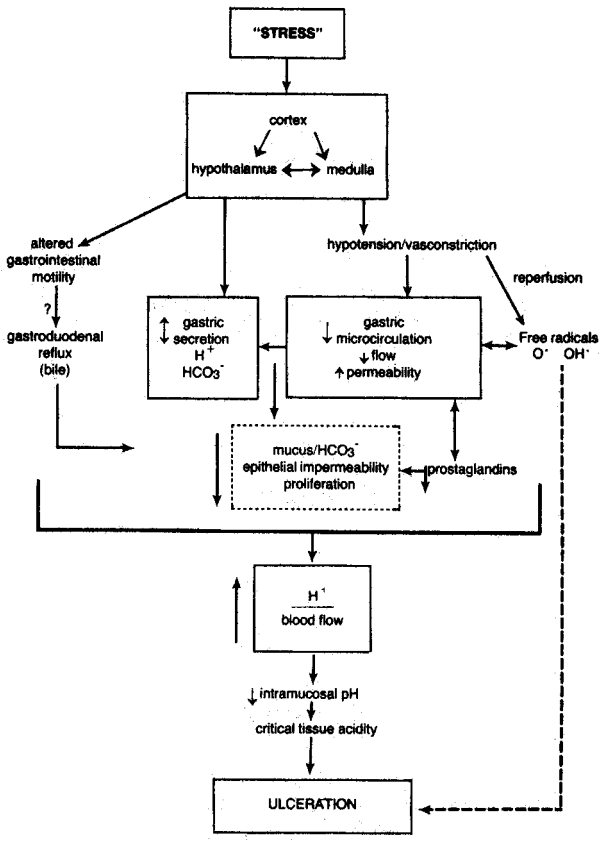

FIGURE 3. Proposed mechanisms for development of stress ulceration. SRMD results from the complex interaction of multiple systems. The specific relationships depicted remain somewhat speculative. Reprinted with permission from Bresalier.[44]

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 Stoutenbeek[43] 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 [H_2]-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 H_2-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 H_2-receptor antagonists.[58] Although routine measurements of gastric pH (especially within the first 24 h) are recommended when H_2-receptor antagonists are used, until now (to our knowledge) no studies have proven the superiority of pH-adjusted dosing over the standard regimen. Like H_2-receptor antagonists, antacids neutralize gastric acid

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

Medication	Mode of Action	Other Protective Mechanisms	Comments/Complications
Antacids	Direct neutralization of gastric acid in a dose-dependent fashion Gastric pH is kept > 3.5–4.0	Binds to bile acids (Al^{+3} based) Increases local PG production improved mucosal blood flow increased mucus/HCO_3 production Stimulates epithelial regeneration	Increased nursing costs Hypermagnesemia (Mg^{+2} based) Hypophosphotemia (Al^{+3} based) Constipation (Al^{+3} based) Diarrhea (Mg^{+2} based) Interferes with absorption of certain drugs (*eg*, tetracycline, quinolones)
H_2-Blockers	Increase gastric pH by blocking H_2-receptors	No beneficial cytoprotective effects	Continuous provides *better* pH control compared to intermittent, but is *not* more effective as a preventive therapy Interstitial nephritis Confusion (especially elderly) Thrombocytopenia Hypotension, sinus bradycardia (rapid IV infusion) P450-mediated effects (particularly cimetidine)
Proton pump inhibitors	Inhibits parietal cell H^+-K^+-adenosine triphosphatase and blocks the final step of H^+ ion production	No beneficial cytoprotective effects	IV form not available in United States Diarrhea P450-mediated effects
Sucralfate	Aluminum sucrose sulfate Does not affect the luminal pH Acts via coating and protection of gastric mucosa	Increases local PG production Stimulates mucus/HCO_3 production (independently of PG) Stimulates epidermal growth factor	Antibacterial effects Costs less than IV H_2-blockers Constipation Interferes with absorption of certain drugs (*eg*, tetracycline, quinolones)
Prostaglandin analogs	Antisecretory and cytoprotective effects on the gastric mucosa	Inhibits 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 Improves mucosal blood flow (2 and 3 can occur independently of PG)	Not available in North America

*PG = prostaglandin.

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 > 4), 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 binding[69] and increased mucosal prostaglandin production[70] (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 (M_1) 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 H_2-blockers as prophylactic therapy, the optimal treatment regimen continues to be the subject of debate.[74] Respondents to this recent survey[74] 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 4 reviews available evidence regarding the effects of the most commonly used and widely studied medications (H_2-receptor antagonists, sucralfate, and antacids) in the prevention of stress ulcer-related GI bleeding. The results of published

Table 4—*Available Evidence on the Effectiveness of Most Commonly Used Medications in Stress Ulcer Prophylaxis (H_2-Receptor Antagonists, Sucralfate, and Antacids)*

Source	Year	Study Design/Medications	Results/Comments
Shuman et al[57]	1987	Meta-analysis (16 prospective trials) Antacids and H_2-blockers (cimetidine)	Antacids and H_2-blockers are equally effective in the prevention of overt SRMD-related bleeding (3.3% vs 2.7%, respectively).
Lacroix et al[75]	1989	Meta-analysis (15 prospective trials) Antacids and H_2-blockers (cimetidine)	Similar to findings in Shuman et al.[57]
Cook et al[76]	1991	Meta-analysis (42 prospective studies) Antacids, H_2-blockers, and sucralfate	H_2-Blockers are more effective than antacids in decreasing overt bleeding. There is a trend favoring antacids over sucralfate in the outcome of clinically important bleeding; however, there are insufficient data to evaluate H_2-blockers vs sucralfate. A significant reduction in clinically important GI hemorrhage is evident only with H_2-blockers. Mortality rates in critically ill are *not* decreased by stress ulcer prophylaxis.
Tryba[60]	1991	Meta-analysis (45 prospective trials) Antacids, H_2-blockers, and sucralfate	Antacids and sucralfate are equally effective and superior to H_2-antagonists in prevention of overt stress ulcer-related hemorrhage. Prophylaxis with H_2-blockers is associated with a higher incidence of nosocomial pneumonia compared to those with sucralfate.
Cook et al[37]	1996	Meta-analysis (63 prospective trials) Antacids, H_2-blockers, and sucralfate	H_2-Blockers are more efficacious than antacids in reducing overt GI bleeding. Sucralfate, antacids, and H_2-blockers do *not* significantly differ with respect to the prevention of clinically important bleeding. There is a trend toward an increased risk of pneumonia associated with H_2-blockers as compared with no prophylaxis. Sucralfate is associated with a *reduced* mortality rate relative to antacids and to H_2-blockers probably due to lower incidence of nosocomial pneumonia.
Cook et al[42]	1998	Multicenter, randomized, double blinded, placebo controlled (1,200 patients) Sucralfate vs H_2-blockers (ranitidine)	Risk of GI bleeding was lower in patients receiving ranitidine compared to those who are given sucralfate. *No* significant difference in the incidence of pneumonia between each treatment groups.

meta-analyses[37,57,60,75,76] 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[57] and Lacroix et al[75] found that H_2-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[60] confirmed these findings, and even suggested a tendency in favor of antacids. Contradicting these results, Cook and colleagues[37,76] found that antacids were less efficacious than H_2-blockers and had only a nonsignificant trend toward decreased overt bleeding when compared with no prophylaxis.

Similarly, differences among meta-analyses of sucralfate vs H_2-blockers exist. Although both initial meta-analyses[60,76] suggested that sucralfate was associated with a lower rate of overt bleeding than H_2-blockers, this reduction reached statistical significance in only one study.[60] A more recent meta-analysis by Cook et al[37] 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 H_2-blockers differ with respect to the prevention of clinically important bleeding.[37] Complicating these previous results, a more recent randomized trial[42] demonstrated a significantly lower risk of clinically important GI hemorrhage in patients receiving H_2-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,[42] both sucralfate and H_2-blockers appear to be effective in prevention of clinically important stress ulcer bleeding. Finally, studies[77–80] that have examined the efficacy of various combination therapies, including H_2-blockers with antacids and H_2-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.[38,81,82] 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 alkalinization of gastric fluid.[38,83,84] 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.[84] While a recent randomized multicenter trial[38] reported that H_2-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, H_2-receptor antagonists, and sucralfate are uncommon and occur in $< 1\%$ of patients, particularly when administered on a short-term basis.[74] 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 H_2-blockers in critically ill patients.[85–87] Stress ulcer prophylaxis with antacids and/or H_2-blockers raises gastric pH and increases colonization of the stomach with Enterobacteriaceae.[88,89] Retrograde oropharyngeal contamination by colonized gastric contents and subsequent aspiration to the lower airways have been suggested to cause nosocomial pneumonia.[85,90] Studies[91,92] 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.[93]

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.[94,95] Confirming the role of gastric acidity and the importance of gastro-oropharyngeal route are studies[96–98] 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).[97] A recent meta-analysis and a large randomized controlled trial by Cook et al[37,42] 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[94,99–101] have challenged the importance of the gastro-oropharyngeal route. In a randomized trial of 141 patients receiving MV, Bonten et al[94] 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.[102] A recent small prospective trial[103] 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 alkalinization 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, H_2 antagonists remain the only option for IV use in North America. When enteral

administration is feasible, both H_2 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[104] 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[104] 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,[105] 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.[58,106] Moreover, no evidence is available (to our knowledge) to suggest that stress ulcer prophylaxis improves mortality in critically ill patients.[76] 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[107] 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[34,35,108,109] suggests that patients with respiratory failure requiring MV for >48 h and those with coagulopathy (defined as a platelet count of $<50{,}000/\mu L$, 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%).[34] 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.[38] 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).[35,52,110]

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.[111,112] Potential mechanisms of esophageal injury in critically ill patients are nasogastric tubes, gastroesophageal reflux (GER), and duodenogastroesophageal (bile) reflux.[113,114]

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.[113] 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[114] 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,[115] 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[116] 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-

Table 5—*Risk Factors for Clinically Significant Bleeding From SRMD*

Respiratory failure requiring MV >48 h
Coagulopathy
Platelet count $<50{,}000/\mu L$
International normalized ratio >1.5
Partial thromboplastin time more than twice the control value
Sepsis
Hypotension
Hepatic failure
Renal failure
Major trauma
Extensive burns ($>25\%$ of body surface)
Intracranial hypertension
Tetraplegia

induced mucosal damage a less likely explanation for esophagitis.[113,117] In a study[111] 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.[88,118]

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, Montejo[119] 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 ± 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 al[120] and Bosscha et al[121] 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 duodenogastric reflux and colonization of the stomach by enteric Gram-negative pathogens.[123] In a recent study, Dive and colleagues[124] showed the presence of duodenogastric 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[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[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.[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.[6,144–146] Although many factors have been implicated, the etiology of diarrhea in ICU is unknown and probably multifactorial (Table 6[6,144,146–149]). 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.[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.[147,151–153] Smith and colleagues[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, Heimburger et al[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.[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.[149] Animal studies have shown that prolonged starvation causes diffuse atrophy of the gut, including the terminal ileum.[157,158] Hernandez et al[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[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.[160] The administration of bile acid-binding agents improved diarrhea in this study.

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

Enteral nutrition
Hyperosmolar formulas[147]
High infusion rates (> 50 mL/h)[147]
Dietary lipids[146]
Infection
C difficile
Medications
Antacids (Mg^{+3} based)[6]
H_2-Receptor antagonists (with or without antacids)[6,144]
Antibiotics
Hypoalbuminemia
Particularly those with chronic severe hypoalbuminemia (< 2.6 g/dL)[148]
Prolonged fasting (> 5 d)[149]
Interfering with bile acid homeostasis due to intestinal mucosal atrophy

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.[161] Five to 38% of patients receiving antibiotics develop antibiotic-associated diarrhea.[162] The incidence has increased fivefold over 10 years, probably because of increasing use of cephalosporins in the early 1990s.[163] 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.[161] 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.[163] 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.[164] 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.[165,166] 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%).[167] 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.[168] 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 semiformed (as opposed to watery) stools, and cephalosporin use.[168] Interestingly, a commonly used drug, sucralfate, has been suggested to interfere with *C difficile* cytotoxin-B assays,[169] by either direct binding to the toxin itself or through its antibacterial effects.[170,171]

Hypoalbuminemia has been implicated as a predisposing factor for diarrhea in critically ill patients.[148,172,173] However, another study[149] 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[148] 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[173] 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 enteric 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 hypoosmolar 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.[174–176] 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.[177,178] 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.[172]

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

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

Blood Flow	Effects of PEEP on Regional Blood Flow	Effects of Restoration of Cardiac Output
Mesenteric artery	↓ in parallel to reduction in cardiac output due to vasoconstriction in mesenteric bed	Improves, but does not normalize
Portal vein	↓ in parallel to reduction in cardiac output due to (1) elevation in downstream (right atrial) pressure (2) increased hepatic sinusoidal resistance via mechanical compression by the diaphragm (3) diminished arterial inflow into the gut	Returns to pre-PEEP levels
Hepatic artery	↓ in parallel to reduction in cardiac output due to elevation in downstream pressure	Returns to pre-PEEP levels

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[12] studied the effects of increasing levels of PEEP on mesenteric perfusion in rats. Addition of 10 cm H_2O 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[12] noted that decreased arteriolar diameter suggested reflex vasoconstriction. Supporting this hypothesis, dopexamine, a potent β_2-adrenoceptor and dopaminergic agonist, has been shown to selectively improve mesenteric blood flow during MV.[179,180] Results from the studies of the effects of dopamine on PEEP-induced mesenteric hypoperfusion have been controversial. Two studies[181,182] report that dopamine and dobutamine at low and high doses (2.5 μg/kg/min and 12.5 μg/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.[183] Hemodynamic consequences of PEEP in the pancreas parallel reductions in cardiac output, but occur even when mean arterial pressure is maintained.[184] In animals, high levels of PEEP (15 cm H_2O) have been shown to cause pancreatitis, evidenced by inflammation, vacuolization, necrosis, and hemorrhage on histology and increased serum amylase and lipase levels.[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,[186] but whether these findings represent clinically significant pancreatitis is unknown. An autopsy study[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.[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.[188–193] Volume expansion restores cardiac output to pre-PEEP levels and improves hepatic blood flow in these studies.[189,190] Interestingly, institution of enteral feeding may improve PEEP-associated changes in hepatic blood flow and oxygen delivery.[194] In animals, positive-pressure ventilation with PEEP has been shown to elevate portal and hepatic venous pressures[195] and cause hepatic congestion.[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).[196]

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

cise role of arterial resistance is still controversial, the expected increase in the hepatic arterial resistance during PEEP[198] has been shown to be counterbalanced by vasodilatation, described as "hepatic buffer response," which compensates for reduced portal blood flow.[191,199]

Studies[189,191,200] 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.[201] Indeed, reduction in hepatic venous oxygen saturation has been associated with subsequent hyperbilirubinemia and elevation in transaminase levels in humans.[202] 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.[203] Furthermore, hepatic clearance of drugs that are highly extracted at the hepatic level and therefore primarily depend on hepatic blood flow (*eg*, lidocaine) can be impaired by positive-pressure ventilation.[200,204] 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%.[205–207] MV (72 h) has been implicated among other risk factors, including shock, sepsis, multiple transfusions, dehydration, prolonged enteral fasting, total parenteral nutrition, and medications (*eg*, sedatives and opiates; Table 8).[205,208–210] 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.[211] 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.[212] 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.[213] Motility changes were detected as early as 24 h after admission to the ICU.[213] 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.

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

MV (≥ 72 h)
Shock
Systemic inflammatory response syndrome/sepsis
Multiple transfusions
Dehydration
Prolonged enteral fasting
Total parenteral nutrition
Medications (especially opiates, sedatives, and vasopressors)

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.[214,215] Diagnosis may often go unrecognized because of the complexity of underlying medical and surgical problems,[216] and lack of reproducible signs and biochemical parameters.[205,208,217] Aspiration of the gallbladder has a limited role in diagnosis of ACC owing to its low sensitivity.[218,219] Therefore, diagnosis of ACC relies on imaging studies, particularly ultrasonography, which has become the modality of choice.[208,217,218,220] Major ultrasonographic criteria for ACC include biliary sludge, gallbladder distention (hydrops), and gallbladder wall thickening in the absence of ascites and hypoalbuminemia.[208,217] Unfortunately, these findings are not specific, but only suggestive. Other criteria are even less reliable and include striated thickening of gallbladder wall and pericholecystic fluid collection, which is often associated with gallbladder perforation.[208] 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.[217] To differentiate ACC from commonly seen gallbladder abnormalities in the ICU, scoring systems based on the combination of sonographic findings have been suggested.[208,214,219] To overcome the limited sensitivity of these systems, other investigators[221] have recommended serial ultrasonographic examinations.[221] 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.[219,222] Because of high false-positive rates in critically ill patients who fre-

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 cholecytostomy has been shown to be an acceptable option with low procedure-related risk and success rates between 59% and 88%.[215,223,224] 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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References

1 Mutlu GM, Factor P. Complications of mechanical ventilation. Respir Care Clin North Am 2000; 6:213–252
2 Lucas CE, Sugawa C, Riddle J, et al. Natural history and surgical dilemma of "stress" gastric bleeding. Arch Surg 1971; 102:266–273
3 Czaja AJ, McAlhany JC, Pruitt BA Jr. Acute gastroduodenal disease after thermal injury: an endoscopic evaluation of incidence and natural history. N Engl J Med 1974; 291:925–929
4 Peura DA, Johnson LF. Cimetidine for prevention and treatment of gastroduodenal mucosal lesions in patients in an ICUs. Ann Intern Med 1985; 103:173–177
5 Dive A, Moulart M, Jonard P, et al. Gastroduodenal motility in mechanically ventilated critically ill patients: a manometric study. Crit Care Med 1994; 22:441–447
6 Dark DS, Pingleton SK. Nonhemorrhagic gastrointestinal complications in acute respiratory failure. Crit Care Med 1989; 17:755–758
7 Bion JF. Multiple organ failure. In: Webb AR, Shapiro MJ, Singer M, et al, eds. Oxford textbook of critical care. New York, NY: Oxford University Press, 1999; 923–926
8 Antonsson JB, Engstrom L, Rasmussen I, et al. Changes in gut intramucosal pH and gut oxygen extraction ratio in a porcine model of peritonitis and hemorrhage. Crit Care Med 1995; 23:1872–1881
9 Bohlen GH. Tissue oxygenation and splanchnic blood flow. In: Shepherd AP, Granger DN, eds. Physiology of intestinal circulation. New York, NY: Raven Press, 1984; 143–151
10 Haglund U. The gastrointestinal and hepatic systems: normal physiology; the gastrointestinal system. In: Webb AR, Shapiro MJ, Singer M, et al, eds. Oxford textbook of critical care. New York: Oxford University Press, 1999; 297–300
11 Welsh DA, Summer WR, deBloisblanc B, et al. Hemodynamic consequences of mechanical ventilation. Clin Pulm Med 1999; 6:52–65
12 Love R, Choe E, Lippton H, et al. Positive end-expiratory pressure decreases mesenteric blood flow despite normalization of cardiac output. J Trauma 1995; 39:195–199
13 Sellden H, Sjovall H, Ricksten SE. Sympathetic nerve activity and central hemodynamics during mechanical ventilation with positive end-expiratory pressure in rats. Acta Physiol Scand 1986; 127:51–60
14 Tanaka S, Sagawa S, Miki K, et al. Changes in muscle sympathetic nerve activity and renal function during positive-pressure breathing in humans. Am J Physiol 1994; 266:R1220–R1228
15 Chernow B, Soldano S, Cook D, et al. Positive end-expiratory pressure increases plasma catecholamine levels in non-volume loaded dogs. Anaesth Intensive Care 1986; 14:421–425
16 Cullen JJ, Ephgrave KS, Caropreso DK. Gastrointestinal myoelectric activity during endotoxemia. Am J Surg 1996; 171:596–599
17 Aneman A, Ponten J, Fandriks L, et al. Hemodynamic, sympathetic and angiotensin II responses to PEEP ventilation before and during administration of isoflurane. Acta Anaesthesiol Scand 1997; 41:41–48
18 Klemm K, Moody FG. Regional intestinal blood flow and nitric oxide synthase inhibition during sepsis in the rat. Ann Surg 1998; 227:126–133
19 Spain DA, Kawabe T, Keelan PC, et al. Decreased α-adrenergic response in the intestinal microcirculation after 'two-hit' hemorrhage/resuscitation and bacteremia. J Surg Res 1999; 84:180–185
20 Bassiouny HS. Nonocclusive mesenteric ischemia. Surg Clin North Am 1997; 77:319–326
21 Heaney ML, Golde DW. Soluble receptors in human disease. J Leukoc Biol 1998; 64:135–146
22 Michie HR, Wilmore DW. Sepsis, signals, and surgical

sequelae (a hypothesis). Arch Surg 1990; 125:531–536
23 Schwartz MD, Moore EE, Moore FA, et al. Nuclear factor-κ B is activated in alveolar macrophages from patients with acute respiratory distress syndrome. Crit Care Med 1996; 24:1285–1292
24 Meduri GU. Host defense response and outcome in ARDS. Chest 1997; 112:1154–1158
25 Lodato RF, Khan AR, Zembowicz MJ, et al. Roles of IL-1 and TNF in the decreased ileal muscle contractility induced by lipopolysaccharide. Am J Physiol 1999; 276:G1356–G1362
26 Cullen JJ, Caropreso DK, Ephgrave KS, et al. The effect of endotoxin on canine jejunal motility and transit. J Surg Res 1997; 67:54–57
27 Cullen JJ, Caropreso DK, Hemann LL, et al. Pathophysiology of adynamic ileus. Dig Dis Sci 1997; 42:731–737
28 Tremblay L, Valenza F, Ribeiro SP, et al. Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. J Clin Invest 1997; 99:944–952
29 von Bethmann AN, Brasch F, Nusing R, et al. Hyperventilation induces release of cytokines from perfused mouse lung. Am J Respir Crit Care Med 1998; 157:263–272
30 Slutsky AS, Tremblay LN. Multiple system organ failure: is mechanical ventilation a contributing factor? Am J Respir Crit Care Med 1998; 157:1721–1725
31 Lecuona E, Saldias F, Comellas A, et al. Ventilator-associated lung injury decreases lung ability to clear edema in rats. Am J Respir Crit Care Med 1999; 159:603–609
32 Ranieri VM, Suter PM, Tortorella C, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. Jama 1999; 282:54–61
33 Nahum A, Hoyt J, Schmitz L, et al. Effect of mechanical ventilation strategy on dissemination of intratracheally instilled *Escherichia coli* in dogs. Crit Care Med 1997; 25:1733–1743
34 Cook DJ, Fuller HD, Guyatt GH, et al. Risk factors for gastrointestinal bleeding in critically ill patients: Canadian Critical Care Trials Group. N Engl J Med 1994; 330:377–381
35 Schuster DP, Rowley H, Feinstein S, et al. Prospective evaluation of the risk of upper gastrointestinal bleeding after admission to a medical ICUs. Am J Med 1984; 76:623–630
36 Terdiman JP, Ostroff JW. Gastrointestinal bleeding in the hospitalized patient: a case-control study to assess risk factors, causes, and outcome. Am J Med 1998; 104:349–354
37 Cook DJ, Reeve BK, Guyatt GH, et al. Stress ulcer prophylaxis in critically ill patients: resolving discordant meta-analyses. JAMA 1996; 275:308–314
38 Cook D, Heyland D, Griffith L, et al. Risk factors for clinically important upper gastrointestinal bleeding in patients requiring mechanical ventilation: Canadian Critical Care Trials Group. Crit Care Med 1999; 27:2812–2817
39 Weinstein WM. Gastritis, and gastropathy. In: Sivak MVJ, ed. Gastroenterologic endoscopy (vol 1). 2nd ed. Philadelphia, PA: WB Saunders, 2000; 642–670
40 Gurman G, Samri M, Sarov B, et al. The rate of gastrointestinal bleeding in a general ICU population: a retrospective study. Intensive Care Med 1990; 16:44–49
41 Silen W. Pathogenetic factors in erosive gastritis. Am J Med 1985; 79:45–48
42 Cook D, Guyatt G, Marshall J, et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation: Canadian Critical Care Trials Group. N Engl J Med 1998; 338:791–797
43 Zandstra DF, Stoutenbeek CP. The virtual absence of stress-ulceration related bleeding in ICU patients receiving prolonged mechanical ventilation without any prophylaxis: a prospective cohort study. Intensive Care Med 1994; 20:335–340
44 Bresalier RS. The clinical significance and pathophysiology of stress-related gastric mucosal hemorrhage. J Clin Gastroenterol 1991; 13:S35–S43
45 Miller TA. Mechanisms of stress-related mucosal damage. Am J Med 1987; 83:8–14
46 Cho CH, Koo MW, Garg GP, et al. Stress-induced gastric ulceration: its etiology and clinical implications. Scand J Gastroenterol 1992; 27:257–262
47 Skillman JJ, Gould SA, Chung RS, et al. The gastric mucosal barrier: clinical and experimental studies in critically ill and normal man, and in the rabbit. Ann Surg 1970; 172:564–584
48 Stannard VA, Hutchinson A, Morris DL, et al. Gastric exocrine "failure" in critically ill patients: incidence and associated features. BMJ 1988; 296:155–156
49 Cook DJ, Laine LA, Guyatt GH, et al. Nosocomial pneumonia and the role of gastric pH: a meta-analysis. Chest 1991; 100:7–13
50 Bowen JC, Fleming WH, Thompson JC. Increased gastrin release after penetrating central nervous system injury. Surgery 1974; 75:720–724
51 O'Neill JA Jr. The influence of thermal burns on gastric acid secretion. Surgery 1970; 67:267–271
52 Peura DA. Stress-related mucosal damage: an overview. Am J Med 1987; 83:3–7
53 Cheung LY. Gastric mucosal blood flow: its measurement and importance in mucosal defense mechanisms. J Surg Res 1984; 36:282–288
54 Menguy R, Desbaillets L, Masters YF. Mechanism of stress ulcer: influence of hypovolemic shock on energy metabolism in the gastric mucosa. Gastroenterology 1974; 66:46–55
55 Peura DA, Koretz RL. Controversies, dilemmas, and dialogues: prophylactic therapy of stress-related mucosal damage; why, which, who, and so what? Am J Gastroenterol 1990; 85:935–937
56 Laine L. Acute and chronic gastrointestinal bleeding. In: Feldman M, Scharschmidt BF, Sleisenger MH, eds. Sleisenger & Fordtran's gastrointestinal and liver disease (vol 1). Philadelphia, PA: WB Saunders, 1998; 198–219
57 Shuman RB, Schuster DP, Zuckerman GR. Prophylactic therapy for stress ulcer bleeding: a reappraisal. Ann Intern Med 1987; 106:562–567
58 Tryba M, Cook D. Current guidelines on stress ulcer prophylaxis. Drugs 1997; 54:581–596
59 Phillips JO, Metzler MH, Palmieri MT, et al. A prospective study of simplified omeprazole suspension for the prophylaxis of stress-related mucosal damage. Crit Care Med 1996; 24:1793–1800
60 Tryba M. Prophylaxis of stress ulcer bleeding: a meta-analysis. J Clin Gastroenterol 1991; 13:S44–S55
61 Martin LF, Booth FV, Reines HD, et al. Stress ulcers and organ failure in intubated patients in surgical ICUs. Ann Surg 1992; 215:332–337
62 Baghaie AA, Mojtahedzadeh M, Levine RL, et al. Comparison of the effect of intermittent administration and continuous infusion of famotidine on gastric pH in critically ill patients: results of a prospective, randomized, crossover study. Crit Care Med 1995; 23:687–691
63 Ballesteros MA, Hogan DL, Koss MA, et al. Bolus or intravenous infusion of ranitidine: effects on gastric pH and acid secretion: a comparison of relative efficacy and cost. Ann Intern Med 1990; 112:334–339
64 Priebe HJ, Skillman JJ. Methods of prophylaxis in stress

ulcer disease. World J Surg 1981; 5:223–233
65 Peterson WL, Sturdevant RA, Frankl HD, et al. Healing of duodenal ulcer with an antacid regimen. N Engl J Med 1977; 297:341–345
66 Isenberg JI, Peterson WL, Elashoff JD, et al. Healing of benign gastric ulcer with low-dose antacid or cimetidine: a double-blind, randomized, placebo-controlled trial. N Engl J Med 1983; 308:1319–1324
67 Rydning A, Weberg R, Lange O, et al. Healing of benign gastric ulcer with low-dose antacids and fiber diet. Gastroenterology 1986; 91:56–61
68 Kumar N, Vij JC, Karol A, et al. Controlled therapeutic trial to determine the optimum dose of antacids in duodenal ulcer. Gut 1984; 25:1199–1202
69 Clain JE, Malagelada JR, Chadwick VS, et al. Binding properties *in vitro* of antacids for conjugated bile acids. Gastroenterology 1977; 73:556–559
70 Domschke W, Hagel J, Ruppin H, et al. Antacids and gastric mucosal protection. Scand J Gastroenterol Suppl 1986; 125:144–150
71 McCarthy DM. Sucralfate. N Engl J Med 1991; 325:1017–1025
72 Wilson DE. Antisecretory and mucosal protective actions of misoprostol: potential role in the treatment of peptic ulcer disease. Am J Med 1987; 83:2–8
73 Walt RP. Misoprostol for the treatment of peptic ulcer and anti-inflammatory-drug–induced gastroduodenal ulceration. N Engl J Med 1992; 327:1575–1580
74 ASHP. Therapeutic guidelines on stress ulcer prophylaxis. Am J Health Syst Pharm 1999; 56:347–379
75 Lacroix J, Infante-Rivard C, Jenicek M, et al. Prophylaxis of upper gastrointestinal bleeding in ICUs: a meta-analysis. Crit Care Med 1989; 17:862–869
76 Cook DJ, Witt LG, Cook RJ, et al. Stress ulcer prophylaxis in the critically ill: a meta-analysis. Am J Med 1991; 91:519–527
77 Koelz HR, Aeberhard P, Hassler H, et al. Prophylactic treatment of acute gastroduodenal stress ulceration: low-dose antacid treatment without and with additional ranitidine. Scand J Gastroenterol 1987; 22:1147–1152
78 More DG, Raper RF, Watson CJ, et al. Combination therapy with ranitidine and pirenzepine for control of intragastric pH in the critically ill. Crit Care Med 1985; 13:651–655
79 Engelhardt D, Karl R, Kolb HJ, et al. Comparison between cimetidine-pirenzepine and antacids for the prevention of stress hemorrhage in intensive care patients: a controlled clinical study on 125 patients. Dtsch Med Wochenschr 1985; 110:908–914
80 Krakamp B, Rommel T, Edelmann M, et al. Prevention of stress-induced hemorrhage of the upper gastrointestinal tract in neurosurgical intensive care patients: a controlled, randomized double-blind study with ranitidine alone and in combination with pirenzepine. Med Klin 1989; 84:133–134, 172
81 Pingleton SK, Hadzima SK. Enteral alimentation and gastrointestinal bleeding in mechanically ventilated patients. Crit Care Med 1983; 11:13–16
82 Raff T, Germann G, Hartmann B. The value of early enteral nutrition in the prophylaxis of stress ulceration in the severely burned patient. Burns 1997; 23:313–318
83 Bonten MJ, Gaillard CA, van Tiel FH, et al. Continuous enteral feeding counteracts preventive measures for gastric colonization in ICUs patients. Crit Care Med 1994; 22:939–944
84 Ruiz-Santana S, Ortiz E, Gonzalez B, et al. Stress-induced gastroduodenal lesions and total parenteral nutrition in critically ill patients: frequency, complications, and the value of prophylactic treatment; a prospective, randomized study. Crit Care Med 1991; 19:887–891
85 du Moulin GC, Paterson DG, Hedley-Whyte J, et al. Aspiration of gastric bacteria in antacid-treated patients: a frequent cause of postoperative colonization of the airway. Lancet 1982; 1:242–245
86 Craven DE, Steger KA, Barat LM, et al. Nosocomial pneumonia: epidemiology and infection control. Intensive Care Med 1992; 18:S3–S9
87 Heyland D, Mandell LA. Gastric colonization by Gram-negative bacilli and nosocomial pneumonia in the ICUs patient: evidence for causation. Chest 1992; 101:187–193
88 Hillman KM, Riordan T, O'Farrell SM, et al. Colonization of the gastric contents in critically ill patients. Crit Care Med 1982; 10:444–447
89 Garvey BM, McCambley JA, Tuxen DV. Effects of gastric alkalization on bacterial colonization in critically ill patients. Crit Care Med 1989; 17:211–216
90 Inglis TJ, Sproat LJ, Sherratt MJ, et al. Gastroduodenal dysfunction as a cause of gastric bacterial overgrowth in patients undergoing mechanical ventilation of the lungs. Br J Anaesth 1992; 68:499–502
91 Kollef MH. Ventilator-associated pneumonia: a multivariate analysis. JAMA 1993; 270:1965–1970
92 Drakulovic MB, Torres A, Bauer TT, et al. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. Lancet 1999; 354:1851–1858
93 Centers for Disease Control and Prevention. Guidelines for prevention of nosocomial pneumonia. MMWR Morb Mortal Wkly Rep 1997; 46:1–79
94 Bonten MJ, Gaillard CA, van der Geest S, et al. The role of intragastric acidity and stress ulcus prophylaxis on colonization and infection in mechanically ventilated ICU patients: a stratified, randomized, double-blind study of sucralfate versus antacids. Am J Respir Crit Care Med 1995; 152:1825–1834
95 Torres A, El-Ebiary M, Soler N, et al. Stomach as a source of colonization of the respiratory tract during mechanical ventilation: association with ventilator-associated pneumonia. Eur Respir J 1996; 9:1729–1735
96 Driks MR, Craven DE, Celli BR, et al. Nosocomial pneumonia in intubated patients given sucralfate as compared with antacids or histamine type 2 blockers: the role of gastric colonization. N Engl J Med 1987; 317:1376–1382
97 Prod'hom G, Leuenberger P, Koerfer J, et al. Nosocomial pneumonia in mechanically ventilated patients receiving antacid, ranitidine, or sucralfate as prophylaxis for stress ulcer: a randomized controlled trial. Ann Intern Med 1994; 120:653–662
98 Tryba M. Sucralfate versus antacids or H_2-antagonists for stress ulcer prophylaxis: a meta-analysis on efficacy and pneumonia rate. Crit Care Med 1991; 19:942–949
99 Bonten MJ, Gaillard CA, van Tiel FH, et al. The stomach is not a source for colonization of the upper respiratory tract and pneumonia in ICU patients. Chest 1994; 105:878–884
100 Reusser P, Zimmerli W, Scheidegger D, et al. Role of gastric colonization in nosocomial infections and endotoxemia: a prospective study in neurosurgical patients on mechanical ventilation. J Infect Dis 1989; 160:414–421
101 de Latorre FJ, Pont T, Ferrer A, et al. Pattern of tracheal colonization during mechanical ventilation. Am J Respir Crit Care Med 1995; 152:1028–1033
102 Bonten MJ, Gaillard CA, de Leeuw PW, et al. Role of colonization of the upper intestinal tract in the pathogenesis

of ventilator-associated pneumonia. Clin Infect Dis 1997; 24:309–319
103 Heyland DK, Cook DJ, Schoenfeld PS, et al. The effect of acidified enteral feeds on gastric colonization in critically ill patients: results of a multicenter randomized trial; Canadian Critical Care Trials Group. Crit Care Med 1999; 27:2399–2406
104 Khuroo MS, Yattoo GN, Javid G, et al. A comparison of omeprazole and placebo for bleeding peptic ulcer. N Engl J Med 1997; 336:1054–1058
105 Daneshmend TK, Hawkey CJ, Langman MJ, et al. Omeprazole versus placebo for acute upper gastrointestinal bleeding: randomised double blind controlled trial. BMJ 1992; 304:143–147
106 Lam NP, Le PD, Crawford SY, et al. National survey of stress ulcer prophylaxis. Crit Care Med 1999; 27:98–103
107 Ben-Menachem T, McCarthy BD, Fogel R, et al. Prophylaxis for stress-related gastrointestinal hemorrhage: a cost effectiveness analysis. Crit Care Med 1996; 24:338–345
108 Ben-Menachem T, Fogel R, Patel RV, et al. Prophylaxis for stress-related gastric hemorrhage in the medical ICUs: a randomized, controlled, single-blind study. Ann Intern Med 1994; 121:568–575
109 Harris SK, Bone RC, Ruth WE. Gastrointestinal hemorrhage in patients in a respiratory ICUs. Chest 1977; 72:301–304
110 Cook DJ. Stress ulcer prophylaxis: gastrointestinal bleeding and nosocomial pneumonia; best evidence synthesis. Scand J Gastroenterol Suppl 1995; 210:48–52
111 Wilmer A, Tack J, Frans E, et al. Duodenogastroesophageal reflux and esophageal mucosal injury in mechanically ventilated patients. Gastroenterology 1999; 116:1293–1299
112 Plaisier PW, van Buuren HR, Bruining HA. An analysis of upper GI endoscopy done for patients in surgical intensive care: high incidence of, and morbidity from reflux oesophagitis. Eur J Surg 1997; 163:903–907
113 Ibanez J, Penafiel A, Raurich JM, et al. Gastroesophageal reflux in intubated patients receiving enteral nutrition: effect of supine and semirecumbent positions. JPEN J Parenter Enteral Nutr 1992; 16:419–422
114 Orozco-Levi M, Torres A, Ferrer M, et al. Semirecumbent position protects from pulmonary aspiration but not completely from gastroesophageal reflux in mechanically ventilated patients. Am J Respir Crit Care Med 1995; 152:1387–1390
115 Ferrer M, Bauer TT, Torres A, et al. Effect of nasogastric tube size on gastroesophageal reflux and microaspiration in intubated patients. Ann Intern Med 1999; 130:991–994
116 Dotson RG, Robinson RG, Pingleton SK. Gastroesophageal reflux with nasogastric tubes: effect of nasogastric tube size. Am J Respir Crit Care Med 1994; 149:1659–1662
117 Torres A, Serra-Batlles J, Ros E, et al. Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: the effect of body position. Ann Intern Med 1992; 116:540–543
118 Drasar BS, Hill MJ, Shiner M. The deconjugation of bile salts by human intestinal bacteria. Lancet 1966; 1:1237–1238
119 Montejo JC. Enteral nutrition-related gastrointestinal complications in critically ill patients: a multicenter study: The Nutritional and Metabolic Working Group of the Spanish Society of Intensive Care Medicine and Coronary Units. Crit Care Med 1999; 27:1447–1453
120 Heyland DK, Tougas G, King D, et al. Impaired gastric emptying in mechanically ventilated, critically ill patients. Intensive Care Med 1996; 22:1339–1344
121 Bosscha K, Nieuwenhuijs VB, Vos A, et al. Gastrointestinal motility and gastric tube feeding in mechanically ventilated patients. Crit Care Med 1998; 26:1510–1517
122 Hagger R, Finlayson C, Jeffrey I, et al. Role of the interstitial cells of Cajal in the control of gut motility. Br J Surg 1997; 84:445–450
123 Inglis TJ, Sherratt MJ, Sproat LJ, et al. Gastroduodenal dysfunction and bacterial colonization of the ventilated lung. Lancet 1993; 341:911–913
124 Dive A, Michel I, Galanti L, et al. Gastric acidity and duodenogastric reflux during nasojejunal tube feeding in mechanically ventilated patients. Intensive Care Med 1999; 25:574–580
125 Levein NG, Thorn SE, Wattwil M. Dopamine delays gastric emptying and prolongs orocaecal transit time in volunteers. Eur J Anaesthesiol 1999; 16:246–250
126 Levein NG, Thorn SE, Lindberg G, et al. Dopamine reduces gastric tone in a dose-related manner. Acta Anaesthesiol Scand 1999; 43:722–725
127 Rex DK. Colonoscopy and acute colonic pseudo-obstruction. Gastrointest Endosc Clin North Am 1997; 7:499–508
128 Channick R, Curley FJ, Irwin RS. Indications of rectal tube use in critically ill patients. J Intensive Care Med 1988; 3:321–326
129 Dive A, Miesse C, Galanti L, et al. Effect of erythromycin on gastric motility in mechanically ventilated critically ill patients: a double-blind, randomized, placebo-controlled study. Crit Care Med 1995; 23:1356–1362
130 Annese V, Janssens J, Vantrappen G, et al. Erythromycin accelerates gastric emptying by inducing antral contractions and improved gastroduodenal coordination. Gastroenterology 1992; 102:823–828
131 Fraser R, Shearer T, Fuller J, et al. Intravenous erythromycin overcomes small intestinal feedback on antral, pyloric, and duodenal motility. Gastroenterology 1992; 103:114–119
132 Feighner SD, Tan CP, McKee KK, et al. Receptor for motilin identified in the human gastrointestinal system. Science 1999; 284:2184–2188
133 Mathis C, Malbert CH. Erythromycin gastrokinetic activity is partially vagally mediated. Am J Physiol 1998; 274:G80–G86
134 Jooste CA, Mustoe J, Collee G. Metoclopramide improves gastric motility in critically ill patients. Intensive Care Med 1999; 25:464–468
135 Harrington RA, Hamilton CW, Brogden RN, et al. Metoclopramide: an updated review of its pharmacologic properties and clinical use. Drugs 1983; 25:451–494
136 Valenzuela JE, Dooley CP. Dopamine antagonists in the upper gastrointestinal tract. Scand J Gastroenterol Suppl 1984; 96:127–136
137 Orihata M, Sarna SK. Contractile mechanisms of action of gastroprokinetic agents: cisapride, metoclopramide, and domperidone. Am J Physiol 1994; 266:G665–G676
138 Heyland DK, Tougas G, Cook DJ, et al. Cisapride improves gastric emptying in mechanically ventilated, critically ill patients: a randomized, double-blind trial. Am J Respir Crit Care Med 1996; 154:1678–1683
139 Spapen HD, Duinslaeger L, Diltoer M, et al. Gastric emptying in critically ill patients is accelerated by adding cisapride to a standard enteral feeding protocol: results of a prospective, randomized, controlled trial. Crit Care Med 1995; 23:481–485
140 Sturm A, Holtmann G, Goebell H, et al. Prokinetics in patients with gastroparesis: a systematic analysis. Digestion 1999; 60:422–427
141 MacLaren R, Kuhl DA, Gervasio JM, et al. Sequential single doses of cisapride, erythromycin, and metoclopramide in critically ill patients intolerant to enteral nutrition: a ran-

domized, placebo-controlled, crossover study. Crit Care Med 2000; 28:438–444
142 Ponec RJ, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. N Engl J Med 1999; 341:137–141
143 Child CS. Prevention of neostigmine-induced colonic activity: a comparison of atropine and glycopyrronium. Anesthesia 1984; 39:1083–1085
144 Kelly TW, Patrick MR, Hillman KM. Study of diarrhea in critically ill patients. Crit Care Med 1983; 11:7–9
145 Woolfson AM, Saour JN, Ricketts CR, et al. Prolonged nasogastric tube feeding in critically ill and surgical patients. Postgrad Med J 1976; 52:678–682
146 Ringel AF, Jameson GL, Foster ES. Diarrhea in the intensive care patient. Crit Care Clin 1995; 11:465–477
147 Smith CE, Marien L, Brogdon C, et al. Diarrhea associated with tube feeding in mechanically ventilated critically ill patients. Nurs Res 1990; 39:148–152
148 Brinson RR, Kolts BE. Hypoalbuminemia as an indicator of diarrheal incidence in critically ill patients. Crit Care Med 1987; 15:506–509
149 DeMeo M, Kolli S, Keshavarzian A, et al. Beneficial effect of a bile acid resin binder on enteral feeding induced diarrhea. Am J Gastroenterol 1998; 93:967–971
150 Chang RW, Jacobs S, Lee B. Gastrointestinal dysfunction among ICUs patients. Crit Care Med 1987; 15:909–914
151 Binder HJ. Pathophysiology of acute diarrhea. Am J Med 1990; 88:2S–4S
152 Cataldi-Betcher EL, Seltzer MH, Slocum BA, et al. Complications occurring during enteral nutrition support: a prospective study. JPEN J Parenter Enteral Nutr 1983; 7:546–552
153 Jones BJ, Lees R, Andrews J, et al. Comparison of an elemental and polymeric enteral diet in patients with normal gastrointestinal function. Gut 1983; 24:78–84
154 Heimburger DC, Sockwell DG, Geels WJ. Diarrhea with enteral feeding: prospective reappraisal of putative causes. Nutrition 1994; 10:392–396
155 Clausen MR, Bonnen H, Tvede M, et al. Colonic fermentation to short-chain fatty acids is decreased in antibiotic-associated diarrhea. Gastroenterology 1991; 101:1497–1504
156 Rao SS, Edwards CA, Austen CJ, et al. Impaired colonic fermentation of carbohydrate after ampicillin. Gastroenterology 1988; 94:928–932
157 Johnson LR, Copeland EM, Dudrick SJ, et al. Structural and hormonal alterations in the gastrointestinal tract of parenterally fed rats. Gastroenterology 1975; 68:1177–1183
158 Lo CW, Walker WA. Changes in the gastrointestinal tract during enteral or parenteral feeding. Nutr Rev 1989; 47: 193–198
159 Hernandez G, Velasco N, Wainstein C, et al. Gut mucosal atrophy after a short enteral fasting period in critically ill patients. J Crit Care 1999; 14:73–77
160 Van der Meer R, Welberg JW, Kuipers F, et al. Effects of supplemental dietary calcium on the intestinal association of calcium, phosphate, and bile acids. Gastroenterology 1990; 99:1653–1659
161 Liolios A, Oropello JM, Benjamin E. Gastrointestinal complications in the ICUs. Clin Chest Med 1999; 20:329–345
162 Cleary RK. *Clostridium difficile*-associated diarrhea and colitis: clinical manifestations, diagnosis, and treatment. Dis Colon Rectum 1998; 41:1435–1449
163 Jobe BA, Grasley A, Deveney KE, et al. *Clostridium difficile* colitis: an increasing hospital-acquired illness. Am J Surg 1995; 169:480–483
164 Settle CD. *Clostridium difficile*. Br J Hosp Med 1996; 56:398–400
165 Gerding DN, Olson MM, Peterson LR, et al. *Clostridium difficile*-associated diarrhea and colitis in adults: a prospective case-controlled epidemiologic study. Arch Intern Med 1986; 146:95–100
166 Brown E, Talbot GH, Axelrod P, et al. Risk factors for *Clostridium difficile* toxin-associated diarrhea. Infect Control Hosp Epidemiol 1990; 11:283–290
167 Kelly CP, Pothoulakis C, LaMont JT. *Clostridium difficile* colitis. N Engl J Med 1994; 330:257–262
168 Manabe YC, Vinetz JM, Moore RD, et al. *Clostridium difficile* colitis: an efficient clinical approach to diagnosis. Ann Intern Med 1995; 123:835–840
169 Jensen GL, Bross JE, Bourbeau PP, et al. Risk factors for *Clostridium difficile* stool cytotoxin b among critically ill patients: role of sucralfate. J Infect Dis 1994; 170:227–230
170 Bergmans D, Bonten M, Gaillard C, et al. *In vitro* antibacterial activity of sucralfate. Eur J Clin Microbiol Infect Dis 1994; 13:615–620
171 West AP, Abdul S, Sherratt MJ, et al. Antibacterial activity of sucralfate against *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* in batch and continuous culture. Eur J Clin Microbiol Infect Dis 1993; 12:869–871
172 Brinson RR, Kolts BE. Diarrhea associated with severe hypoalbuminemia: a comparison of a peptide-based chemically defined diet and standard enteral alimentation. Crit Care Med 1988; 16:130–136
173 Hwang TL, Lue MC, Nee YJ, et al. The incidence of diarrhea in patients with hypoalbuminemia because of acute or chronic malnutrition during enteral feeding. Am J Gastroenterol 1994; 89:376–378
174 Heimburger DC, Geels WJ, Thiesse KT, et al. Randomized trial of tolerance and efficacy of a small-peptide enteral feeding formula versus a whole-protein formula. Nutrition 1995; 11:360–364
175 Heimburger DC, Geels VJ, Bilbrey J, et al. Effects of small-peptide and whole-protein enteral feedings on serum proteins and diarrhea in critically ill patients: a randomized trial. JPEN J Parenter Enteral Nutr 1997; 21:162–167
176 Mowatt-Larssen CA, Brown RO, Wojtysiak SL, et al. Comparison of tolerance and nutritional outcome between a peptide and a standard enteral formula in critically ill, hypoalbuminemic patients. JPEN J Parenter Enteral Nutr 1992; 16:20–24
177 Dobb GJ, Towler SC. Diarrhea during enteral feeding in the critically ill: a comparison of feeds with and without fiber. Intensive Care Med 1990; 16:252–255
178 Hart GK, Dobb GJ. Effect of a fecal bulking agent on diarrhea during enteral feeding in the critically ill. JPEN J Parenter Enteral Nutr 1988; 12:465–468
179 Steinberg S, Azar G, Love R, et al. Dopexamine prevents depression of mesenteric blood flow caused by positive end-expiratory pressure in rats. Surgery 1996; 120:597–601
180 Maynard ND, Bihari DJ, Dalton RN, et al. Increasing splanchnic blood flow in the critically ill. Chest 1995; 108:1648–1654
181 Lee RD, Choe E, Flint L, et al. Neither dopamine nor dobutamine corrects mesenteric blood flow depression caused by positive end-expiratory pressure in a rat model of acute lung injury. Crit Care Med 1998; 26:1875–1880
182 Azar G, Love R, Choe E, et al. Neither dopamine nor dobutamine reverses the depression in mesenteric blood flow caused by positive end-expiratory pressure. J Trauma 1996; 40:679–685
183 Beyer J, Schosser R, Conzen P, et al. Regional blood flow in splanchnic organs during positive end-expiratory pressure ventilation [in German]. Langenbecks Arch Surg Suppl 1980; 353:239–242

184 Halden E, Jakobson S, Janeras L, et al. Effects of positive end-expiratory pressure on cardiac output distribution in the pig. Acta Anaesthesiol Scand 1982; 26:403–408
185 Fleischer GM, Beau I, Herden P, et al. Is there a PEEP-induced pancreatitis in experiments? Langenbecks Arch Chir 1984; 362:185–192
186 Kahle M, Lippert J, Willemer S, et al. Effects of positive end-expiratory pressure (PEEP) ventilation on the exocrine pancreas in minipigs. Res Exp Med 1991; 191:309–325
187 Warshaw AL, O'Hara PJ. Susceptibility of the pancreas to ischemic injury in shock. Ann Surg 1978; 188:197–201
188 Bredenberg CE, Paskanik AM. Relation of portal hemodynamics to cardiac output during mechanical ventilation with PEEP. Ann Surg 1983; 198:218–222
189 Matuschak GM, Pinsky MR, Rogers RM. Effects of positive end-expiratory pressure on hepatic blood flow and performance. J Appl Physiol 1987; 62:1377–1383
190 Fujita Y. Effects of PEEP on splanchnic hemodynamics and blood volume. Acta Anaesthesiol Scand 1993; 37:427–431
191 Brienza N, Revelly JP, Ayuse T, et al. Effects of PEEP on liver arterial and venous blood flows. Am J Respir Crit Care Med 1995; 152:504–510
192 Sha M, Saito Y, Yokoyama K, et al. Effects of continuous positive-pressure ventilation on hepatic blood flow and intrahepatic oxygen delivery in dogs. Crit Care Med 1987; 15:1040–1043
193 Bonnet F, Richard C, Glaser P, et al. Changes in hepatic flow induced by continuous positive pressure ventilation in critically ill patients. Crit Care Med 1982; 10:703–705
194 Purcell PN, Branson RD, Hurst JM, et al. Gut feeding and hepatic hemodynamics during PEEP ventilation for acute lung injury. J Surg Res 1992; 53:335–341
195 Risoe C, Hall C, Smiseth OA. Splanchnic vascular capacitance and positive end-expiratory pressure in dogs. J Appl Physiol 1991; 70:818–824
196 Lovett JV, Morriss LL, Bomberger RA, et al. The effects of positive expiratory pressure on peritoneovenous shunt flow. J Surg Res 1992; 53:1–3
197 Beyer J, Beckenlechner P, Messmer K. The influence of PEEP ventilation on organ blood flow and peripheral oxygen delivery. Intensive Care Med 1982; 8:75–80
198 Manny J, Justice R, Hechtman HB. Abnormalities in organ blood flow and its distribution during positive end-expiratory pressure. Surgery 1979; 85:425–432
199 Lautt WW, Legare DJ, d'Almeida MS. Adenosine as putative regulator of hepatic arterial flow (the buffer response). Am J Physiol 1985; 248:H331–H338
200 Richard C, Berdeaux A, Delion F, et al. Effect of mechanical ventilation on hepatic drug pharmacokinetics. Chest 1986; 90:837–841
201 Maynard ND, Bihari DJ, Dalton RN, et al. Liver function and splanchnic ischemia in critically ill patients. Chest 1997; 111:180–187
202 Kainuma M, Nakashima K, Sakuma I, et al. Hepatic venous hemoglobin oxygen saturation predicts liver dysfunction after hepatectomy. Anesthesiology 1992; 76:379–386
203 Trager K, Radermacher P, Georgieff M. PEEP and hepatic metabolic performance in septic shock. Intensive Care Med 1996; 22:1274–1275
204 Perkins MW, Dasta JF, DeHaven B. Physiologic implications of mechanical ventilation on pharmacokinetics. DICP 1989; 23:316–323
205 Rady MY, Kodavatiganti R, Ryan T. Perioperative predictors of acute cholecystitis after cardiovascular surgery. Chest 1998; 114:76–84
206 Savino JA, Scalea TM, Del Guercio LR. Factors encouraging laparotomy in acalculous cholecystitis. Crit Care Med 1985; 13:377–380
207 Cornwell EEd, Rodriguez A, Mirvis SE, et al. Acute acalculous cholecystitis in critically injured patients: preoperative diagnostic imaging. Ann Surg 1989; 210:52–55
208 Helbich TH, Mallek R, Madl C, et al. Sonomorphology of the gallbladder in critically ill patients: value of a scoring system and follow-up examinations. Acta Radiol 1997; 38:129–134
209 Gately JF, Thomas EJ. Acute cholecystitis occurring as a complication of other diseases. Arch Surg 1983; 118:1137–1141
210 Stevens PE, Harrison NA, Rainford DJ. Acute acalculous cholecystitis in acute renal failure. Intensive Care Med 1988; 14:411–416
211 Lee SP. Pathogenesis of biliary sludge. Hepatology 1990; 12:200S–203S
212 Savoca PE, Longo WE, Pasternak B, et al. Does visceral ischemia play a role in the pathogenesis of acute acalculous cholecystitis? J Clin Gastroenterol 1990; 12:33–36
213 Nies C, Zielke A, Hasse C, et al. Atony of the gallbladder as a risk factor for acalculous cholecystitis: what is the effect of intensive care? Zentralbl Chir 1994; 119:75–80
214 Johnson LB. The importance of early diagnosis of acute acalculous cholecystitis. Surg Gynecol Obstet 1987; 164: 197–203
215 Melin MM, Sarr MG, Bender CE, et al. Percutaneous cholecystostomy: a valuable technique in high-risk patients with presumed acute cholecystitis. Br J Surg 1995; 82:1274–1277
216 Madl C, Grimm G, Mallek R, et al. Diagnosis of gallbladder perforation in acute acalculous cholecystitis in critically ill patients. Intensive Care Med 1992; 18:245–246
217 Molenat F, Boussuges A, Valantin V, et al. Gallbladder abnormalities in medical ICU patients: an ultrasonographic study. Intensive Care Med 1996; 22:356–358
218 McGahan JP, Lindfors KK. Acute cholecystitis: diagnostic accuracy of percutaneous aspiration of the gallbladder. Radiology 1988; 167:669–671
219 Mirvis SE, Vainright JR, Nelson AW, et al. The diagnosis of acute acalculous cholecystitis: a comparison of sonography, scintigraphy, and CT. AJR Am J Roentgenol 1986; 147: 1171–1175
220 Shuman WP, Rogers JV, Rudd TG, et al. Low sensitivity of sonography and cholescintigraphy in acalculous cholecystitis. AJR Am J Roentgenol 1984; 142:531–534
221 Jeffrey RB Jr, Sommer FG. Follow-up sonography in suspected acalculous cholecystitis: preliminary clinical experience. J Ultrasound Med 1993; 12:183–187
222 Blankenberg F, Wirth R, Jeffrey RB Jr, et al. Computed tomography as an adjunct to ultrasound in the diagnosis of acute acalculous cholecystitis. Gastrointest Radiol 1991; 16:149–153
223 Browning PD, McGahan JP, Gerscovich EO. Percutaneous cholecystostomy for suspected acute cholecystitis in the hospitalized patient. J Vasc Interv Radiol 1993; 4:531–537
224 Boland GW, Lee MJ, Leung J, et al. Percutaneous cholecystostomy in critically ill patients: early response and final outcome in 82 patients. AJR Am J Roentgenol 1994; 163: 339–342
225 Brugge WR, Friedman LS. A new endoscopic procedure provides insight into an old disease: acute acalculous cholecystitis. Gastroenterology 1994; 106:1718–1720