CME CREDIT

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Stress ulcer prophylaxis: The case for a selective approach

ABSTRACT

Although stress-related mucosal damage is common (and potentially serious) in critically ill patients, the risk of clinically significant gastrointestinal bleeding appears to be confined to patients with certain factors: mechanical ventilation, coagulopathy, multiple trauma, increased intracranial pressure, and multiorgan dysfunction. Because prophylactic therapy also poses risks, we advocate reserving it for patients in these high-risk groups.

KEY POINTS

Drugs used to prevent mucosal damage by increasing gastric pH may increase the risk of nosocomial pneumonia.

Sucralfate seems to be the most cost-effective agent for preventing stress-related mucosal damage. However, it can be given only by mouth or nasogastric tube and thus may not be suitable for all critically ill patients.

There is still debate about the relative efficacy and advantages of different agents for preventing stress-related mucosal damage. For any particular patient, the physician has to consider the route of administration available and the drug interactions, side effects, and cost of these agents when prescribing them.

STRESS-RELATED MUCOSAL DAMAGE is a syndrome of erosive gastritis that occurs in critically ill patients.[1] The problem is so common and potentially serious that most intensive-care patients now routinely receive drugs to prevent it,[2,3] and some physicians give these drugs to all their hospitalized patients. However, we believe that this approach is wrong. In this article, we review the prophylactic drugs for stress-related mucosal damage and argue for using them selectively, in high-risk patients only.

A COMMON AND SERIOUS PROBLEM

Approximately three fourths of all patients show some endoscopic evidence of gastrointestinal damage as early as 24 hours after admission into an intensive care unit.[4,5] Gastrointestinal bleeding, a common manifestation of mucosal injury, occurs in approximately 20% of intensive-care patients who do not receive prophylactic therapy.[6,7] In only 2% to 6% of patients[8] is the bleeding clinically serious—ie, massive enough to cause a worrisome drop in blood pressure or hematocrit or requiring a blood transfusion. But in those patients the mortality rate is more than 50%.[9]

WHY NOT GIVE PROPHYLACTIC DRUGS TO EVERYONE?

In the past 20 years, the incidence of overt bleeding has declined. Even though prophylactic therapy is being used commonly, there are several reasons why we believe that prophylactic drugs should *not* be given to all intensive-care patients.

TABLE 1

RISK FACTORS FOR STRESS ULCERS AND GASTROINTESTINAL BLEEDING IN CRITICALLY ILL PATIENTS

Coagulopathy
Head injury
Hepatic or renal failure
Hypotension, shock
Major trauma, polytrauma
Major surgery
Mechanical ventilation
Multiple organ failure
Sepsis
Severe burns

SOURCE: FISHER RL, PIPKIN GA, WOOD JR. STRESS-RELATED MUCOSAL DISEASE: PATHOPHYSIOLOGY, PREVENTION AND TREATMENT. CRIT CARE CLINICS 1995;11:327–345.

Patients without risk factors have a very low risk of bleeding

- Prophylactic drugs can cause side effects; notably, drugs that decrease the acidity of the stomach may contribute to nosocomial pneumonia by making the environment of the stomach more hospitable to bacterial growth.
- Prophylactic drugs increase the complexity of care by interfering with the actions of other drugs and, with some of them, by necessitating gastric pH monitoring to calibrate their dosage.
- Universal prophylactic drug therapy is not cost-effective, as the risk of serious gastrointestinal bleeding appears to be confined to certain well-defined groups.
- Prophylactic drug therapy has not been proved unequivocally to reduce the mortality rate, as studies have yielded conflicting results.

WHO IS AT RISK FOR STRESS ULCERS?

There is controversy about what pre-existing conditions warrant stress ulcer prophylaxis in the critically ill[10]; TABLE 1 lists the generally accepted risk factors that were identified in recent studies.[11–15]

Cook et al[11] conducted a multicenter trial involving 2,252 patients in medical and surgical intensive care units. Only 1.5% of all patients had an episode of clinically important bleeding, and 69.7% of these patients were already receiving prophylaxis. Only two independent risk factors for gastrointestinal bleeding were identified: respiratory failure requiring mechanical ventilation and coagulopathy. The overall risk of developing a stress hemorrhage without those risk factors was 0.1%. These findings call into question the need for prophylaxis in patients at low risk.

Further evidence comes from a randomized, controlled study in medical intensive-care patients, conducted by Ben-Menachem et al,[12] who found that the only identifiable risk factors for bleeding were high-dose steroid use and respiratory failure. Further, the incidence of clinically important bleeding was not significantly lower in patients who received the prophylactic drugs sucralfate or cimetidine than in control patients.

In surgical patients, other studies identified several other risk factors: multiple trauma, head trauma, increased intracranial pressure, and burns.[10,13,14] A multicenter study found that mechanically ventilated postoperative patients with hypotension or sepsis were at significant risk of stress-related mucosal damage even if prophylaxis was provided; other risk factors identified were coagulopathy and renal, hepatic, and respiratory failure.[15]

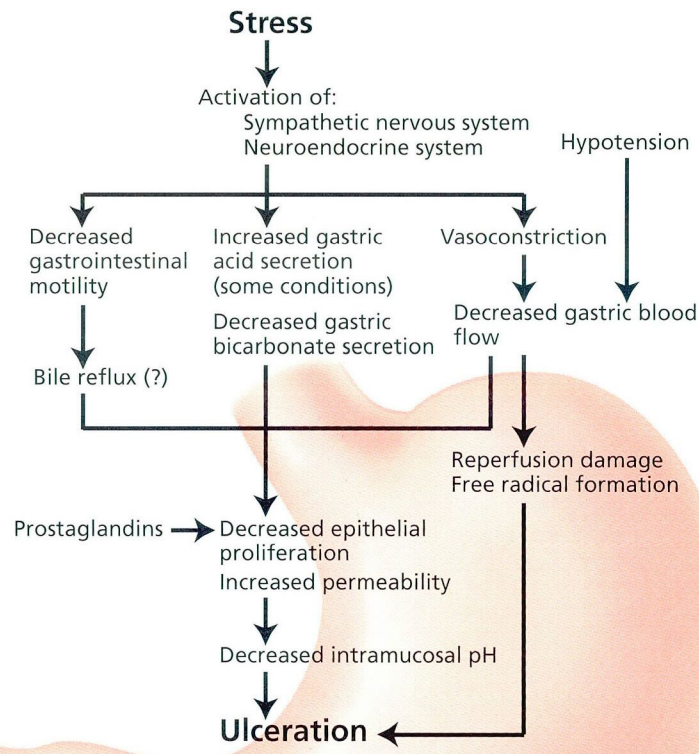
DOES PROPHYLACTIC THERAPY REDUCE MORTALITY?

Prophylactic therapy remains controversial because no study has clearly demonstrated that it reduces mortality.[12,16] One reason why it is difficult to derive firm conclusions is that the studies conducted to date have varied considerably in their design, patient populations, definitions of stress-related mucosal damage, and medication regimens.[10,16] The overall incidence of overt bleeding appears to be decreasing.[17] However, recent studies show a lack of reduction in clinically important bleeding

What causes stress ulcers?

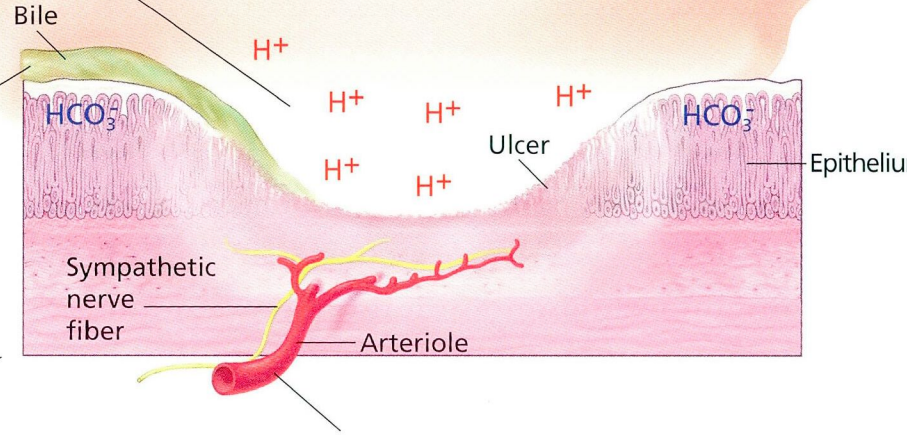
The pathogenesis of stress-related mucosal damage is not fully understood but most likely is multifactorial.[17,36,48–50] Basically, physiologic stress may lead to breakdown of the stomach wall through several interrelated processes (shown schematically at right and in a cross-section of the gastric epithelium below).

Of note, *Helicobacter pylori*, an organism known to contribute to the pathogenesis of peptic ulcers, has recently been implicated in the development of stress-related mucosal damage as well.[50] More studies are needed to confirm this finding.



Decreased bicarbonate secretion allows gastric acid to damage the epithelium, as hydrogen ions diffuse into an epithelium made more permeable by ischemia, resulting in intramural acidosis, cell death, and ulceration.

Decreased gastric motility may, in theory, facilitate bile reflux and breakdown of the mucosal barrier.



Activation of the sympathetic nervous system and the neurohormonal system, triggered by the stress, in turn causes decreased gastric motility, decreased gastric blood flow, and decreased bicarbonate secretion.

Decreased gastric blood flow is due to vasoconstriction (mediated by the alpha adrenergic nervous system and the neuroendocrine system) or to hypotension. The resulting ischemia causes decreased secretion of bicarbonate in the stomach and duodenum, decreased mucosal proliferation, and increased permeability of the gastric epithelium. Reperfusion damage leads to formation of free radicals.

SOURCE: ALGORITHM ADAPTED FROM BRESALIER, REFERENCE 15

TABLE 2

FACTORS TO CONSIDER IN SELECTING DRUGS

Factor	Sucralfate	H_2 receptor	
		Cimetidine	Famotidine
Route	Oral Nasogastric	Oral Nasogastric Duodenal Intravenous	Oral Nasogastric Duodenal Intravenous
pH Monitoring	No	Yes	Yes
Drug interactions	Decreases levels of: Oral quinolones Digoxin Theophylline Phenytoin	Increases levels of many drugs, especially: Warfarin Phenytoin Propranolol Decreases levels of: Ketoconazole Itraconazole	Decreases levels of: Warfarin Itraconazole
Side effects	Hypophosphatemia (rare) Constipation	Diarrhea Headache Mental status changes Hyperprolactinemia Reduced androgen production	Diarrhea Headache Mental status changes
Nosocomial pneumonia risk	Less	More	More
Dosage	1 g by mouth or nasogastric tube every 6 hours	Intravenous: 50 mg/hour or 300 mg every 6 hours Oral, enteral: 400 mg twice a day	20 mg by mouth or intravenously twice a day
Approximate cost per day	$3.05	Intravenous: $29.64 Oral: $3.21	Intravenous: $6.46 Oral: $3.19
Disadvantages	No intravenous form Drug interactions	Drug interactions Nosocomial pneumonia risk Dosage must be lowered in patients with renal insufficiency	More expensive IV Dosage must be lowered in patients with renal insufficiency Nosocomial pneumonia risk

*Lansoprazole has been studied less than omeprazole for this indication.

Universal prophylactic drug therapy is not cost-effective

despite the use of prophylactic agents.[11,12] The decline in bleeding from stress-related mucosal damage is theorized to be due to overall improvements in intensive care, with better resuscitation (ie, more aggressive fluid replacement, cardiac support, and ventilatory support) and earlier enteral nutrition.[2,3,17]

SELECTING AN AGENT

The medications commonly used for preventing stress-related mucosal damage are sucral-

TO PREVENT STRESS-RELATED MUCOSAL DAMAGE

antagonists		Antacids	Proton-pump inhibitors
Nizatidine	Ranitidine		Omeprazole*
Oral	Oral Nasogastric Duodenal Intravenous	Oral Nasogastric	Oral Nasogastric Duodenal
Yes	Yes	Yes	Yes
Decreases levels of: Ketoconazole Itraconazole	May increase levels of: Warfarin Decreases levels of: Ketoconazole Itraconazole	Decrease levels of: Iron Oral quinolones Ketoconazole Itraconazole H_2 receptor antagonists Digoxin Phenytoin Theophylline	Increases levels of: Phenytoin Warfarin Decreases levels of: Ketoconazole Itraconazole
Headache Diarrhea Dizziness	Rash Nausea Vomiting Headache Drowsiness	Hypermagnesemia GI distension Hypophosphatemia Diarrhea Constipation	Minimal
More	More	More	More?
150 mg twice a day by mouth or enteral tube	Intravenous: 50 mg every 6–8 hours or 6.25–8.3 mg/hour Oral, enteral: 150 mg 1–2 times a day	15 cc every 2–6 hours by mouth or nasogastric tube	20 mg daily by mouth
$3.00	Intravenous: $23.64 Oral: $3.19	$0.82	$3.63
Nosocomial pneumonia risk Dosage must be lowered in patients with renal insufficiency	Nosocomial pneumonia risk Dosage must be lowered in patients with renal insufficiency	Frequent dosing (every 2 hours) Side effects Nosocomial pneumonia risk	Expensive Less studied in stress-related mucosal damage

SOURCE: DRUG PRICES FROM: DRUGS FOR TREATMENT OF PEPTIC ULCERS. MED LETT. JAN 3 1997; 39:1–3; AND DRUG TOPICS RED BOOK UPDATE. NOVEMBER 1996.

No study has proved that prophylactic drugs reduce mortality

fate, histamine type-2 (H_2) receptor antagonists, and antacids (TABLE 2). Of these, only cimetidine, an H_2 receptor antagonist, has been approved by the Food and Drug Administration for this indication. However some trials have demonstrated a reduction in overt or occult bleeding with all these types of agents.[16,18–22] Newer medications such as omeprazole (a proton-pump inhibitor) and misoprostol (a prostaglandin analog) are used occasionally in clinical practice but have not been well studied.

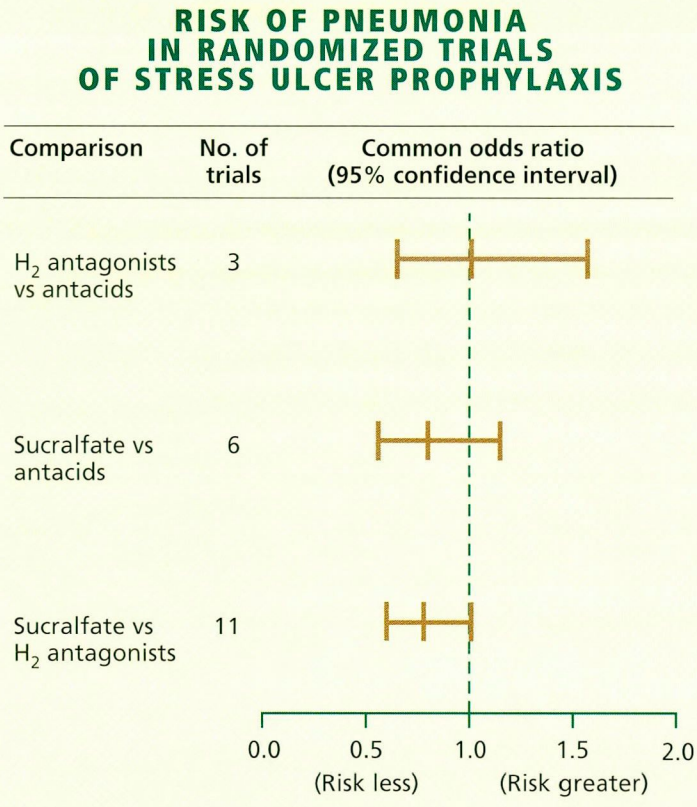


FIGURE 2. According to a meta-analysis of randomized trials of prophylactic therapy to prevent stress ulcers, the risk of nosocomial pneumonia is less in patients treated with sucralfate than with antacids or histamine$_2$ receptor antagonists, although the trend was not statistically significant. The common odds ratio indicates the extent of risk: if the odds ratio is 1.0, the chance of developing the outcome of interest is the same, regardless of treatment group. An odds ratio of 0.5 means that the odds of a patient in the treatment group developing the outcome of interest would be half that of the control group.

SOURCE: MODIFIED FROM COOK ET AL, REFERENCE 21.

Sucralfate

Sucralfate degrades in the presence of acid and binds to the gastric mucosal layer, releasing an aluminum base.[23] It protects the mucosa by acting as a barrier to hydrogen ions, rather than by increasing the gastric pH. Sucralfate has not been well studied in critically ill neurosurgical and burn patients[10]; therefore, H_2 antagonists may be preferable as first-line agents in these populations.

Drug interactions. Sucralfate decreases absorption of other oral drugs,[23] particularly quinolones, tetracycline, theophylline, digoxin, and phenytoin. It should therefore be avoided in patients who require oral quinolone antibiotics,[23] and should be given at least 2 hours after doses of digoxin, tetracycline, or phenytoin.

Side effects. Because sucralfate is relatively nonabsorbable, it has minimal side effects; the most common are hypophosphatemia and constipation due to the aluminum component.

Dosage. One gram by mouth or nasogastric tube every 6 hours. Giving this agent via a feeding tube in the duodenum bypasses the gastric mucosa and may reduce its efficacy.

Cost. Sucralfate is relatively inexpensive compared with other agents and does not require pH monitoring or intravenous access.[10]

H_2 receptor antagonists

The availability of H_2 receptor antagonists in intravenous formulations makes them the most frequently used drugs for stress ulcer prophylaxis. These agents competitively and selectively inhibit the binding of histamine to H_2 receptors in the parietal cells of the stomach, decreasing the secretion of hydrogen ions and raising the gastric pH.[24]

Drug interactions. Cimetidine has multiple drug interactions because it binds to the P450 enzyme system in the liver and inhibits the metabolism of drugs that are metabolized by this system.[24] Ranitidine binds less to the P450 enzyme system than does cimetidine, and famotidine and nizatidine do not bind to it appreciably. All H_2 receptor antagonists inhibit the absorption of ketoconazole and itraconazole, which have a pH-dependent absorption. Because antacids decrease the absorption of H_2 receptor antagonists when given orally, these two types of drugs should be given 2 hours apart. Combination therapy with sucralfate has not been studied.

Side effects are infrequent and include diarrhea, headache, and mental status changes, primarily in the elderly. In case reports, thrombocytopenia has been documented; however, the incidence is less than

RELATIVE EFFECTIVENESS OF PROPHYLACTIC DRUGS IN RANDOMIZED TRIALS OF STRESS ULCER PROPHYLAXIS

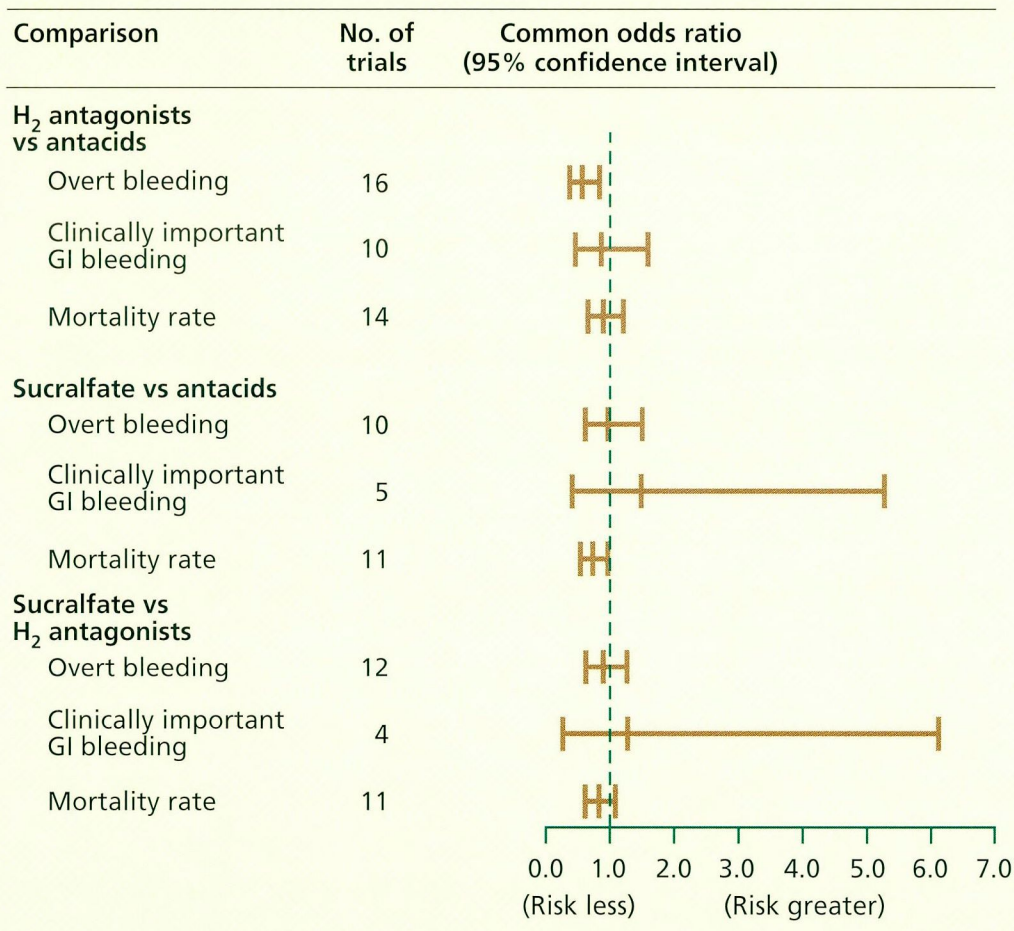


FIGURE 3. The results of randomized trials of stress ulcer prophylaxis have varied and depend on the outcome measured.

SOURCE: MODIFIED FROM COOK ET AL, REFERENCE 21.

The role of *H pylori* in stress ulcers is unclear

1%.[24–26] Cimetidine also induces hyperprolactinemia and reduces androgen production.[29]

H_2 receptor antagonists, by increasing the gastric pH, have also been implicated in bacterial colonization of the gastric mucosa and the development of nosocomial pneumonia.[27] Numerous studies have detected a higher incidence of pneumonia in patients receiving these agents than in those receiving sucralfate[11,16–20,27–29]; the incidence also appears to be higher in patients receiving antacids (FIGURE 2).[21] However, the link between H_2 receptor antagonists and pneumonia is somewhat controversial, because the reported incidence has varied widely, from 0% to 50%.[11,30]

Dosage. H_2 receptor antagonists can be given by mouth, nasogastric or duodenal tube, or intravenously in bolus doses or as continuous infusions. The advantage of a continuous infusion is that it can keep the gastric pH at 3.5 or higher, whereas intermittent adminis-

tration allows more fluctuation.[31–34] The gastric pH is often used as a marker of efficacy, but the exact pH needed to prevent stress ulcers remains uncertain. One study found that the incidence of bleeding from stress-related mucosal damage was lower at a pH greater than 3.5.[35] However, even though they control pH better, continuous infusions of H_2 receptor antagonists have not been shown to decrease the incidence of bleeding compared with bolus administration.[34]

Dosages of H_2 receptor antagonists should be decreased in patients with renal insufficiency.

Antacids

Antacids have been proved to prevent stress-related mucosal damage.[16,20,35] However, their frequent dosing, side effects, and possible link to nosocomial pneumonia in clinical trials[19,29] have led to a decline in their clinical use.[10,12,36]

Proton-pump inhibitors

Consider switching to an enteral preparation when possible

Proton-pump inhibitors covalently bind to the hydrogen-potassium pump in the parietal cells and decrease gastric acid production.[37] Two proton-pump inhibitors are currently available: omeprazole and lansoprazole. However, there is not enough information about lansoprazole available at this time to suggest its use in preventing stress-related mucosal damage.

Side effects are minimal.

Drug interactions. Like H_2 receptor antagonists, proton-pump inhibitors inhibit the absorption of pH-dependent drugs, such as quinolone antibiotics. Omeprazole may also inhibit the metabolism of phenytoin and warfarin.

Dosage and administration. The lack of an intravenous form or stable oral liquid preparation of omeprazole in the United States has limited its use for stress-related mucosal damage in intensive-care patients. Recently, Phillips et al[38] reported that no clinically significant upper gastrointestinal bleeding occurred in a series of mechanically ventilated surgical and burn patients who received a specially made omeprazole suspension; however, the pneumonia rate was 12%, again raising the question of acid inhibition leading to microbial colonization and infection.

Clinical trials are needed to compare the efficacy and cost of proton-pump inhibitors, H_2 receptor antagonists, and sucralfate.

Prostaglandin analogues

Prostaglandin analogues, such as misoprostol, are used to prevent gastric ulcers in patients taking nonsteroidal anti-inflammatory drugs.[39] Misoprostol has also been used to treat duodenal and gastric ulcers. A study that compared cimetidine, antacids, and misoprostol for preventing stress-related mucosal damage in surgical patients found them all equally effective.[14] However, the use of prostaglandin analogues has been limited by frequent adverse effects such as abdominal pain, diarrhea, and abortifacient activity.[39] Until more definitive trials are conducted, these agents should not be used routinely in critically ill patients.

WHAT AGENT IS MOST EFFECTIVE?

Comparative studies have shown that antacids, H_2 receptor antagonists, and sucralfate are all effective for preventing stress-related mucosal damage.[16–22] However, the data conflict as to what agent is best. For example, a meta-analysis of studies conducted before 1995 found that the risk of overt bleeding was significantly lower with H_2 receptor antagonists than with antacids (FIGURE 3).[21] The incidence of overt bleeding was approximately equal with sucralfate compared with H_2 receptor antagonists, and approximately equal with sucralfate compared with antacids. However, there was a trend toward more clinically important bleeding with sucralfate than with H_2 receptor antagonists or antacids. On the other hand, only sucralfate was associated with a decrease in mortality. Previous meta-analyses showed different results.[18,20] Because of these conflicting data, comparative efficacy remains relatively equivocal. Criteria for selecting agents should include the adverse effect profile, drug interactions, route of administration, and cost.[22]

ECONOMIC IMPLICATIONS

Even though recent studies found that only a small percentage of intensive-care patients are

at risk of stress-related bleeding, most patients still receive prophylactic therapy. Some researchers argue that the benefit of prophylaxis outweighs its risks and cost.[40,42] However, the overall cost to the institution can be significant.[3] A 1994 survey of pharmacy departments of academic health centers revealed that each institution could save $60,000 to $200,000 per year by using H_2 receptor antagonists only in intensive-care patients at risk, and giving them orally or enterally instead of intravenously, when possible.[43,44] Once a patient's medical condition improves (as indicated by extubation or ICU discharge), physicians should consider discontinuing prophylactic agents.

It has been suggested that H_2 receptor antagonists should be reserved for intensive-care patients with respiratory failure requiring more than 48 hours of mechanical ventilation, coagulopathy (thrombocytopenia, disseminated intravascular coagulation, prolonged prothrombin time, or partial thromboplastin time), or concomitant administration of steroids in high doses (> 250 mg of hydrocortisone or an equivalent daily).[43] The least expensive but effective agent should be used. Therefore, we recommend switching to an oral preparation as soon as possible.

Evidence suggests that enteral feedings alone may be adequate to reduce stress-related mucosal damage and bleeding.[45,46] The mechanism remains unknown, but one proposed mechanism is by alkalinization of the stomach.[45] Nutrition itself, whether parenteral or enteral, may maintain the integrity and promote repair of the gastric mucosa.[45,47]

According to a cost-effectiveness analysis,[30] prophylactic therapy with sucralfate cost $103,715 per bleeding episode averted in a low-risk population such as patients with a 0.1% risk of hemorrhage, but was much more cost-effective in high-risk patients such as those with a 12% to 33% risk of bleeding. The same researchers calculated that therapy with cimetidine costs 6.5 times as much as with sucralfate, assuming that sucralfate and cimetidine are equally effective and taking into account the risk of nosocomial pneumonia with cimetidine.

THE AUTHORS' RECOMMENDATIONS

We recommend that only intensive-care patients with risk factors that may predispose them to stress-related mucosal damage should receive prophylaxis; these risk factors include mechanical ventilation, coagulopathy, multiple trauma, increased intracranial pressure, and multi-organ dysfunction.

Sucralfate seems to be the most cost-effective agent for preventing stress-related mucosal damage, since it has few adverse effects and has been implicated less in the development of nosocomial pneumonia. However, sucralfate can be given only by mouth or nasogastric tube and thus may not be suitable for all critically ill patients. There is still debate about the relative efficacy and advantages of the different agents for preventing this disorder. One has to consider route of administration available, drug interactions, side effects, and cost of these agents when choosing drug therapy.

More research is needed to calculate more accurately the risk of bleeding in various populations and the risk of pneumonia with various agents, to provide cost-effective stress ulcer prophylaxis.

Earlier enteral feeding may decrease ulcer risk by itself

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