ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis

DEVELOPED THROUGH THE ASHP COMMISSION ON THERAPEUTICS AND APPROVED BY THE ASHP BOARD OF DIRECTORS ON NOVEMBER 14, 1998

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Despite the publication of more than 100 studies of the frequency, risk factors, and prophylaxis of stress ulcer bleeding, these subjects continue to generate controversy. Several meta-analyses pertaining to stress ulcer bleeding have been published, including one designed to resolve the discordant results of the others. Given the sheer volume of published information, it is understandable that health care providers experience frustration when confronting this topic.

Stress ulcers are superficial lesions commonly (but not exclusively) involving the mucosal layer of the stomach that appear after major stressful events such as surgery and trauma. Endoscopic studies have found gastroduodenal erosions (shallow ulcers) to be common in patients who have had such stressful events, and these may lead to ulceration and bleeding. Microscopic bleeding associated with gastroduodenal lesions can be detected by occult blood testing (e.g., guaiac test) in patients with gastric tubes. However, other factors may influence the results of occult testing. Simply placing tubes in the upper respiratory or GI tract may injure the mucosa and result in microscopic or macroscopic (i.e., overt) bleeding. Because not all episodes of microscopic bleeding are clinically relevant, studies using only microscopic bleeding as an endpoint artificially inflate the reported frequency of GI bleeding.

Making clinical use of these inflated estimates has patient care implications and cost implications, because stress ulcer prophylaxis adds to the number of medications given and increases the risk and cost of adverse reactions.

It is important to determine the frequency of clinically important bleeding due to stress-induced erosions or ulcerations. Although endoscopy is a specific and sensitive test for GI bleeding, it is an invasive and expensive procedure. For endoscopy to be used as a diagnostic tool, it would need to be repeated during the period the patient remains at risk for clinically important bleeding. Gastroduodenal bleeding associated with clinically important complications, such as hemodynamic compromise and the need for blood transfusions or surgery, has been suggested in the literature as a useful definition for clinically important bleeding. This definition was used to evaluate the clinical trials in order to develop these guidelines. The reported frequency of clinically important bleeding has varied widely, although the general perception is that the frequency of stress-related bleeding has been decreasing in recent years. Whether this decrease is related to the use of stress ulcer prophylaxis medications, improvements in technology, or improvements in patient care is not known, because a variety of factors (e.g., type...
of resuscitative technique) may contribute to clinically important stress-related bleeding.7

The presence of patient risk factors for clinically important bleeding, not just admission to an intensive care unit (ICU), should determine the need for stress ulcer prophylaxis. The purpose of this document is to help health care professionals to identify appropriate candidates for stress ulcer prophylaxis and select cost-effective modalities for prophylaxis when prophylaxis is indicated. An economic evaluation has been provided that can be adapted to individual practice sites.

Scope

These guidelines pertain to stress-induced bleeding associated with events such as trauma, surgery, and acute organ failure. In general, they apply to the days immediately after the stressful event, when endogenous healing processes or exogenous manipulations by health care professionals have yet to substantially improve the underlying disease process. However, a patient may have resolution of the initial problem but then have reactivation or initiation of a stressful event that could precipitate stress-induced bleeding. These are not unexpected occurrences in patients with ICU stays of more than a few days and could lead to periodic institution of prophylaxis to prevent bleeding.

The guidelines focus on agents that are used for stress ulcer prophylaxis in the United States, whether or not the agents have FDA-approved labeling for this indication. A majority of studies have involved histamine H 2-receptor antagonists, antacids, or sucralfate, and these agents are discussed in detail. Few controlled, comparative studies have been conducted to assess the efficacy of misoprostol or proton-pump inhibitors (e.g., lansoprazole, omeprazole) in preventing clinically important bleeding. The potential advantages and disadvantages of the latter medications for stress ulcer prophylaxis are discussed.

The guidelines include information for patients in all age groups for which there is literature. When age groups are not specifically cited, the discussion refers to the adult patient population. Few prospective, randomized studies in the pediatric population have been published, particularly with regard to clinically important bleeding. Where appropriate, the lack of age-specific data is specified. It is hoped that the guidelines will stimulate research in these areas.

The guidelines are not intended to apply to the prevention of bleeding associated with chronic diseases or long-term medication use. However, the contribution of pre-existing diseases and the use of ulcerogenic medications as aggravating risk factors for stress-induced bleeding are considered appropriate issues for review.

Guideline development and use

The ASHP Therapeutic Guidelines on Stress Ulcer
Prophylaxis were prepared by the University of Arizona under contract to ASHP. The project was coordinated by two pharmacy specialists, one with expertise in critical care and the other with expertise in drug information, who consulted with two physicians and a nurse specialist from the Arizona Health Sciences Center. The project coordinators worked in conjunction with an independent multidisciplinary panel of seven clinical specialists (a surgeon, a nurse, and five pharmacists) representing adult or pediatric critical care. The panel was appointed by ASHP. Panel members and contractors were required to disclose any possible conflicts of interest before their appointment. The guidelines underwent multidisciplinary field review in order to evaluate their validity, reliability, and utility in clinical practice. The final document was approved by the ASHP Commission on Therapeutics and the ASHP Board of Directors.

The recommendations in this document may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgment of the clinician and must take into account individual patient circumstances and available resources. These guidelines reflect current knowledge (at the time of publication) on the use of stress ulcer prophylaxis in critically ill patients. Given the dynamic nature of scientific information and technology, periodic review, updating, and revision are to be expected.

Literature search

Detailed and exhaustive literature searches of MEDLINE from 1966 to 1997 and International Pharmaceutical Abstracts (IPA) from 1970 to 1997 were performed. The searches of the two databases were compared to check for duplicates and were subsequently compared with the references listed in a recent meta-analysis by Cook et al.5 for completeness.

Ten key articles pertinent to stress ulcer prophylaxis were identified and entered into MEDLINE to capture appropriate MeSH headings. Applicable MeSH headings were combined with relevant text words into five sets. Set A1 combined terms for the condition to be avoided in broad terms (e.g., peptic ulcer) by using the subheadings prevention and control and complications. Set A2 covered terms more specific to the condition being treated (e.g., peptic ulcer hemorrhage) by using the same subheadings. Set B included terms describing patient location (e.g., intensive care) or condition (e.g., critical illness). Set C covered terms related to the treatments to be considered (e.g., H2-receptor antagonists) with the subheadings adverse effects and therapeutic use, and set D was the free-text term stress ulcer prophylaxis. The sets were combined as [(A1 or A2) and B] or D]. All relevant citations were printed and reviewed for pertinent articles, which were subsequently retrieved and copied. The reference lists of the retrieved articles were studied for investigations that may have been missed through the computerized search.

Periodic literature searches using the same method were conducted during the compilation of the guidelines. The reference lists of review articles were examined for potentially pertinent references. Unpublished abstracts (e.g., those presented at meetings) and abstracts in foreign languages were not included in the evaluation.

Although all relevant articles were reviewed, they are not necessarily referenced in this document. In particular, isolated case reports or case series involving fewer than 25 patients were not routinely included unless they provided unique information that would substantially affect the recommendations. Similarly, pharmacokinetic and pharmacodynamic studies of medications were not included unless there was some applicability to stress ulcer prophylaxis.

Level of evidence for recommendations

There are several methods for assessing the literature by using evidence tables. The methods of Guyatt et al. and the American College of Chest Physicians (1995 revision) were determined to be most applicable to
the literature to be reviewed because they involved meta-analysis and distinctions based on confidence intervals, homogeneity, and heterogeneity. These methods were modified slightly and expanded to include a category D that represents a panel consensus based on the clinical experience of the panel members and a paucity of quality supporting literature. Before reviewing the literature, the panel of experts agreed that a meta-analysis carried more weight than a randomized, controlled trial (RCT) in determining a recommendation unless at least two RCTs had similar results or one RCT was designed with a sample large enough to detect a difference of 50% or less in bleeding rates (considered the primary outcome) between the treatment and control groups with a power of ≥80% and an α of ≤0.05.

The recommendations in this document were categorized according to the strength of the evidence. Category A corresponds to levels of evidence I+, I, and I–; category B to levels II+; II, and II–; and category C to levels III+, III, IV+, IV, and V. Table 1 includes definitions for each level of evidence. The level of evidence was evaluated for each trial. When there were multiple RCTs of comparable power pertaining to a particular recommendation and their levels of evidence differed, the level of evidence for the least stringent trial was used in determining the strength of evidence for a recommendation. Recommendations were assigned to category D if they represented the expert opinion of panel members. For a recommendation based on RCTs to be assigned to category A, there had to be at least two RCTs or one RCT with a sample size sufficient for detecting a difference of 50% or less in rates of clinically important bleeding with a power of ≥0.8 and an α of ≤0.05.

One problem with both the grading systems on which this system was based is the relative inability to distinguish the quality of individual investigations. Two RCTs may each be ranked similarly, but one may have been better designed and reported than the other. Therefore, in addition to listing levels of evidence for the various trials, the superscript wd was used to signify a well-designed and well-reported trial when the guidelines were sent to the panel of experts and other reviewers to aid them in evaluating the literature presented. More than 30 criteria, some of which have been published, were used in the analysis of the investigations. The criteria represented a nonnumerical assessment and were not used as a scoring system for the formal statistical analysis.

The levels of evidence were used to evaluate those studies that assessed the frequency of clinically important bleeding (i.e., gastroduodenal bleeding associated with hemodynamic compromise or the need for blood transfusion or surgery) and nosocomial pneumonia. Analysis of the number and type of risk factors associated with bleeding by a rigid evidence-based evaluation may be misleading for a number of reasons, including the following: studies used various definitions of bleeding and risk factors associated with bleeding, various risk factors were studied, various risk factors were used as inclusion criteria, the analysis of risk factors often was not a study objective, and, in many studies, multivariate analysis was not used to determine which risk factors might be independent predictors of bleeding. Observational trials with large numbers of patients are often used appropriately to assess risk factors for bleeding, although the strength of evidence would never be higher than C.

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<thead>
<tr>
<th>Level of Evidence</th>
<th>Definition</th>
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<tr>
<td>I+</td>
<td>Meta-analysis of randomized, controlled trials (RCTs) with homogeneity of results and a 95% confidence interval (CI) that lies entirely on one side of the numerical threshold for clinically important benefit</td>
</tr>
<tr>
<td>I</td>
<td>Meta-analysis of RCTs with homogeneity of results but with a 95% CI that includes the threshold for clinically important benefit</td>
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<tr>
<td>I–</td>
<td>RCT in which the entire 95% CI lies on one side of the threshold for clinically important benefit</td>
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<tr>
<td>II+</td>
<td>Meta-analysis of RCTs with heterogeneity of results and a 95% CI that lies entirely on one side of the threshold for clinically important benefit</td>
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<td>II</td>
<td>Meta-analysis of RCTs with heterogeneity of results and a 95% CI that includes the threshold for clinically important benefit</td>
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<td>II–</td>
<td>RCT in which the 95% CI includes the threshold for clinically important benefit</td>
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<td>III+</td>
<td>Nonrandomized concurrent cohort study in which the entire 95% CI lies on one side of the threshold for clinically important benefit</td>
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<td>III</td>
<td>Nonrandomized concurrent cohort study in which the 95% CI includes the threshold for clinically important benefit</td>
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<td>IV+</td>
<td>Nonrandomized historic cohort study in which the entire 95% CI lies on one side of the threshold for clinically important benefit</td>
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<td>IV</td>
<td>Nonrandomized historic cohort study in which the 95% CI includes the threshold for clinically important benefit</td>
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<td>V</td>
<td>Case series suggesting clinically important benefit</td>
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*Adapted from references 9 and 10.

*Various definitions of homogeneity were used in the literature (e.g., the difference between the risk reductions or odds ratios between the two most disparate trials is less than 20% and the difference between 95% confidence intervals for the two most disparate trials is less than 5%); the fact that homogeneity was tested for is more important than the precise method used.

*This assumes the availability of comparative data for calculating 95% CIs.
Pathophysiology of stress-induced lesions

Stress ulceration is a form of hemorrhagic gastritis that may occur in patients who have had a major stressful event such as trauma, surgery, organ failure, sepsis, or thermal injury. In general, the histological and macroscopic appearance of stress-induced fundal lesions are similar to those associated with nonsteroidal anti-inflammatory drugs (NSAIDs) seen in the antrum and the body of the stomach. However, in contrast to NSAID-induced lesions, stress-induced lesions often cause more congestion and bleeding, and they eventually involve multiple sites in the upper GI tract. Cushing's ulcer, which is associated with CNS injury, often presents as a single deep lesion in the duodenum or in the stomach. Curling's ulcer, which is associated with thermal injury, is morphologically similar to other stress-induced lesions but may appear in the esophagus, the stomach, the small intestine, or the colon.

The pathogenesis of stress-induced lesions is probably multifactorial. Acid hypersecretion is often stated as being particularly important in the formation of ulcers associated with head and thermal injuries. However, acid hypersecretion is not a universal finding in such patients, and higher pH values (>4.5) do not ensure avoidance of lesions. During stressful events, normal protective mechanisms are altered, including epithelial turnover in the gastric mucosa and secretions of mucus and bicarbonate. These events, combined with the release of various mediators (e.g., arachidonic acid metabolites, cytokines, oxygen free radicals), result in erosions that may progress to ulceration and bleeding. Reductions in mucosal blood flow may also be important in ulcer formation. Alterations in blood flow at the microcirculatory level may initiate a series of changes resulting in erosions that could progress to ulceration and bleeding. Necrosis and erosions of the gastric membrane have occurred within 45 minutes of hemorrhagic shock in experiments in rats. In adult humans, erosions may occur very quickly (i.e., during the first 24 hours of hospital admission) in association with a stressful event, although the time from the inciting event to the diagnosis of bleeding may be much longer (e.g., 10–14 days).

Other less well-studied factors may be involved in the pathogenesis of stress-related lesions. For example, elevated concentrations of anti-Helicobacter pylori immunoglobulin A have been found in the serum of critically ill patients. Although the association between H. pylori and chronic ulceration has been established, few studies have been performed in acute care settings.

It is not known whether differences in basal or maximal gastric acid production seen in various age groups affect the frequency of ulceration and clinically important bleeding. For example, premature infants typically produce less gastric acid than full-term infants, albeit with substantial interinfant variability. Newborns often have slightly acidic gastric pH values that become more acidic within a few hours of birth.

Gastric pH values in infants begin to approach those of healthy adults during the first six months of life. However, stress ulcer lesions may occur at any age, including in preterm infants, lending additional support to a multifactorial process.

The frequency of ulceration, the number of ulcers, and the sites of ulceration may be different between children and adults, depending on the stress-related event. In one retrospective study involving 93 children less than 10 years of age and 178 adults who died of burn-related injuries, 13 (14.0%) of the children had duodenal ulceration on postmortem examination compared with 13 (7.3%) of the adults. In addition, 21 (22.6%) of the children had gastric ulceration compared with 20 (11.2%) of the adults. No relationship between sex and ulceration was found. Another review of infants less than one year of age with stress ulceration found that single duodenal ulcers were common, in contrast to the multiple gastric erosions usually found in adults.

Frequency of bleeding, efficacy of prophylaxis, and risk factors for bleeding in general (medical, surgical, respiratory, pediatric) ICU populations

Acute bleeding in critically ill patients has been described in the medical literature since the 1800s. To determine the true frequency of, and risk factors associated with, stress-induced bleeding in general ICU populations, studies that contained at least one defined group of patients who did not receive prophylaxis were evaluated. As will be seen in the following discussion, determining a true frequency of clinically important bleeding is complicated by the difficulty in measuring endpoints, the variability in endpoints used, the variability in definitions of endpoints, and the heterogeneity of the patient populations.

In general, the studies included in this section of the document on general ICU populations determined the frequency of stress ulcer lesions and the risk factors associated with clinically important bleeding in patients in medical, surgical, or respiratory ICUs. Only two of the studies involved a relatively homogeneous sample of patients with a single-system disease or surgery. One study was conducted in patients with respiratory disease, and the other involved patients undergoing abdominal surgery. These studies were included because the patient populations were similar to those enrolled in other investigations. Studies enrolling patients with single-system injuries (e.g., head or spinal cord surgery), patients with thermal injuries, or patients undergoing transplantation were not included (see the section on special populations) because of presumed differences in the pathophysiology or frequency of stress-induced bleeding.

Frequency of bleeding. In all studies conducted before 1978, the frequency of clinically important...
bleeding and related complications ranged from 5.3% to 33%. From 1978 on, substantial differences in the frequency of stress-induced bleeding have been recorded among trials. For example, in an RCT published by Pinilla et al. in 1985, the frequency of bleeding was 1.6% (1 of 61 patients), and it was not clear whether this patient had clinically important bleeding. In contrast, an RCT published by Peura and Johnson in the same year, involving adult patients in a medical ICU, found a 39% frequency (7 of 18 patients) of endoscopically confirmed, clinically important, stress-induced bleeding in patients not receiving prophylaxis. Articles published from 1984 to 1994 on the frequency of clinically important bleeding in patients not receiving prophylaxis indicate that the average frequency of bleeding is 6% (0.1–39%).

With regard to the pediatric population, it is difficult to estimate the frequency of clinically important bleeding because of the small numbers of patients enrolled in published investigations and the use of endpoints other than clinically important bleeding (e.g., endoscopic evidence of bleeding or overt bleeding). There are important exceptions, albeit with differing results. In one study involving 140 children from birth to 20 years of age, the frequency of clinically important bleeding was 20% in a control group and 5.7% in a combined treatment group. In contrast, the frequency of clinically important bleeding (not defined in the published abstract) was 1.6% in a study of 1006 admissions to a pediatric ICU, although it was not stated whether the children received any form of stress ulcer prophylaxis.

**Efficacy.** Prophylaxis versus no prophylaxis. Two studies conducted in the 1990s can be used to illustrate the disparate results of the more than 20 RCTs of prophylaxis conducted in general ICU populations. The first trial, conducted in 1993 by Martin et al., was a multicenter, double-blind, placebo-controlled study involving general medical and surgical ICU patients with an expected length of stay of at least 36 hours and at least one risk factor (of eight studied) for bleeding. The study had 90% power to detect a 75% difference in bleeding rates between the control and cimetidine groups. In the control group, 16 (24.2%) of 66 patients had overt and clinically important bleeding (some bleeding was not cleared by lavage, but the patients did not require transfusion), compared with 5 (7.7%) of 65 patients in the treatment group (p = 0.009). Six (10.0%) of 66 patients in the control group and 4 (6.2%) of 65 in the treatment group had clinically important bleeding. Statistical testing of this endpoint was not performed.

The second study, a single-blind RCT, was conducted in 1994 by Ben-Menachem et al. In that trial, only medical ICU patients who were expected to have a length of ICU stay of at least 24 hours were enrolled. The study was designed to have 80% power to detect a 75% treatment-related reduction in bleeding. Patients could be randomly assigned to a control (no placebo) group, a pH-adjusted cimetidine group, or a sucralfate group. There were no significant differences between groups with respect to clinically important bleeding episodes (including some patients whose bleeding did not clear by lavage): 6 of 100 patients in the control group, 5 of 100 patients in the cimetidine group, and 5 of 100 patients in the sucralfate group. In addition, there were no significant differences between groups when respiratory failure and coagulopathy were studied as risk factors. If the different findings between this trial and that of Martin et al. can be attributed to differences in the populations being studied, it might be reasonable to consider withholding prophylaxis in general medical ICU patients. However, it should be stressed that the trial by Ben-Menachem et al. was not designed to detect a difference of less than 75% in bleeding between groups, even though a smaller difference might be clinically important.

Another study enrolled 90 intensive care patients with septic shock, severe head injury, and trauma. The patients were randomly assigned to receive pirenzepine 30 mg/day, omeprazole 80 mg/day, or no prophylaxis. A rating scale of zero (normal mucosa) to four (>25 hemorrhages, erosions, or invasive ulcers) was used to evaluate all patients at baseline and after five days of prophylaxis. Although all patients were at high risk for stress ulcer hemorrhage, no patients developed severe bleeding from stress lesions, and no difference in endoscopic evaluations was noted at baseline or at five days among the three groups.

Because individual trials have demonstrated conflicting results with respect to the frequency of bleeding with or without prophylaxis, several meta-analyses have sought to resolve this issue (Table 2). Abstracts and non-English-language articles were frequently included in the data sets of these analyses, as were reports of studies involving populations that other studies specifically excluded (e.g., patients with head or thermal injuries). One meta-analysis was published in 1989, and three were published in 1991, so the number of trials combined for each analysis was limited. Despite this difference in time frame, there was definite overlap among the meta-analyses in the studies that were included. Only one of the meta-analyses investigated the difference in bleeding rates with sucralfate compared with no prophylaxis.

The meta-analysis conducted by Lacroix et al. included randomized studies only. The frequency of bleeding in patients receiving no prophylaxis (or placebo) ranged from 3.4% to 52.7%. Use of cimetidine and antacids was associated with a significantly lower frequency of bleeding compared with no prophylaxis. Among the limitations of this meta-analysis were that the evaluated studies had methodological problems,
demonstrated heterogeneous effects, and investigated the frequency of occult or overt—but not necessarily clinically important—bleeding, defined as hemodynamic instability or the need for blood transfusion.

In a meta-analysis published by Tryba in 1991, overt and clinically important bleeding (i.e., need for blood transfusion) were combined in the definition of upper GI bleeding. Randomized and nonrandomized studies were included. The odds ratios (ORs) and 95% confidence intervals (CIs) calculated for H$_2$-receptor antagonists or antacids compared with no prophylaxis were all less than one (i.e., treatment was effective in preventing bleeding). The frequency of bleeding was 5.3% in the group receiving H$_2$-receptor antagonists versus 16.1% with no prophylaxis and 5.6% in the group receiving antacids versus 14.9% with no prophylaxis. A second meta-analysis by Tryba in 1991 included only studies with clinically important bleeding. The results were similar to those of Tryba's previous meta-analysis.

Two meta-analyses published by Cook et al. in 1991 and 1996 included only randomized, controlled trials. The investigations looked at clinically important bleeding, defined as overt bleeding with hemodynamic changes (a 20-mm Hg decrease in blood pressure within 24 hours or a 10-mm Hg decrease plus a 20-beat/min increase in heart rate on standing) or the need for transfusion (a decrease in hemoglobin of 2 g/dL plus transfusion of two units of blood in 24 hours). In the 1991 analysis, H$_2$-receptor antagonists were found to be more efficacious in preventing clinically important bleeding than no prophylaxis.

The 1996 meta-analysis was performed to resolve...
some of the inconsistencies associated with the previously conducted meta-analyses and to incorporate more recent studies. The methodology was similar to that of the earlier meta-analysis. Only H₂-receptor antagonists were found to have a 95% CI of <1 for preventing clinically important bleeding compared with no prophylaxis. However, only three trials with an antacid group and one with a sucralfate group were available for comparison with no prophylaxis. Because the 1996 meta-analysis was the most recent and comprehensive, its results are used in this document whenever the findings from previous meta-analyses are conflicting.

To date, the study with the largest number of prospectively enrolled patients was published by Cook et al. in 1994. This multicenter follow-up trial enrolled 2252 patients older than 16 years of age who were admitted to medical and surgical ICUs. Approximately half of the enrolled patients were admitted for cardiovascular surgery. Some subgroups (head or spinal cord injuries, multiple trauma or thermal injuries, and transplantation) had few patients. This limits the generalizability of the results to these populations. Lack of resources at three of the four hospitals prohibited enrollment of consecutive patients as intended, and physicians were not required to withhold prophylaxis. Various prophylactic medications were used, and the dosage and duration of prophylaxis were not controlled. Clinically important bleeding occurred in 10 (0.6%) of 1578 patients not receiving prophylaxis and 23 (3.4%) of 674 patients receiving prophylaxis (22 of the 33 bleeding episodes were confirmed). This suggests that, in this observational design, physicians were probably able to predict who was at risk for bleeding and administer prophylaxis; it does not necessarily represent failure of prophylaxis.

Prophylaxis in pediatric patients. The number of stress-induced lesions progressing to clinically important bleeding with or without prophylaxis is not well studied in pediatric patients. Lacroix et al. compared prophylaxis with no prophylaxis in 40 patients from birth to 18 years of age. When the results were reported, overt bleeding was not distinguished from clinically important bleeding, and no differences in upper GI bleeding were noted between the cimetidine group (9 of 19 patients) and the placebo group (8 of 21 patients). Six patients had massive bleeding, defined as the presence of nasogastric blood with changes in blood pressure or hemoglobin levels. It was not stated which groups these patients were in, and it was noted that five of these patients had bleeding at other sites due to disseminated intravascular coagulation. The researchers concluded that routine prophylaxis in medical pediatric patients is not warranted.

In another study, 165 pediatric patients admitted to an ICU were randomly assigned to one of three active-treatment groups or a no-treatment group. The investigators used clinically important bleeding as an outcome. A significant (p < 0.05) difference between the active-treatment groups and the no-treatment group was achieved only if the results for the three active-treatment groups were combined. Two studies focused on a neonatal population but did not use clinically important bleeding as an endpoint. In one of these studies that had a control group, the risk of endoscopically diagnosed gastric lesions in mechanically ventilated infants was found to be lower with ranitidine prophylaxis (OR = 0.03; 95% CI, 0.003–0.178). Surfactant therapy, which was used to treat infants with respiratory distress syndrome, was also associated with a lower rate of formation of lesions (OR = 0.083; 95% CI, 0.009–0.788). The mechanism for the apparent protective effect of surfactant on the GI tract remains to be elucidated. No RCT conducted to date in pediatric patients has conclusively demonstrated a significant difference in clinically important bleeding when prophylaxis was compared with no prophylaxis.

Risk factors. In Cook’s prospective observational study, two risk factors were found to be significant predictors of stress-induced bleeding: respiratory failure, as defined by mechanical ventilation for at least 48 hours (OR = 15.6; CI not reported, p < 0.001), and coagulopathy, defined as a platelet count of <50,000 mm³, an International Normalized Ratio of >1.5, or a partial thromboplastin time of >2 times the control value (OR = 4.3; CI not reported, p < 0.001). The frequency of bleeding was 3.7% (95% CI, 2.5–5.2%) if one or both of these risk factors were present and 0.1% (95% CI, 0.02–0.5%) if neither factor was present. Patients who had received prophylaxis and those who had not were included. Simple regression analysis showed that sepsis, renal insufficiency, hepatic failure, enteral feeding, and the use of glucocorticoids, heparin, and warfarin were risk factors for bleeding; multiple regression analysis showed that only mechanical ventilation and coagulopathy were independently predictive of clinically important bleeding.

The finding that enteral feeding was a risk factor for bleeding (OR = 3.8, p < 0.001) is of interest because previous retrospective studies in adults have found various effects of enteral feedings on pH and the frequency of bleeding. These differences may be due to differences in location of the enteral feeding tubes. For example, feedings placed into the stomach may alkalize stomach contents, and jejunal feedings may stimulate gastric acid secretion. The fact that patients are able to tolerate tube feedings may mean they are less ill than patients who cannot tolerate such feedings, and this may determine the differences noted. Other factors may be specific to certain types of injury, such as the development of GI edema after thermal injury.

Conflicting associations with total parenteral nutrition (TPN) and bleeding have been noted. Ben-Menachem et al. found that the frequency of bleeding was not related to the use of TPN. Ruiz-Santana et al.
concluded that TPN was protective, but their sample size was small, and their findings require confirmation in larger randomized trials.

The most recently published large-sample retrospective study of risk factors in ICU trauma patients involved 2574 patients. The only patients receiving prophylaxis (antacids) were those with a history of gastroduodenal ulcerations. The published abstract does not reveal how many of the 2574 patients received antacids. Clinically important bleeding was not analyzed separately from GI bleeding. GI bleeding was noted in 60 (2.3%) of the patients. The risk factors associated with a higher risk of bleeding included male sex, spinal cord injury, respiratory failure, acute renal failure, and severe sepsis.

Of the other trials in which risk factors were studied, a majority of those conducted in adults showed a higher risk of bleeding as the number of risk factors increased. The results of most trials are consistent with those of the 1994 study by Cook et al. in that mechanical ventilation (as a measure for respiratory failure) and coagulopathy are the primary risk factors for bleeding. Other risk factors associated with bleeding in adult patients in some studies include sepsis, length of ICU stay greater than one week, presence of occult bleeding for at least six days, and administration of high doses of corticosteroids (>250 mg/day of hydrocortisone or equivalent). However, the studies by Cook et al. did not find use of corticosteroids, heparin, warfarin, or NSAIDs to be independent risk factors for bleeding when respiratory failure and coagulopathy were considered.

Prophylaxis does not necessarily prevent bleeding in patients with documented risk factors, and the effectiveness of prophylaxis varies in different populations. Some potential risk factors for bleeding have not been adequately studied, and it is unclear whether they are independent predictors of bleeding. A majority of investigations excluded patients with a history of GI disease, particularly ulcers and bleeding. It is unknown whether a history of ulceration or bleeding increases the risk of acute, stress-induced bleeding. Similarly, ulcerogenic medications with well-documented associations with bleeding problems, such as long-term use of NSAIDs, have not been adequately studied as risk factors for stress-induced bleeding. Typically, patients receiving such medications either were not discussed in the methods section of study reports or were prohibited from enrolling in the studies.

In pediatric patients (birth to 19 years of age), coagulopathy, shock, surgery lasting for longer than three hours, trauma, and pneumonia were associated with an increased risk of bleeding, while the use of enteral nutrition reduced the risk of bleeding. The results were not stratified by age. One study in pediatric patients (median age, 34.9 months) found that a Pediatric Risk of Mortality Score of ≥10 was associated with an increased risk of bleeding. Another study in mechanically ventilated preterm and full-term infants found that 20 (80%) of 25 patients had stress-induced lesions as determined by endoscopic evaluation when no prophylaxis was administered. That study and others demonstrated that gastric lesions due to stress may occur in the very young despite their possible physiological differences from adults.

The rate of progression of these lesions to clinically important bleeding is not known. In a study in pediatric ICU patients (1006 admissions), 16 (1.6%) clinically important bleeding episodes occurred. Because this was an observational investigation, physicians were not hindered from prescribing medications for stress ulcer prophylaxis. Among the 110 patients who received prophylaxis, there were 10 clinically important bleeding episodes. The authors noted that the three strongest independent risk factors for clinically important bleeding were respiratory failure (OR = 10.2), coagulopathy (OR = 9.3), and a Pediatric Risk of Mortality Score of ≥10 (OR = 4.0). Of the 16 patients with clinically significant bleeding, 9 (56%) had all three risk factors and 14 (88%) had at least two.

Summary. The reported frequency of stress-induced bleeding has varied substantially since approximately 1978 and depends on the number and type of risk factors. Data from large prospective, observational investigations in children and adults have found that general medical and surgical ICU patients who have either coagulopathy or respiratory failure requiring mechanical ventilation have a substantially higher risk of clinically important bleeding. The studies often excluded neurosurgery, burn, and transplant patients. Another risk factor for children is a Pediatric Risk of Mortality Score of ≥10. A number of other risk factors have been associated with overt bleeding in isolated studies (prolonged ICU stay or occult bleeding and administration of high-dose corticosteroids in adults; prolonged shock or surgery and trauma in children), but it is unknown whether these are independent predictors of clinically important bleeding, except in the case of coagulopathy or respiratory failure. Several studies that included both medical and surgical ICU patients suggest that, as the number of risk factors increases, the frequency of clinically important bleeding increases. It has been proposed that adult medical ICU patients may not necessarily need stress ulcer prophylaxis, even if they have respiratory failure or coagulopathy. However, there are concerns related to inadequate sample sizes in the studies that resulted in this conclusion. Overall, according to RCTs, about 6% (range, 0.1–39%) of adult medical and surgical patients at risk for stress ulcers who do not receive prophylaxis have clinically important bleeding. Observational studies involving large numbers of pediatric or adult patients suggest that the risk may be substantially lower.

Recommendation (adults): Risk factors for ICU patients have been delineated in trials comparing prophylaxis with no
prophylaxis by using clinically important bleeding as an endpoint. Prophylaxis is recommended in patients with coagulopathy or patients requiring mechanical ventilation for more than 48 hours. [Strength of evidence = C] Prophylaxis is also recommended in patients with a history of GI ulceration or bleeding within one year before admission and in patients with at least two of the following risk factors: sepsis, ICU stay of more than one week, occult bleeding lasting six days or more, and use of high-dose corticosteroids (>250 mg per day of hydrocortisone or equivalent). [Strength of evidence = D] (Table 3) Recommendations for specific prophylactic medications can be found in the Medications used for prophylaxis section.

Recommendation (pediatrics): Although various risk factors have been associated with bleeding in pediatric patients, published RCTs have either not used clinically important bleeding as an outcome or had insufficient power to enable a definitive conclusion that prophylaxis provides protection. Risk factors that have been associated with clinically important bleeding include respiratory failure, coagulopathy, and a Pediatric Risk of Mortality Score of ≥10. (Strength of evidence = C)

Frequency of bleeding, efficacy of prophylaxis, and risk factors for bleeding in special populations (single-system injuries, thermal injuries, transplantation, miscellaneous)

Patients with head or spinal cord injuries or patients undergoing surgical exploration for suspected disease have usually been studied as defined groups rather than as part of general ICU populations.77-84 A majority of these studies in special populations were conducted in adults, although two studies included younger patients (mean age, 28 years, range, 2–74; mean age, 35 years, range 13–76) who were not discussed separately when the results were reported.77,79 Five of the trials were RCTs.78,81-84 Three of these trials found significantly lower rates of clinically important bleeding with H₂-receptor antagonist prophylaxis than with no prophylaxis.78,83,84 However, in the RCT with the largest number of patients (n = 167), the number of patients with clinically important bleeding was not reported.82 Only two of the studies looked at a possible association between the number of risk factors and the frequency of bleeding. In both studies, the frequency of bleeding increased with the number of risk factors.82,84

In general, the studies demonstrate an increasing frequency of bleeding as the severity of injury increases. Two RCTs demonstrated substantial increases in clinically important bleeding (27.8–45.8%) with severe head injury (inability to obey simple commands in one trial and Glasgow Coma Score of ≤10 in the other), irrespective of corticosteroid administration.78,84 In another RCT involving patients with head injuries, no association was found among 12 specific risk factors and bleeding, although bleeding rates were significantly higher when more than five risk factors were present.82 In patients undergoing surgery for nontraumatic cerebral disease, cimetidine prophylaxis was more likely to fail when the preoperative Glasgow Coma Score was <15 (impaired consciousness) or when the syndrome of inappropriate antidiuretic hormone secretion was present.85

Patients with thermal injuries represent another population that has usually been studied separately with regard to stress ulcer prophylaxis and bleeding.85-91 In the only trial that appeared to be randomized (48 patients), the frequency of clinically important bleeding was 29.2% in patients who received no prophylaxis and 4.2% in patients given antacids (p < 0.02).90 Only patients with thermal injury to >35% of their body surface area (BSA) were included in this trial. In other published investigations, the number and types of risk factors (other than the thermal injury that may have contributed to bleeding) were not studied, except for a possible association between sepsis and ulceration. The retrospective study by Solem et al.91 was one of the first to suggest that enteral feedings might be effective prophylaxis for stress-induced bleeding, but the feedings were administered only if ulcers were unlikely to develop, a situation that was not defined. In addition, some patients received both antacids and enteral feedings.

While many of the thermal injury studies included injuries in children (35 days to 13 years of age), only
Stress ulcer prophylaxis

Recommendation (adults): Prophylaxis is recommended for ICU patients with a Glasgow Coma Score of ≤10 (or the inability to obey simple commands) or thermal injuries to >35% of their BSA. (Strength of evidence = B) ICU patients with partial hepatectomy may also benefit from prophylaxis. (Strength of evidence = C) Prophylaxis may also be indicated in ICU patients with multiple trauma (e.g., Injury Severity Score of ≥16), transplantation patients in the ICU perioperatively, ICU patients with hepatic failure, and ICU patients with spinal cord injuries. (Strength of evidence = D) (Table 3)

Recommendation (pediatrics): For pediatric patients (one month of age or older) with thermal injuries, prophylaxis is recommended, but there is insufficient evidence to recommend prophylaxis based on any given percentage of BSA. (Strength of evidence = D) For other pediatric surgery or trauma patients, insufficient evidence is available to allow recommendations about prophylaxis to be made.

Medications used for prophylaxis

In general, medications used for preventing stress-induced bleeding exert their pharmacologic effect through one of the following mechanisms: inhibition of gastric acid secretion, neutralization of gastric acid secretions, and protective mechanisms unrelated to acid secretion or neutralization.103 The H₂-receptor antagonists, prostaglandin analogues, and proton-pump inhibitors act primarily as antisecretory agents by inhibiting gastric acid secretion. But, other explanations for the beneficial actions of these agents have been proposed. For example, H₂-receptor antagonists have immunomodulatory actions at the cellular and mediator levels.104 However, mediation of cytokine concentrations is a complex process, and the cytokine concentrations fluctuate widely in critically ill patients, often not correlating with more global physiological derangements.105 Similarly, the prostaglandin analogue misoprostol prevents gastric mucosal damage by irritants that do not appear to depend on acid or acid secretion and is sometimes referred to as a cytoprotective agent.106 There is no convincing evidence to establish that “cytoprotection” with misoprostol plays an important role in preventing stress-induced lesions.107 Although alternative explanations for the effectiveness of antisecretion drugs in preventing stress-induced bleeding have been proposed (e.g., stimulation of prostaglandin release), neutralization of gastric acid is the primary mechanism of action.108 In contrast, sucralfate has multiple actions on the GI tract besides providing a direct protective barrier, including modulation of pepsin and
mucus activity, arachidonic acid metabolism, bicarbonate secretion, and tissue growth or repair. Which, if any, of these mechanisms is of primary importance for stress ulcer prophylaxis is not clear.

The H₂-receptor antagonists that are available commercially in the United States are cimetidine, famotidine, nizatidine, and ranitidine. Only cimetidine administered as a continuous intravenous infusion has FDA-approved labeling for the prevention of bleeding in critically ill patients, although there is no reason to suspect any substantial difference in prophylactic efficacy when other H₂-receptor antagonists are given in equipotent doses. However, other reasons may preclude their use, such as the lack of an i.v. dosage form (as with nizatidine). No RCTs of adequate sample size have compared dosage regimens (e.g., intermittent versus continuous i.v. administration) or routes (e.g., i.v. versus oral) of H₂-receptor antagonists by using clinically important bleeding as a study endpoint.

One concern with using oral H₂-receptor antagonists and proton-pump inhibitors in critically ill patients is the potential for malabsorption. Because these agents must be absorbed to exert their effects, the patient must have a functioning GI tract. A functioning GI tract is usually presumed when tube feedings are tolerated without nausea, vomiting, abdominal distention, or diarrhea. In patients with nasogastric tubes, the clinician may monitor the gastric residual volume when feeding formulas are administered into the stomach. Residuals refer to the feedings and gastric secretions that accumulate with GI dysfunction. A volume of more than 200 mL or an amount greater than the volume infused over a two-hour period is usually indicative of dysfunction.

Although widely used for stress ulcer prophylaxis, sucralfate is not labeled for this indication. Because sucralfate appears to exert its predominant effects locally, it must be administered either orally or by a nasogastric, orogastric, or gastrostomy tube. Sucralfate should not be administered with nasogastric tube feedings (see Adverse effects of prophylactic agents). Neither should it be administered by feeding duodenal or jejunalostomy tubes because the medication will miss the site of action.

Similar to sucralfate, antacids have local actions and must be administered directly into the stomach. A number of antacid products have been routinely used for stress ulcer prophylaxis. Several formulations carry FDA-approved labeling for this indication.

Misoprostol is available in tablet form, while proton-pump inhibitors such as omeprazole and lansoprazole are available in delayed-release capsules. These medications have not been well studied for stress ulcer prophylaxis and are not labeled for this indication. The delayed-release dosage forms of the proton-pump inhibitors create administration problems when oral intake is not possible, although some interesting compounding techniques for omeprazole have been reported. In addition, lansoprazole has FDA-approved labeling for administration by nasogastric tube with some fruit juices. One open-label study involving 75 mechanically ventilated surgery patients found a compounded omeprazole suspension effective in preventing stress-induced bleeding. Larger comparative studies are needed to determine efficacy and assess the potential for adverse effects such as pneumonia (from increased gastric pH, as postulated for the H₂-receptor antagonists) and other unanticipated problems.

Although medications may have different mechanisms for their protective effects, there is no evidence that combination therapy is more effective than a single agent for initial prophylaxis, but the potential risk of adverse effects would increase with combination therapy. Therefore, combination therapy for initial prophylaxis cannot be recommended. Combination therapy for the prevention of recurrent bleeding is discussed further in this document (see Prevention of recurrent bleeding).

**Efficacy of prophylactic agents: Prevention of bleeding**

A substantial number of clinical trials, a majority of which were randomized, have involved comparisons of medications used for stress ulcer prophylaxis. In general, no significant differences between medications used for the prophylaxis of clinically important bleeding have been found. However, in a majority of studies, the sample size needed to detect a difference between treatment groups in clinically important bleeding was not calculated. Therefore, the number of patients enrolled in any given study was often insufficient to preclude a Type II statistical error. Other studies have found substantial differences in bleeding between groups, but the frequency of bleeding was unexpectedly high for one of the groups. For example, Phillips et al. reported clinically important bleeding (the definition of clinically important was different than the definition used in these guidelines) in 4 (16%) of 25 patients receiving ranitidine by continuous i.v. infusion and 1 (3%) of 33 patients receiving omeprazole suspension. Compared with the results of other studies, 16% is a high rate of bleeding with ranitidine.

In the largest RCT published to date, 1200 patients who required mechanical ventilation for at least 48 hours were assigned to receive either nasogastric sucralfate slurry (1 g every 6 hours) and i.v. placebo or i.v. ranitidine (50 mg every 8 hours) and nasogastric placebo. The patients in this multicenter study were admitted to medical and surgical services (approximately 60% and 40%, respectively). There were relatively few patients from special populations: CNS surgery, 49 patients; trauma, 158; burns, 12; and transplantation, 19. These special populations were not discussed separately. Although the estimated sample size was based on the power to detect differences in rates of pneumo-
nia (power, or $1-\beta = 75\%$), the rates of clinically important bleeding and mortality were additional study objectives, and the trial’s power to detect a difference in bleeding rate was 90%. A significant difference in favor of the H₂-receptor antagonist (ranitidine) compared with sucralfate was noted. Ten (1.7%) of the 596 patients in the ranitidine group and 23 (3.8%) of 604 patients in the sucralfate group had clinically important bleeding (relative risk, 0.44; 95% CI, 0.21–0.92; p = 0.02). Endoscopic confirmation of an upper GI source of bleeding was obtained for 3 patients in the ranitidine group and 10 in the sucralfate group. An additional patient in the ranitidine group had an upper GI source of bleeding confirmed by angiography and red blood cell scanning. Because invasive diagnostic testing was left to the discretion of participating physicians, the source of bleeding was not found for 19 patients. In addition, no differences were noted in the overall length of stay or mortality. Therefore, the largest RCT conducted to date has not definitively determined the agent of choice for the prevention of clinically important GI bleeding.

Five meta-analyses have been conducted to resolve some of the discrepancies noted between RCTs, including the issue of inadequate sample size.5-68,71 None of these meta-analyses included the recently published RCT by Cook et al. (1998) and the Canadian Critical Care Trials Group (Table 2).176 The other major limitations of these analyses have been discussed previously. In general, the meta-analyses found H₂-receptor antagonists and antacids to be more effective than no prophylaxis, but in some cases the 95% CIs were wide, indicating substantial variation in the data. Only one trial compared sucralfate with no prophylaxis, and this trial was included in the 1996 meta-analysis by Cook et al.5 The results of these meta-analyses were conflicting when medications were compared. In the meta-analyses by Lacroix et al.68 and Tryba,69 H₂-receptor antagonists were compared with antacids, but the 95% CIs included 1, indicating that the two regimens did not differ significantly. In the 1991 meta-analysis by Cook et al.,70 H₂-receptor antagonists were significantly more effective than antacids for preventing overt bleeding, but the therapies were similar in preventing clinically important bleeding.

Tryba71 found sucralfate to be significantly more effective than H₂-receptor antagonists and similar in efficacy to antacids (OR = 0.532; 95% CI, 0.303–0.933). Cook et al.70 (1991) found sucralfate to be similar to H₂-receptor antagonists or antacids for preventing overt and clinically important bleeding.

Given the disparities noted in the previous meta-analyses, Cook et al.5 (1996) conducted a meta-analysis to resolve the apparent discrepancies. This meta-analysis included studies that were not available when the initial meta-analyses were completed. In addition to being significantly more effective than no prophylaxis, H₂-receptor antagonists were found to be significantly more effective than antacids in preventing overt bleeding but not clinically important bleeding. Sucralfate was similar to antacids or H₂-receptor antagonists for prophylaxis of both overt bleeding and clinically important bleeding.

While useful, this meta-analysis raises some important questions.3 For example, the definitions for overt and clinically important bleeding are very explicit, which contrasts to the definitions used in many of the randomized investigations that were analyzed. It is not possible to derive rates of clinically important bleeding from many of the trials, particularly if a rigid definition is used. The meta-analysis also included RCTs from a variety of populations that have usually been studied as distinct populations (e.g., patients with head and thermal injuries). Even if one assumes that the pathogenesis of bleeding is similar, there may be differences in the frequencies of bleeding compared with populations studied more frequently (e.g., general medical and surgical ICU patients). If the frequency of bleeding has decreased over time as a result of improvements in the care of the ICU patient (which is difficult to verify because many recent studies have not included a no-treatment group), this could have also influenced the results of the meta-analysis. Finally, the results of this meta-analysis are somewhat inconsistent with the findings of the large RCT recently published by the same lead authors with regard to possible differences in medication efficacy.176

**Recommendation (adults):** Given the conflicting results of several meta-analyses and a recent RCT (both with strengths of evidence = A), the choice among antacids, H₂-receptor antagonists, and sucralfate for use as prophylactic agents to prevent clinically important bleeding associated with stress in adult patients admitted to general medical and surgical ICUs should be made on an institution-specific basis. This choice should take into account concerns regarding administration (e.g., functioning GI tract), adverse-effect profile, and total costs. (Strength of evidence = D) Insufficient data on misoprostol or the proton-pump inhibitors are available to allow any recommendation about these agents to be made.

**Recommendation (pediatrics and special populations):** The lack of comparative trials of these agents in pediatric and special populations (e.g., patients with burns, trauma patients, patients undergoing neurosurgical procedures or with neurologic disorders, and transplantation patients) precludes definitive recommendations as to the agent of choice in these situations. The choice of agent should be made on an institution-specific basis and should take into account concerns about administration (e.g., functioning GI tract), adverse-effect profile, and total costs.

### Efficacy of prophylactic agents: Mortality

Many of the available studies did not include mortality outcomes, and still fewer specifically associated mortality with bleeding. In the largest RCT to date, there was not a significant difference in mortality between ranitidine recipients and sucralfate recipients.
despite the finding of a lower frequency of clinically important bleeding with ranitidine. This may be partially explained by the relatively low frequency of bleeding in both groups. Any attempt to attribute differences in mortality to any single intervention in ICU patients must be interpreted with caution given the problems with controlling multiple confounding variables. Furthermore, the limitations associated with the extraction and interpretation of this information from the original trials must be appreciated during consideration of the results of published meta-analyses that have investigated the mortality associated with various forms of prophylaxis.

In a meta-analysis by Tryba in 1991, sucralfate was associated with a lower mortality rate than use of either a H2-receptor antagonist or an antacid. No significant differences in mortality were found between any of the groups in the 1991 meta-analysis by Cook et al. (Table 4). In contrast to the finding of the 1991 meta-analysis, sucralfate was associated with a lower rate of mortality than antacids in two other meta-analyses conducted by Cook et al. (1994 and 1996). When medications were compared with no prophylaxis, all the CIs in the published meta-analyses included 1, the threshold of importance, suggesting no substantial differences in mortality.

### Adverse effects of prophylactic agents

Most adverse effects attributable to antacids, H2-receptor antagonists, and sucralfate are uncommon and occur in less than 1% of adult patients, particularly when given on a short-term basis (e.g., for less than two weeks). The frequency of adverse effects may increase if certain diseases are present, such as renal failure, when electrolyte accumulation secondary to antacid administration or CNS disturbances secondary to administration of H2-receptor antagonists may occur. Sucralfate may cause substantial elevations in serum aluminum concentrations in adult patients with chronic renal insufficiency or in the elderly, although this does not appear to be a problem when the drug is used for less than two weeks in critically ill patients. Elevated aluminum concentrations and resultant toxicity are more of a concern in children with renal dysfunction, particularly given that well-defined dosage guidelines have not been established. Although aluminum hydroxide-containing antacids and sucralfate may be used to lower phosphate levels in patients with uremia, they may cause unwanted hypophosphatemia in patients with normal renal function.

Some products given by oral, nasogastric, or enteral administration may result in local adverse effects. For example, constipation may occur with aluminum-containing antacids and sucralfate and diarrhea may occur with magnesium-containing antacids at frequencies higher than 1%. Sucralfate and antacids may occlude feeding tubes. If the occlusion cannot be removed, the tube may have to be replaced, potentially causing patient discomfort and resulting in complications from placement of a new tube (e.g., esophageal perforation, aspiration, inappropriate placement in the trachea).

Although not well studied, there are potential interactions between enteral feeding products and medications administered enterally for prophylaxis. Such interactions could result in clogged feeding tubes or diminished medication efficacy (e.g., by inhibiting the local actions of sucralfate or interfering with the ab-

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<td>11</td>
<td>OR = 0.70, CI = 0.52–0.94 (lower rate of mortality with sucralfate)</td>
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H2-RAs = histamine H2-receptor antagonists. OR = odds ratio, CI = 95% confidence interval. Exact values provided when available; some values were extrapolated from figures.
tion, particularly in premature infants. Consequently, sucralfate and antacids should be used with caution. Also, bezoars, hypermagnesemia, and intestinal complications such as intestinal obstruction and perforation have been reported with liquid antacids. For example, intestinal obstruction and perforation were reported with sucralfate in a low-birth-weight infant who was given 250 mg every eight hours by nasogastric tube. Also, bezoars, hypermagnesemia, and intestinal perforation have been reported with liquid antacids used in premature infants and newborns. Therefore, sucralfate and antacids should be used with caution, particularly in premature infants.

The H2-receptor antagonists and proton-pump inhibitors have the potential for drug-drug interactions with these agents is beyond the scope of these guidelines; however, comprehensive reviews have been published. Case reports suggest that sucralfate may contribute to esophageal and GI bezoar formation, especially when given in conjunction with enteral feedings in patients with motility disorders. In addition to technical problems related to the removal of bezoars, complications such as intestinal obstruction and perforation have been reported in pediatric patients. For example, intestinal obstruction and perforation were reported with sucralfate in a low-birth-weight infant who was given 250 mg every eight hours by nasogastric tube. This may lead to a consultation with a specialist, a diagnosis, and is associated with substantial adverse effects. The proton-pump inhibitors have few clinically important adverse effects. The most common concerns are mild GI or CNS toxicities. The exact frequency of each of these problems is difficult to determine, but estimates range from 0.0023% for cytopenia to 1.9% for CNS toxicity. The low rate of these adverse effects in adults and limitations associated with postmarketing surveillance studies prohibit accurate comparisons of the frequencies of such effects among medications in this class. The lack of studies in the pediatric population precludes an accurate assessment of the frequency of particular adverse effects. There is a possibility that pediatric patients may be more susceptible to some adverse effects (e.g., thrombocytopenia associated with cimetidine) than adults. Similarly, the lack of information related to pediatric dosing could result in either underdosing with diminished efficacy or overdosing with increased adverse effects.

H2-receptor antagonists and proton-pump inhibitors have the potential for drug-drug, drug-nutrient, and drug-test interactions through a variety of mechanisms. For example, some drug-drug interactions are mediated through effects on the cytochrome P-450 systems in the liver. Although a number of interactions with some of these acid-suppressing agents are of potential concern (e.g., warfarin, ketoconazole, phenytoin, theophylline), few are clinically important when patients are adequately monitored. However, there may be other reasons for avoiding particular medications. For example, cimetidine may increase serum creatinine concentrations without affecting the glomerular filtration rate by competition for tubular secretion in the kidneys. This could be interpreted as renal dysfunction in patients receiving nephrotoxic medications, leading to inappropriate reductions in the dosage of the suspected medication. Other interactions may occur as a result of the acid-suppressing properties of these two classes of agents.

Sucralfate and antacids can affect the absorption of other medications. Although most problems can be avoided if doses of sucralfate and antacids are separated from doses of potentially interacting substances, this practice is often not used. Potentially interacting medications should be administered one to two hours before the sucralfate dose. Furthermore, medications may interact with sucralfate and antacids despite separation (e.g., the bioavailability of quinolone antimicrobials has been substantially reduced by sucralfate even when the two products were separated by two or more hours).

Test interference is a cause for concern with all medications used for stress ulcer prophylaxis. This concern also applies to agents that do not alter pH (e.g., sucralfate interferes with at least one method of occult blood testing).

A full discussion of all potential drug-drug interactions with these agents is beyond the scope of these guidelines; however, comprehensive reviews have been published. The proton-pump inhibitors have few clinically important adverse effects. The most common concerns are mild GI or CNS toxicities. The prostaglandin analogue misoprostol is rarely used clinically for prophylaxis and is associated with substantial adverse effects compared with placebo (nausea, abdominal pain, diarrhea).

Lansoprazole (pregnancy risk category B) and omeprazole (FDA pregnancy risk category C) should be used in pregnant or nursing mothers only when the potential benefits exceed the potential risks. Similar caution is advised for the H2-receptor antagonists (pregnancy risk category B for cimetidine, famotidine, and ranitidine; pregnancy risk category C for nizatidine) and sucralfate (pregnancy risk category B). Misoprostol is an abortifacient, may result in miscarriage (pregnancy risk category X), and is generally contraindicated in pregnant women, women of childbearing age, and nursing mothers.

Pneumonia. The frequency of nosocomial pneumonia associated with stress ulcer prophylaxis has been widely debated. In addition to patient morbidity and economic concerns, mortality rates associated with
pneumonia may be as high as 70%.\textsuperscript{215} There are multiple mechanisms by which bacteria may enter the lungs, including inhalation, hematogenous spread, contiguous spread, direct inoculation, aspiration of secretions, and translocation from the GI tract.\textsuperscript{216} The vast majority of studies investigating a possible connection between pneumonia and stress ulcer prophylaxis have been conducted in adults. In the few studies involving pediatric patients receiving stress ulcer prophylaxis, pneumonia was usually not studied. When pneumonia was reported, it was typically not a primary endpoint.\textsuperscript{65}

Early reports of adult patients receiving antacids and cimetidine demonstrated that the stomach and upper airways had similar bacterial flora, suggesting retrograde transmission from the stomach.\textsuperscript{217} Gastric colonization was uniformly seen in patients with alkalinized stomach contents.\textsuperscript{218} However, a positive correlation between increased gastric pH and colonization with bacteria does not mean there is a linear relationship between acid-suppressing drugs and pneumonia.

It is also important to keep in mind that the techniques used to diagnose pneumonia have continued to evolve. Bronchoscopy, which is now a widely used and accepted diagnostic tool in research, was not performed in older studies of medication-associated pneumonia. Although the sensitivity and specificity of bronchoscopy for diagnosis of infection have been improved by newer techniques such as use of a protected-specimen brush, morbidity and economic concerns have been expressed about its widespread clinical use.\textsuperscript{219} Other methods are less invasive but often have lower sensitivity and specificity, particularly when not performed appropriately.

Agents that do not alter gastric pH, such as sucralfate, may be less likely to result in pneumonia through retrograde transmission or translocation of bacteria.\textsuperscript{220,221} When protected specimens, bronchoalveolar lavage, or both were used, one prospective randomized, double-blind study involving 141 patients showed no difference in the effect of antacids or sucralfate on gastric acidity or rates of bacterial colonization or ventilator-associated pneumonia.\textsuperscript{245} Decreased gastric acidity was observed in conjunction with greater colonization of the stomach but not of the upper respiratory tract. In another prospective investigation in which samples were obtained by bronchoscopy, mechanically ventilated patients were randomly assigned to receive either antacids or sucralfate and then studied for risk factors associated with colonization and pneumonia.\textsuperscript{222} As in the previous study, gastric colonization was not associated with the development of pneumonia, but duration of mechanical ventilation and upper-respiratory-tract colonization were found to be risk factors. A more recent study on this issue had a double-blind, double-dummy design and compared the growth of gastric pathogens in 140 patients undergoing elective surgery who were randomly assigned to receive either sucralfate or antacids.\textsuperscript{223} Patients’ gastric and respiratory tract contents were cultured for routine aerobic bacteria and fungi before surgery and daily throughout the hospitalization until the patient was discharged or died. Clinical endpoints included upper GI tract bleeding (grossly bloody fluid in nasogastric aspirate that failed to clear with saline lavage), pneumonia, wound infection, and urinary tract infection. New gastric microorganisms appeared in 24% of the patients receiving sucralfate and 51% of the patients receiving antacids. The rates of gastric bleeding, pneumonia, and nosocomial infection were not significantly different.

Other risk factors for nosocomial pneumonia have been identified and ranked according to supporting evidence.\textsuperscript{224} In addition to host factors (e.g., gastric hypoaclidity) and environmental factors, the use of a nasogastric tube to administer medications (with the attendant risks of aspiration and guaiac-positive stools from nasogastric manipulation), along with the volume and pH of medications and feedings administered, determines the frequency of pneumonia. However, despite these other risk factors, a committee associated with the Centers for Disease Control and Prevention has recommended that non-pH-altering medications (e.g., sucralfate) be used for prophylaxis in mechanically ventilated patients (ages not specified).\textsuperscript{225} The recommendation was “suggested for implementation in many hospitals.” While sucralfate may not contribute to translocation or colonization of the airways by bacteria, animal models of aspiration pneumonia have demonstrated that the volume of fluid administered with sucralfate and the drug’s minimal buffering activity may increase the risk of acid aspiration and pulmonary edema.\textsuperscript{226}

In the RCT by Cook et al.\textsuperscript{176} that involved 1200 patients, the determination of ventilator-associated pneumonia was based on criteria modified from the Centers for Disease Control and Prevention. The study had sufficient power to detect a 25% difference in rates of pneumonia (power = 75%). Bronchoalveolar lavage or protected specimen brush sampling was used for diagnostic confirmation in patients with pneumonia suspected by clinical criteria. One potentially confounding variable was the use of enteral feedings by a majority (approximately 70%) of patients in each group. Pneumonia was diagnosed in 114 (19.1%) of 596 patients in the ranitidine group and 98 (16.3%) of 604 patients in the sucralfate group, a difference that was not significant (relative risk, 1.18; 95% CI, 0.92–1.51; p = 0.19). It is possible that a significant, albeit small, difference in favor of sucralfate would be found if a larger trial were conducted. There were five patients with “definite” pneumonia in the ranitidine group (0.8%) but none in the sucralfate group (95% CI, 0.1–1.6; p = 0.03).

Five meta-analyses of the frequency of nosocomial pneumonia associated with stress ulcer prophylaxis have also been conducted (Table 5). Two of the investi-
had a lower rate of pneumonia than patients who received an antacid or an H₂-receptor antagonist. However, in the other two meta-analyses, no significant differences among any of the treatments were found.⁶,⁷ The second meta-analysis showed a lower rate of pneumonia with sucralfate than with H₂-receptor antagonists and for sucralfate than with antacids. The other three meta-analyses were conducted by Cook et al. and were published in the 1990s. In the 1994 meta-analysis by Cook et al.,⁸ the 1994 meta-analysis by Cook et al.,¹⁷ both meta-analyses showed a lower rate of pneumonia with sucralfate than with H₂-receptor antagonists and for sucralfate than with antacids. The second meta-analysis showed a lower rate of pneumonia with sucralfate than with either an H₂-receptor antagonist or an antacid. The second meta-analysis showed a lower rate of pneumonia with sucralfate than with H₂-receptor antagonists and for sucralfate than with antacids. The second meta-analysis showed a lower rate of pneumonia with sucralfate than with H₂-receptor antagonists and for sucralfate than with antacids.

Summary. Antacids, H₂-receptor antagonists, and sucralfate have been used for many years and have well-delineated adverse-effect profiles, with the notable exception of nosocomial pneumonia associated with pH-altering agents in critically ill patients. Although data from RCTs or large surveillance studies are lacking for pediatric patients, all these agents have been used in various age groups for multiple GI disorders with relatively few adverse effects. Experience with the proton-pump inhibitors for stress ulcer prophylaxis is limited, but experience treating peptic ulcers suggests that these agents have a low rate of serious adverse effects in adults when used on a short-term basis. When compared with that of other agents, the adverse-effect profile of misoprostol, as well as the fact that there are limited studies of efficacy, precludes its use for stress ulcer prophylaxis.

Recommendation (adults and pediatrics): It is recommended that patients with a history of serious reactions to antacids, H₂-receptor antagonists, proton-pump inhibitors, or sucralfate avoid future use of the offending agent. There are no other absolute contraindications that would preclude the use of any of these medications for stress ulcer prophylaxis. However, unless the benefits clearly exceed the risks, it is recommended that sucralfate and antacids be avoided in neonates (particularly premature neonates) because of the possibility of adverse effects (e.g., bezoar formation, accumulation of aluminum and magnesium). Also, it is recommended that aluminum-containing products such as sucralfate be avoided in children with renal failure because dosing information has not been well established. Whether acid-suppressing agents are associated with a higher rate of pneumonia than sucralfate is unresolved, although any difference between these medications would appear to be small. It is recommended that potential adverse effects be considered as part of the economic analysis when an agent is chosen (see Economic analysis). (Strength of evidence = D)

Initial dosage

Some of the dosages listed in Table 6 had to be extracted from the literature because stress ulcer prophylaxis is not an FDA-approved indication for most of the medications used for this purpose. The dosages included in Table 6 have been commonly used for initiating prophylaxis against stress-induced bleeding in adults. In some of the studies, dosages were subsequently adjusted according to gastric pH measurements. Dosages for patients with renal dysfunction

Table 5. Meta-analyses Investigating the Risk of Pneumonia with Medications Used for Stress Ulcer Prophylaxis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Comparison</th>
<th>No. Trials</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>69</td>
<td>Sucralfate versus H₂-RAs or antacids (combined group)</td>
<td>6</td>
<td>OR and CI &lt; 1 (lower rate of pneumonia with sucralfate)</td>
</tr>
<tr>
<td>71</td>
<td>Sucralfate versus H₂-RAs</td>
<td>5</td>
<td>OR = 0.498, CI = 0.316–0.783 (lower rate of pneumonia with sucralfate)</td>
</tr>
<tr>
<td></td>
<td>Sucralfate versus antacids</td>
<td>4</td>
<td>OR = 0.402, CI = 0.235–0.687 (lower rate of pneumonia with sucralfate)</td>
</tr>
<tr>
<td>227</td>
<td>Prophylaxis adjusted according to gastric pH versus no adjustment</td>
<td>3</td>
<td>OR = 0.63, CI = 0.24–1.62</td>
</tr>
<tr>
<td></td>
<td>Antacids or H₂-RAs versus placebo versus control (combined group)</td>
<td>4</td>
<td>OR = 0.42, CI = 0.61–1.10</td>
</tr>
<tr>
<td>177</td>
<td>Sucralfate versus antacids or H₂-RAs (combined group)</td>
<td>6</td>
<td>OR = 0.50, CI = 0.21–0.79 (lower rate of pneumonia with sucralfate)</td>
</tr>
<tr>
<td>5</td>
<td>H₂-RAs versus control</td>
<td>8</td>
<td>OR = 1.25, CI = 0.78–2.00</td>
</tr>
<tr>
<td></td>
<td>H₂-RAs versus antacids</td>
<td>3</td>
<td>OR = 1.01, CI = 0.65–1.57</td>
</tr>
<tr>
<td></td>
<td>Sucralfate versus control</td>
<td>2</td>
<td>OR = 2.11, CI = 0.82–5.44</td>
</tr>
<tr>
<td></td>
<td>Sucralfate versus antacids</td>
<td>6</td>
<td>OR = 0.80, CI = 0.56–1.15</td>
</tr>
<tr>
<td></td>
<td>Sucralfate versus H₂-RAs</td>
<td>11</td>
<td>OR = 0.78, CI = 0.62–1.09</td>
</tr>
</tbody>
</table>

Notes:
- OR = odds ratio, CI = 95% confidence interval. Exact values provided when available; some values were extrapolated from figures.
- H₂-RAs = histamine H₂-receptor antagonists.
- aOR = odds ratio, CI = 95% confidence interval. Exact values provided when available; some values were extrapolated from figures.
- bComparison = Reference
- cReference = Table 5."
and children up to 18 years of age. Cimetidine (in three or four divided doses) to preterm newborns i.v. ranitidine was given in dosages of 2–6 mg/kg/day (in continuous i.v. infusion) to neonates with documented gastric bleeding from 0.13 to 0.8 mg/kg. Another study involving ranitidine was noted.

The dosage guidelines in Table 6 are based on limited clinical data and may need to be adjusted according to adverse effects or clinical response.

Dosages for pediatric patients can be estimated from the few studies that have been published on stress ulcer prophylaxis (Table 7), extrapolated from pediatric handbooks that describe dosing for related conditions (e.g., GI bleeding), or extrapolated from pharmacokinetic studies. In published studies, i.v. ranitidine was given in dosages of 2–6 mg/kg/day (in three or four divided doses) to preterm newborns and children up to 18 years of age. Cimetidine was given i.v. in dosages of 15–24 mg/kg/day (in four divided doses) in two studies involving newborns and another study involving patients from birth to 18 years of age (maximum dosage, 1000 mg/day).

Pharmacokinetic or dosage studies in pediatric patients have been published, but these are not necessarily related to the prevention of stress-induced bleeding. For example, Martyn et al. determined the pharmacokinetics of cimetidine in children with burn injuries. Twenty-one children ranging in age from 0.3 to 17.5 years were administered cimetidine in doses of 10–15 mg/kg. These children had higher cimetidine clearances and shorter elimination half-lives than healthy or burned adults (primarily because of greater renal clearance). The authors suggested that in order to maintain a gastric pH of ≥4, continuous infusions of cimetidine would be required.

Another study looked at the pharmacokinetics of cimetidine in 30 critically ill children age 4.5 to 15 years. The patients received a mean dosage of 26 mg/kg/day administered in four doses infused over 15 minutes. Patients receiving ≥20 mg/kg/day maintained plasma cimetidine concentrations at ≥0.5 µg/mL for longer periods. The investigators found a significant (p < 0.001) inverse correlation between age and total body clearance (r = 0.75, p < 0.001) and age and apparent volume of distribution (r = 0.76, p < 0.001). They concluded that a dosage of cimetidine of 20–30 mg/kg/day given in six divided doses would provide more optimal steady-state plasma cimetidine concentrations.

Ranitidine was studied in 12 children ranging in age from 3.5 to 16 years with peptic ulcer disease. Each child received ranitidine by continuous i.v. infusion, with the rate adjusted to achieve at least 90% inhibition of gastric acid secretion. The dosage and response data were used to design intermittent dosage regimens, consisting of i.v. bolus doses given every 6 hours and then oral doses given every 12 hours. The i.v. dose ranged from 0.13 to 0.8 mg/kg. Another study involving ranitidine for neonates with documented gastric bleeding used a loading dose of 0.6 mg/kg followed by a continuous infusion of 0.15 mg/kg/hr. No adverse effects from the ranitidine were noted.

Table 6.
Initial Adult Dosage Regimens for Agents Used for Prophylaxis of Stress-Induced Bleeding

<table>
<thead>
<tr>
<th>Medication</th>
<th>Normal Function</th>
<th>Reduced Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>If Clcr &lt; 30 mL/min: 300 mg</td>
<td>If Clcr &lt; 30 mL/min: 20 mg</td>
</tr>
<tr>
<td>Famotidine</td>
<td>If Clcr &lt; 30 mL/min: 20 mg</td>
<td>If Clcr &lt; 30 mL/min: 20 mg</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>If Clcr &lt; 50 mL/min: 150 mg</td>
<td>If Clcr &lt; 50 mL/min: 150 mg</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>40-mg loading dose, then 20–40 mg daily p.o. or NG</td>
<td>No adjustment necessary</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>1 g four times a day p.o. or NG</td>
<td>No adjustment necessary</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication</th>
<th>Normal Function</th>
<th>Reduced Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clcr &lt; 50 mL/min: 150 mg</td>
<td>If Clcr &lt; 50 mL/min: 150 mg</td>
<td></td>
</tr>
<tr>
<td>Clcr &lt; 30 mL/min: 20 mg</td>
<td>If Clcr &lt; 30 mL/min: 20 mg</td>
<td></td>
</tr>
<tr>
<td>Clcr &lt; 30 mL/min: 20 mg</td>
<td>If Clcr &lt; 30 mL/min: 20 mg</td>
<td></td>
</tr>
<tr>
<td>Clcr &lt; 30 mL/min: 20 mg</td>
<td>If Clcr &lt; 30 mL/min: 20 mg</td>
<td></td>
</tr>
</tbody>
</table>

*NG = by nasogastric tube, Clcr = creatinine clearance. Dosages can be modified on the basis of response or adverse effects.

were mostly taken from published guidelines. No well-documented maximum dosage for each agent has been reported, although studies involving pH determinations often set an arbitrary upper limit. Antacids were not included in Table 6 because of the large number of commercially available products with differing acid-neutralizing capacities and the large number of regimens used in the literature (many adjusted on the basis of gastric pH determinations); the reader is encouraged to consult available studies. The dosage guidelines in Table 6 are based on limited clinical data and may need to be adjusted according to adverse effects or clinical response.

In summary, pharmacokinetic studies suggest that children clear H2-receptor antagonists faster and have
larger volumes of distribution than adults and that doses should be given either by continuous infusion or more frequently than those recommended for adults. Studies addressing the proper dosing of agents for stress ulcer prophylaxis in pediatrics are needed.

In general, there is little dosing information for the neonatal population, in particular, premature neonates. Dosing in premature neonates is further complicated by decreased renal function secondary to disease or lack of maturation. Caution should be exercised when \( H_2 \)-receptor antagonists are used in combination with tolazoline. Tolazoline may still be used in some institutions to treat pulmonary hypertension in neonates and has been associated with gastric bleeding. Case reports have implicated both cimetidine and ranitidine with reversal of tolazoline’s histamine-mediated effects on pulmonary vasculature.\(^{242}\) In general, the use of antacids and sucralfate should be avoided in premature infants because of the possibility of complications (see Adverse effects of prophylactic agents).

Doses of \( H_2 \)-receptor antagonists are often reduced (or the intervals extended) for patients with renal dysfunction, because all these medications have slower clearances and longer half-lives in this population.\(^ {243} \) These alterations in dose or interval have been based on expected serum drug concentrations, because well-controlled studies have not investigated various dosage regimens in preventing stress-induced bleeding. Whether doses or intervals of \( H_2 \)-receptor antagonists need to be adjusted in patients with severe hepatic dysfunction or other diseases that might affect the pharmacokinetic properties of the agents is not known.

### Table 7.

**Studies of Stress Ulcer Prophylaxis in Pediatric Populations**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design and Population (No. Patients or Admissions)</th>
<th>Age</th>
<th>Medication</th>
<th>No. with Clinically Important Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>88</td>
<td>Retrospective; thermal injury to 13–93% BSA; (477)</td>
<td>35 days to 13 yr; mean, 4.3 yr</td>
<td>None stated</td>
<td>36</td>
</tr>
<tr>
<td>230</td>
<td>Retrospective; thermal injury to 5–92% BSA (582)</td>
<td>4 wk to 15 yr</td>
<td>Milk or feeding formula plus diazepam</td>
<td>2</td>
</tr>
<tr>
<td>48</td>
<td>Prospective, randomized; general ICU (40)</td>
<td>Birth to 18 yr; mean, 1.85 yr</td>
<td>Cimetidine 5 mg/kg i.v. every 6 hr (1 g/day maximum)</td>
<td>NA</td>
</tr>
<tr>
<td>231</td>
<td>Prospective, randomized; general ICU (33)</td>
<td>30–41.5 wk</td>
<td>Cimetidine 6 mg/kg i.v. every 6 hr</td>
<td>NA</td>
</tr>
<tr>
<td>232</td>
<td>Prospective, randomized; general ICU (40)</td>
<td>Birth to 18 yr; mean, 2.6–4.3 yr (varied by group)</td>
<td>Ranitidine 2–4 mg/kg NG every 12 hr or 0.75–1.5 mg/kg i.v. every 6 hr</td>
<td>NA</td>
</tr>
<tr>
<td>49</td>
<td>Prospective, randomized; general ICU (100)</td>
<td>Full-term neonates</td>
<td>Cimetidine 3.75–5 mg/kg i.v. every 6 hr</td>
<td>NA</td>
</tr>
<tr>
<td>65</td>
<td>Prospective, randomized; general ICU (140)</td>
<td>Birth to 20 yr; mean, 4.6 yr</td>
<td>Ranitidine 1.5 mg/kg i.v. every 6 hr, sucralfate 0.5 g (&lt;10 kg) or 1 g (&gt;10 kg) every 6 hr, antacid (almagate) 0.25–0.5 mL/kg every 2 hr</td>
<td>7/35 in control group versus 6/105 in combined medication groups (( p &lt; 0.05 )); no significant differences for any single medication versus control group</td>
</tr>
<tr>
<td>56</td>
<td>Prospective, observational; general ICU (208)</td>
<td>Mean ± S.D., 38 ± 53.5 mo</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>57</td>
<td>Prospective, observational; general ICU (984)</td>
<td>Mean ± S.E., 62.6 ± 2.1 mo</td>
<td>Various (per discretion of physician)</td>
<td>2/698 with no prophylaxis versus 2/286 with prophylaxis</td>
</tr>
<tr>
<td>168</td>
<td>Prospective, randomized; cardiac surgery (79)</td>
<td>35 days to 9.85 yr; mean, 2.62 yr</td>
<td>Famotidine or pirenzepine 1 mg/kg/day i.v. (3 doses if &lt;10 kg), 0.5 mg/kg/day if serum creatinine &gt; 3 mg/dL</td>
<td>NA</td>
</tr>
<tr>
<td>63</td>
<td>Prospective, randomized; general ICU (53)</td>
<td>Neonates, mostly preterm; mean, 32 wk gestation</td>
<td>Ranitidine 1.67 mg/kg i.v. every 8 hr</td>
<td>NA</td>
</tr>
<tr>
<td>233</td>
<td>Prospective, observational; general ICU (45)</td>
<td>2 wk to 264 mo; median, 36 mo</td>
<td>Ranitidine 2–6 mg/kg/day i.v. (mean, 3.3 mg/kg/day) given at intervals of 6, 8, or 12 hr(^ b )</td>
<td>None</td>
</tr>
<tr>
<td>66</td>
<td>Prospective, observational; general ICU (1006)</td>
<td>3 days to 18 yr; mean, 61.5 mo</td>
<td>Various (per discretion of physician)</td>
<td>6/990 with no prophylaxis versus 10/110 with prophylaxis</td>
</tr>
</tbody>
</table>

\(^ a \)Only studies with at least 25 patients were included. BSA = body surface area, ICU = intensive care unit, NA = not available, NG = by nasogastric tube. 
\(^ b \)Administered every eight hours in 89% of patients.
There are no adequate dosage guidelines for children with renal dysfunction. Many practitioners recommend adjustment of renal function by established methods for children. Most methods yield creatinine clearances normalized to an average BSA (mL/min/1.73 m²). Adjustments are then made by using adult guidelines for impaired renal function. Still other practitioners may not make adjustments, believing that the risks of excessive dosing would not outweigh the risk of underdosing in children.

Gastric pH monitoring may help in developing dosage regimens, especially in patients with renal dysfunction or immaturity (preterm infants). On days a patient is being dialyzed, it is advisable to administer the medications after dialysis to avoid rapid clearance during the dialysis procedure.

Table 6 lists dosage regimens for commonly used agents in adult patients. Some of the oral dosage regimens are equivalent to the i.v. regimens in terms of total daily dosage (e.g., cimetidine, famotidine), although an argument could be made for larger oral dosages on the basis of bioavailability differences between the two routes of administration. Table 8 provides pediatric doses for the H₂-receptor antagonists and sucralfate. The recommendations were derived from limited data from published studies and were based on toxicity as well as efficacy considerations.

**Monitoring**

For agents that do not affect gastric pH, such as sucralfate, monitoring is limited to potential adverse events and GI bleeding. However, for agents that neutralize gastric acid, particularly antacids, monitoring has frequently included pH determinations. No large, controlled studies have been published that document a benefit to pH monitoring in association with stress ulcer prophylaxis. The issue is further complicated by differences in the validity and reliability of methods used to measure gastric pH. Although monitoring with pH paper is simple and is considered by many clinicians to be a standard of practice for agents that raise gastric pH, this method lacks accuracy. One study found that 33% of gastric pH determinations were not ≥4, despite pH paper testing demonstrating evidence to the contrary.

A number of studies have concluded from gastric pH determinations that continuous infusions of H₂-receptor antagonists are more effective than intermittent dosage schedules. Many factors must be considered in the interpretation of these studies, beginning with the role of gastric acidity in the pathogenesis of stress ulceration. Although gastric acidity may have a role in stress-induced damage, gastric acid is unlikely to be the main cause of bleeding. Not only do many ICU patients have hyposecretion of gastric acid, but gastric pH fluctuates rapidly and may not be controlled.

### Table 8.

**Pediatric Dosage Recommendations for H₂-Receptor Antagonists and Sucralfate**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage*</th>
<th>Medication</th>
<th>Dosage*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neonates</td>
<td>Infants</td>
<td>Children</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>10 (5–20) mg/kg/day i.v. in 2 or 3 divided doses</td>
<td>20–40 mg/kg/day i.v. in 3 or 4 divided doses</td>
<td>30–40 mg/kg/day i.v. (1200 mg/day maximum) in 6 divided doses</td>
</tr>
<tr>
<td>Famotidine</td>
<td>Inadequate information available to make dosage recommendations</td>
<td>1.2 (1–2) mg/kg/day i.v. in 2 or 3 divided doses</td>
<td>1.6 (1–2) mg/kg/day i.v. (40 mg/day maximum) in 3 divided doses</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Continuous i.v. infusion: 0.0625–0.2 mg/kg/hr; Intermittent i.v. doses: If full term, 1.5–3 mg/kg/day in 3 divided doses; if premature, 0.5 mg/kg/day in 2 divided doses</td>
<td>4.5 (3–6) mg/kg/day i.v. in 3 divided doses</td>
<td>6 (3–6) mg/kg/day i.v. (200 mg/day maximum) in 4 divided doses</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>Not recommended</td>
<td>40 mg/kg/day p.o. or NG in 4 divided doses</td>
<td>40–80 mg/kg/day p.o. or NG (lower end of range for younger children, 4000 mg/day maximum) in 4 divided doses</td>
</tr>
</tbody>
</table>

*Dosages are for patients with normal renal function. NG = by nasogastric tube. There is a lack of data to make definitive dosage adjustments in pediatric patients for renal dysfunction, but decreases in the total daily dosage of cimetidine, famotidine, and ranitidine would be logical. This could be done either by decreasing individual doses while keeping the dosage interval the same as for patients with normal renal function or by extending the dosage interval and keeping individual doses the same as for patients with normal renal function. No adjustment in the dosage of sucralfate is required for patients with renal dysfunction.

In general, half-lives were longer in neonates (2–3.4 hours), more than likely because of immature renal function. There is inadequate dosage information on premature neonates with respect to stratification by birth weight or gestational age. Thus, a wide range of dosages have been reported in the literature. Many dosage handbooks and institutions use 5–10 mg/kg/day divided every 12 hours in premature neonates.

Inadequate information is available. Not recommended because of reports of bezoar formation in neonates (particularly premature neonates). Amount of aluminum in adult doses of sucralfate may contribute to hypophosphatemia in neonates.

Dosage not well established. Bezoar formation with obstruction has been reported. Caution is advised when sucralfate is administered to any pediatric patient, especially in cases of impaired gastric motility and dehydration.
even if dosages of antisecretory agents are individualized.256,257 Gastric pH can also be increased by the presence of blood and bile in the GI tract. Although newer methods of pH monitoring, such as noninvasive, intramucosal pH measurements, may prove useful for predicting stress-induced bleeding, such measurements have been studied primarily as indicators of systemic tissue oxygenation and hence of overall mortality rates in critically ill patients.258

Checking for microscopic bleeding by occult blood testing techniques has similar limitations. Most important, there is no proven relationship between microscopic bleeding and outcomes such as clinically important bleeding, although the results of one prospective study suggest that occult bleeding for at least 6 days increases the risk for overt bleeding.35 Overt bleeding is defined as the presence of blood or “coffee-ground” material in nasogastric aspirates, hematemesis, hema-tochezia, or melena. Overt bleeding that results in hemodynamic compromise or the need for blood transfusions or surgery is clinically important. Therefore, patients at risk for stress-related complications should be routinely followed for overt bleeding.

When overt bleeding occurs, the patient should be closely monitored for decreases in blood pressure (e.g., a decrease of 20 mm Hg or more in the diastolic pressure during a 24-hour period), hemoglobin (e.g., ≥3 g/dL during a 24-hour period), and hematocrit (e.g., ≥9% during a 24-hour period), all of which suggest clinically important GI bleeding in the absence of other causes. When overt bleeding, with or without hemodynamic compromise, continues despite conservative therapies such as saline lavage, endoscopy is usually indicated. Endoscopy can be used to confirm a GI source of bleeding.

Recommendation (adults and pediatrics): It is recommended that all patients receiving medications for stress ulcer prophylaxis be monitored for bleeding and adverse drug effects (see Adverse effects of prophylactic agents). Paper techniques for measuring gastric pH have questionable validity and reliability, and there is no evidence that adjusting the dosage of pH-altering medications (antacids, H2-receptor antagonists, proton-pump inhibitors) on the basis of these measurements influences patient morbidity or mortality. Despite the lack of supporting data, pH monitoring for antacids may be appropriate (goal pH of >3.5–4). Such monitoring may also be useful for H2-receptor antagonists when standard dosage regimens might not be appropriate (e.g., in cases of renal dysfunction, for increased dosages due to perceived failure of therapy, in pediatric patients). (Strength of evidence = D)

Other options for prophylaxis

Similar to the principles involved in preventing global ischemia, a primary intervention for reducing the frequency of stress-induced bleeding should be the prevention of GI hypoperfusion and attendant ischemic complications.259,260 If ischemia is prevented during the early stages of injury, stress ulcer prophylaxis may be unnecessary. In fact, acid inhibitors or neutralizers may be harmful. In the case of acid neutralizers, increasing gastric pH allows for bacterial overgrowth, with subsequent spread to other organs.261

As discussed previously, the effect of enteral feedings on the frequency of stress-induced bleeding and pneumonia has not been established through controlled trials. Although gastric acid appears to play a role in stress-induced bleeding, and while it is clear that microbial growth is inhibited at low gastric pH, it has not been conclusively demonstrated that continuous or intermittent enteral feedings consistently raise gastric pH.262 The site of enteral feeding administration (stomach or sites distal to the pylorus) varied in published studies, and potential site-specific effects remain to be elucidated. The possibility that enteral feedings offer protection against bleeding and pneumonia through other mechanisms (e.g., maintenance of a positive nitrogen balance that is important for normal reparative functions of the gastric mucosa) should be explored.

Appropriate supportive care, such as administration of fluids and blood products, nutritional support, ventilatory support, and timely definitive surgery, may preclude the need for stress ulcer prophylaxis in many patients.263,264 Before the widespread use of H2-receptor antagonists for stress ulcer prophylaxis, a number of regimens were used to prevent acute upper GI bleeding in burn patients, including milk and diazepam given to children and vitamin A injection given to adults.230,264 Although corticosteroids have been studied as inciting factors for GI bleeding, other evidence suggests that corticosteroids may protect against bleeding in some populations, including patients with shock.265

Combinations of allopurinol and dimethyl sulfoxide have been studied in two RCTs in patients with leg or pelvic fractures who had clinical evidence of shock.166,266 These agents were studied because of their ability to decrease free-radical formation and, therefore, potentially prevent gastric mucosal injury. Both trials showed significant (p < 0.01) decreases in endoscopically confirmed lesions. Both of these studies are promising but require confirmation in different populations. Comparisons with existing agents that include economic evaluations of the options are also needed.

Recommendation (adults and pediatrics): It is premature to recommend the use of novel therapies (e.g., free-radical scavengers) in place of conventional agents for stress ulcer prophylaxis, although the limited number of studies have had promising results. (Strength of evidence = D)

Prevention of recurrent bleeding

The efficacy of nonsurgical therapies such as antacids and H2-receptor antagonists in preventing recurrent bleeding has varied considerably from study to study.267,269 The number of patients requiring surgery for continued or recurring stress-induced bleeding has steadily decreased since approximately 1978. In a number of published studies, bleeding stopped spontaneous-
ously without intervention. In others, the patients’ bleeding often stopped and did not recur when conservative measures were instituted, usually an increase in the dosage of the current medication, a switch to a different medication, or the addition of another agent, plus gastric lavage. No large controlled trials have compared the various medication options for preventing a recurrence of stress-induced bleeding. However, when combination therapy for prophylaxis is being considered in a patient who bled while receiving single-agent prophylaxis, use of drugs with different mechanisms of action would seem logical. Potential interactions between prophylactic agents from different classes have not been well studied but could occur (e.g., reduced activity of sucralfate with neutral or alkaline gastric pH, binding of agents by sucralfate). Providing any definitive recommendation regarding this issue is difficult. The assumption is, of course, that any medication is of benefit in preventing recurrent bleeding.

Recommendation (adults and pediatrics): The lack of available trials prohibits definitive recommendations for preventing recurrent bleeding after an episode of stress-induced GI bleeding, although consideration could be given to increasing the dosage of the prophylactic agent, adding another medication, or switching to a different agent. (Strength of evidence = D)

**Prophylaxis in non-ICU settings**

It is possible that patients in non-ICU settings could have coagulopathy or other conditions that have been identified as risk factors for bleeding (e.g., transplantation). Only one RCT has addressed stress ulcer prophylaxis in non-ICU settings.44 The study involved 100 adults and was conducted on a general medical and surgical hospital ward in Spain. Bleeding was significantly (p < 0.001) less frequent with antacid prophylaxis than with placebo. However, bleeding was defined broadly to include patients who had a decrease in hematocrit, regardless of whether they required transfusion. Three patients required transfusion in the placebo group and none in the antacid group. Upon institution of antacid and H₂-receptor antagonist therapy, the bleeding stopped in the three patients in the placebo group without subsequent complications. The frequency of all types of bleeding (e.g., overt, clinically important) was significantly lower with prophylaxis only if two or more risk factors for bleeding were present before prophylaxis was initiated.

**Discontinuation of prophylaxis**

An increase in the number of risk factors has been associated with a higher risk of bleeding in multiple studies conducted in the ICU setting and one study conducted on a hospital ward. The risk of clinically important bleeding would probably diminish as the number of risk factors is reduced. In most clinical trials, prophylaxis was discontinued without evidence of clinically important bleeding upon extubation or the patient’s discharge from the ICU. Thus, it is reasonable to assume that prophylaxis can be stopped once risk factors have resolved.

Recommendation (adults): Stress ulcer prophylaxis is not recommended for adult patients in non-ICU settings. (Strength of evidence = B for general medical and surgical patients with fewer than two risk factors for clinically important bleeding; strength of evidence = D for patients with two or more risk factors) (Table 3)

Recommendation (pediatrics): Stress ulcer prophylaxis is not recommended for pediatric general medical and surgical patients or special populations (e.g., transplantation) in non-ICU settings if fewer than two risk factors for bleeding are present. (Strength of evidence = D). Data are insufficient to allow recommendations to be made about the use of prophylaxis in pediatric patients with two or more risk factors. If prophylaxis is given, it should be discontinued once risk factors have resolved. (Strength of evidence = D)

**Economic analysis**

Inappropriate stress ulcer prophylaxis can be costly, but implementing guidelines may decrease the inappropriateness and the expense.270,271 Published economic analyses can be useful for developing institution-specific guidelines for prophylaxis. Two cost-effectiveness analyses have been completed concerning prophylaxis for stress-induced bleeding. In the first investigation, by Schumock et al.,271 an antacid regimen of 30 mL given every 4 hours was compared with sucralfate 1 g given four times daily and three H₂-receptor antagonists (ranitidine 50 mg i.v. every 8 hours, cimetidine 300 mg i.v. every 6 hours, and famotidine 20 mg i.v. every 12 hours), all of which were based on a seven-day course of therapy. The study was conducted from the viewpoint of the payer, with hospital charges measured in 1994 dollars. The authors assumed that the frequency of bleeding would be approximately 70%, 80%, and 36% lower with the use of sucralfate, antacids, and H₂-receptor antagonists, respectively, and that it cost $6128 to treat an episode of bleeding. The frequency of pneumonia was assumed to be unchanged with sucralfate but increased by approximately 7% with antacids and 13% with H₂-receptor antagonists. The net saving associated with prevention of one case of acute upper GI bleeding was $7373 for sucralfate and $4321 for antacids. In contrast, therapy with an H₂-receptor antagonist would cost between $6655 and $7986 to prevent one episode of acute upper GI bleeding. The difference in costs between sucralfate or antacids and H₂-receptor antagonists was related to the assumed higher rates of bleeding and nosocomial pneumonia with H₂-receptor antagonists. One-way sensitivity analysis showed that sucralfate remained the preferred agent regardless of the cost of prophylaxis, the cost of treatment for pneumonia or bleeding, or the presumed frequency of bleeding or nosocomial pneumonia.

The second cost-effectiveness study, by Ben-Men-
achem et al., was based on the perspective of the health care provider. Cimetidine (300 mg i.v. every six hours) was compared with sucralfate (1 g every six hours), both given for seven days. One notable difference from the previous analysis was the assumption that it would cost $595 to treat a GI bleed. It was presumed that both therapies would decrease the frequency of bleeding by 50%; in the sensitivity analysis, the percent reduction was varied over the range of 10–90%. Despite different assumptions from the investigation by Schumock et al., the results were similar in that sucralfate (cost of $1144 per bleeding event averted) was more cost-effective than cimetidine ($7538 per bleeding event averted), even when rates of pneumonia were presumed to be equal.

In one study involving a small number of patients, the costs of enteral and i.v. ranitidine administration were compared, although only enteral administration was used. Ten patients were assigned to receive ranitidine 150 mg every 12 hours and eight patients to receive 300 mg every 12 hours; both dosages were given by nasogastric tube. Both therapies reduced stimulated acid secretion by at least 50%. Drug costs were calculated to be at least 48% less with the enteral administration than with i.v. administration.

A formal economic analysis from an institutional perspective was conducted as part of the guideline development process. The general steps of acceptable cost-effectiveness analysis were followed: identification of clinical choices, determination of costs and benefits, statement of time frame, determination of cost-effectiveness ratio, and performance of a sensitivity analysis. Readers are encouraged to make institution-specific decisions and to use the template to construct their own institution-specific economic analysis.

The medications were assumed to have equal prophylactic efficacy on the basis of the most recent meta-analysis. Although both the meta-analysis and the recent large RCT met our criteria for a grade of A, the meta-analysis had a level of evidence of I and the RCT a level of evidence of I– (see Table 1 for definitions).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cost Assumptions per Episode or Course of Therapy ($)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>10,062</td>
</tr>
<tr>
<td>Bleeding</td>
<td>7,000</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>500</td>
</tr>
<tr>
<td>Gastrointestinal toxicity</td>
<td>500</td>
</tr>
<tr>
<td>Cytopenia</td>
<td>500</td>
</tr>
<tr>
<td>Cardiovascular toxicity</td>
<td>500</td>
</tr>
<tr>
<td>Clogged tubes</td>
<td>160</td>
</tr>
<tr>
<td>Antacids every two hours</td>
<td>78.00</td>
</tr>
<tr>
<td>Histamine H2-receptor antagonist three times dailya</td>
<td>61.50</td>
</tr>
<tr>
<td>Sucralfate four times daily</td>
<td>33.80</td>
</tr>
</tbody>
</table>

Cost Assumptions per Episode or Course of Therapy ($)a

Step 1. Estimate the risk of clinically important bleeding events without prophylaxis (baseline rate stated as a percentage).

Step 2. Estimate the reduction in clinically important bleeding events associated with prophylaxis.

Step 3. Estimate the cost per patient of treating GI bleeding at the institution.

Step 4. Estimate the cost of using sucralfate prophylaxis in 100 patients.

Step 5. Estimate the cost of adverse events per 100 patients if all 100 are given prophylaxis.

Step 6. Estimate the cost of treating bleeding per 100
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Figure 1. Decision tree for stress ulcer prophylaxis. H2-RAs = histamine H2-receptor antagonists, CV = cardiovascular.

Step 7. Estimate the savings with stress ulcer prophylaxis per 100 patients treated $\{(\text{risk of bleeding without prophylaxis}) \times (\text{estimated cost of treating GI bleed per patient})\} \times (\text{cost of treating GI bleed per patient})$.

Step 8. Determine the marginal cost of prophylaxis per 100 patients treated $\{(\text{cost of medication per 100 patients}) + (\text{cost of adverse drug events per 100 patients}) - (\text{savings with stress ulcer prophylaxis in 100 patients})\}$.

Note that positive numbers represent a cost liability, negative numbers a cost saving.

Step 9. Determine the cost-effectiveness ratio $\{(\text{marginal cost of prophylaxis in 100 patients})/(\text{risk of bleeding})(\text{risk reduction with prophylaxis expressed as a decimal})\}$. A negative value indicates a saving.

Table 10 provides an example of how the cost-effectiveness calculation for sucralfate was performed. The cost-effectiveness ratios for the various therapies can be compared in order to choose the appropriate agent. As with any guidelines, patient-specific information should always be used for determining prophylaxis for the individual patient.
analysis for various rates of bleeding and reductions in bleeding associated with prophylaxis, simply vary the values in step 9. Table 11 shows the results of the sensitivity analysis for sucralfate.

Figure 2 is an algorithm for stress ulcer prophylaxis in adult patients that is based on the recommendations contained in this document. The lack of pediatric RCTs involving medications and the age stratification in those studies that did include pediatric patients preclude development of a separate pediatric algorithm. Because the number (≥2) and type (coagulopathy, respiratory failure, and Pediatric Risk of Mortality Score of ≥10) of risk factors for clinically important bleeding have been elucidated,66 the reader is referred to the discussion in the section titled “Adverse effects of prophylactic agents” for help in deciding which medication, if any, should be used for prophylaxis.

The adult algorithm is intended to serve as a template that can be modified according to institution-specific data. The strength of the evidence for prophylaxis varies substantially from one risk factor to the next (Table 3). ICU patients with a history of recent GI pathology are deemed appropriate candidates for prophylaxis, but the recommendation must be graded D because patients with recent histories of GI pathology were often excluded from the published investigations, and thus it is unknown whether these patients are at increased risk for clinically important bleeding. The recommendation for use of oral H2-receptor antagonists in patients with functioning GI tracts (Figure 2) is based on presumption efficacy, because no RCTs are available that have compared i.v. with oral H2-receptor antagonists administration for preventing clinically important bleeding.

Recommendation (adults): Given some of the unresolved issues regarding stress ulcer prophylaxis, it is recommended that institution-specific guidelines be developed on the basis of economic models such as the one included in this document. For institutions willing to accept the assumption that H2-receptor antagonists and sucralfate have equal efficacy, the accompanying economic analysis found sucralfate to be the most cost-effective agent. Exceptions to the use of sucralfate include lack of oral or other gastric access for administration and, potentially, documented failure of prophylaxis with sucralfate. If ranitidine is assumed to be more effective than sucralfate without increasing the risk of pneumonia, ranitidine (and presumably other H2-receptor antagonists) would be the drug of choice and would also result in a cost saving, although less than that achieved with sucralfate.

Recommendation (pediatrics): There are also unresolved issues for pediatric patients. Institution-specific guidelines can be developed by using the economic models included in this document, but the percentages and costs need to be tailored to this population on the basis of institution-specific data. There is supporting evidence in the literature that the risk of stress-induced bleeding is greater in pediatric patients with respiratory failure, coagulopathy, a Pediatric Risk of Mortality Score of ≥10, and thermal injuries. Whether prophylaxis will reduce the risk of bleeding is yet to be proven in this population, so there is no clear agent of choice at this time.

Conclusion

Although medications such as antacids have been used for at least two decades to prevent stress-induced bleeding, many issues remain unresolved. While pro-

Table 10.
Cost-effectiveness Calculations for Sucralfate

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of bleeding without prophylaxis (%)</td>
<td>6.0 (0.1–39)</td>
</tr>
<tr>
<td>Risk reduction with prophylaxis (%)</td>
<td>50 (10–90)</td>
</tr>
<tr>
<td>Cost of treating episode of GI bleeding per patient ($)</td>
<td>7000</td>
</tr>
<tr>
<td>Cost of sucralfate per 100 patients ($)</td>
<td>3380</td>
</tr>
<tr>
<td>Cost of adverse drug events per 100 patients treated ($)</td>
<td>2880</td>
</tr>
<tr>
<td>Cost of treating GI bleeding in 100 patients ($)</td>
<td>42,000</td>
</tr>
<tr>
<td>[(Six episodes of bleeding) × ($7000 cost of treatment)]</td>
<td></td>
</tr>
<tr>
<td>Savings with stress ulcer prophylaxis in 100 patients ($)</td>
<td>21,000</td>
</tr>
<tr>
<td>[(Three episodes of bleeding) × ($7000 cost of treatment)]</td>
<td></td>
</tr>
<tr>
<td>Marginal cost of prophylaxis in 100 patients ($)</td>
<td>−14,740</td>
</tr>
<tr>
<td>[(6,380 + $2880) – ($21,000)]</td>
<td></td>
</tr>
<tr>
<td>Cost-effectiveness ratio for each bleeding episode averted</td>
<td>4913</td>
</tr>
</tbody>
</table>

Table 11.
Cost-effectiveness Ratio for Sucralfate Prophylaxis: Results of Sensitivity Analysisa

<table>
<thead>
<tr>
<th>% Reduction in Risk with Prophylaxis</th>
<th>Risk of Bleeding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>10</td>
<td>619,000</td>
</tr>
<tr>
<td>50</td>
<td>201,667</td>
</tr>
<tr>
<td>70</td>
<td>118,200</td>
</tr>
<tr>
<td>90</td>
<td>82,429</td>
</tr>
</tbody>
</table>

aAssumptions about the risk of bleeding and the effectiveness of prophylaxis were varied from 0.1% to 39% and from 10% to 90%, respectively. The values represent the cost or saving (in parentheses) for each bleeding episode averted. Costs and benefits were presumed to occur within a similar period, making discounting unnecessary.
Figure 2. Algorithm for stress ulcer prophylaxis in adult patients.

Is stress ulcer prophylaxis needed? (Prophylaxis is appropriate for patients admitted to the ICU with one or more of the risk factors listed in Table 3.)

Yes  
No  
Continue periodic assessment

Does patient have gastric access via oral route, nasogastric tube, or gastrostomy?

Yes  

Sucralfate (if continuous nasogastric suction, stop suction for two hours after giving sucralfate)

No  

Continue periodic assessments

Does patient have enteral access (via nasoenteral tube or ostomy) and adequate GI function (i.e., absorption of feedings)?

Yes  

Enteral H₂-blocker  

No  

I.V. H₂-blocker

References


Phylylactic agents have demonstrated efficacy in preventing clinically important bleeding in randomized, controlled trials (and meta-analyses), the frequency of stress-induced bleeding has varied substantially from study to study since approximately 1978. This has led some experts to suggest that prophylactic agents are very effective if used appropriately; other experts conclude that the frequency of clinically important stress-induced bleeding has been decreasing as a result of advances in technology and patient care, not medication prophylaxis. The collection of institution-specific data should help clinicians to resolve this issue, at least for their particular patient populations.

When institution-specific rates of stress-induced bleeding are not available, the recommendations contained in these guidelines can serve as a model for adaptation by the institution. Although the recommendations were made on the basis of data published up to the final guideline review process, changes may be needed as information evolves. The reader is encouraged to consider such changes as they occur rather than wait for revised guidelines.
**Recommendations**

**Indications for prophylaxis**

For adults: Risk factors for ICU patients have been delineated in trials comparing prophylaxis with no prophylaxis by using clinically important bleeding as an endpoint. Prophylaxis is recommended in patients with coagulopathy or patients requiring mechanical ventilation for more than 48 hours. (Strength of evidence = D) Prophylaxis is also recommended in patients with a history of GI ulceration or bleeding within one year before admission and in patients with at least two of the following risk factors: sepsis, ICU stay of more than one week, occult bleeding lasting six days or more, and use of high-dose corticosteroids (>250 mg per day of hydrocortisone or the equivalent). (Strength of evidence = D) (Table 3) Recommendations for specific prophylactic medications can be found in the Medications used for prophylaxis section.

For pediatrics: Although various risk factors have been associated with bleeding in pediatric patients, published randomized, controlled trials (RCTs) have either not used clinically important bleeding as an outcome or had insufficient power to enable a definitive conclusion that prophylaxis provides protection. Risk factors that have been associated with clinically important bleeding include respiratory failure, coagulopathy, and Pediatric Risk of Mortality Score of ≥10. (Strength of evidence = C)

**Indications in special populations**

For adults: Prophylaxis is recommended for ICU patients with a Glasgow Coma Score of ≤10 (or the inability to obey simple commands) or thermal injuries to ≥35% of their body surface area (BSA). (Strength of evidence = B) ICU patients with partial hepatic transplantation also benefit from prophylaxis. (Strength of evidence = C) Prophylaxis may also be indicated in ICU patients with multiple trauma (e.g., Injury Severity Score of ≥16), transplantation patients in the ICU perioperatively, ICU patients with hepatic failure, and ICU patients with spinal cord injuries. (Strength of evidence = D) (Table 3)

For pediatric patients (one month of age or older) with thermal injuries, prophylaxis is recommended, but there is insufficient evidence to recommend prophylaxis based on any given percentage of BSA. (Strength of evidence = D) For other pediatric surgery or trauma patients, insufficient evidence is available to allow recommendations about prophylaxis to be made.

**Agent of choice**

For adults: Given the conflicting results of several meta-analyses and a recent RCT (both with strengths of evidence = A), the choice among antacids, H₂-receptor antagonists, and sucralfate for use as prophylactic agents to prevent clinically important bleeding associated with stress in adult patients admitted to general medical and surgical ICUs should be made on an institution-specific basis. This choice should take into account concerns regarding administration (e.g., functioning GI tract), adverse-effect profile, and total costs. (Strength of evidence = D) Insufficient data on misoprostol or the proton-pump inhibitors are available to allow any recommendation about these agents to be made.

For pediatric patients and special populations: The lack of comparative trials of these agents in pediatric and special populations (e.g., patients with burns, trauma patients, patients undergoing neurosurgical procedures or with neurologic disorders, and transplantation patients) precludes definitive recommendations as to the agent of choice in these situations. The choice of agent should be made on an institution-specific basis and should take into account concerns about administration (e.g., functioning GI tract), adverse-effect profile, and total costs.

**Adverse effects**

For adults and pediatrics: It is recommended that patients with a history of serious reactions to antacids, H₂-receptor antagonists, proton-pump inhibitors, or sucralfate avoid future use of the offending agent. There are no other absolute contraindications that would preclude the short-term use of any of these medications for stress ulcer prophylaxis. However, unless the benefits clearly exceed the risks, it is recommended that sucralfate and antacids be avoided in neonates (particularly premature neonates) because of the possibility of adverse effects (e.g., bowel formation, accumulation of aluminum and magnesium). Also, it is recommended that aluminum-containing products such as sucralfate be avoided in children with renal failure because dosing information has not been well established. Whether acid-suppressing agents are associated with a higher rate of pneumonia than sucralfate is unresolved, although any difference between these medications would appear to be small. It is recommended that potential adverse effects be considered as part of the economic analysis when an agent is chosen (see Economic analysis). (Strength of evidence = D)

**Monitoring**

For adults and pediatrics: It is recommended that all patients receiving medications for stress ulcer prophylaxis be monitored for bleeding and adverse drug effects (see Adverse effects of prophylactic agents). Paper techniques for measuring gastric pH have questionable validity and reliability, and there is no evidence that adjusting the dosage of pH-altering medications (antacids, H₂-receptor antagonists, proton-pump inhibitors) on the basis of these measurements influences patient morbidity or mortality. Despite the lack of supporting data, pH monitoring for antacids may be appropriate (goal pH of 3.5–4). Such monitoring may also be useful for H₂-receptor antagonists when standard dosage regimens might not be appropriate (e.g., in cases of renal dysfunction, for increased dosages due to perceived failure of therapy, in pediatric patients). (Strength of evidence = D)

**Other options**

For adults and pediatrics: It is premature to recommend the use of novel therapies (e.g., free-radical scavengers) in place of conventional agents for stress ulcer prophylaxis, although the limited number of studies have had promising results. (Strength of evidence = D)

**Prevention of recurrent bleeding**

For adults and pediatrics: The lack of available trials prohibits definitive recommendations for preventing recurrent bleeding after an episode of stress-induced GI bleeding, although consideration could be given to increasing the dosage of the prophylactic agent, adding another medication, or switching to a different agent. (Strength of evidence = D)

**Non-ICU patients**

For adults: Stress ulcer prophylaxis is not recommended for adult patients in non-ICU settings. (Strength of evidence = B for general medical and surgical patients with fewer than two risk factors for clinically important bleeding; strength of evidence = D for patients with two or more risk factors) (Table 3)

For pediatrics: Stress ulcer prophylaxis is not recommended for pediatric general medical and surgical patients or special populations (e.g., transplantation) in non-ICU settings if fewer than two risk factors for bleeding are present. (Strength of evidence = D) Data are insufficient to allow recommendations to be made about the use of prophylaxis in pediatric patients with two or more risk factors. If prophylaxis is given, it should be discontinued once risk factors have resolved. (Strength of evidence = D)

**Institution-specific guidelines**

For adults: Given some of the unresolved issues regarding stress ulcer prophylaxis, it is recommended that institution-specific guidelines be developed on the basis of economic models such as the one included in this document. For institutions willing to accept the assumption that H₂-receptor antagonists and sucralfate have equal efficacy, the accompanying economic analysis found sucralfate to be the most cost-effective agent. Exceptions to the use of sucralfate include lack of oral or other gastric access for administration and, potentially, documented failure of prophylaxis with sucralfate. If ranitidine is assumed to be more effective than sucralfate, the accompanying economic analysis found ranitidine to be the most cost-effective agent. Whether acid-suppressing agents are associated with a higher rate of pneumonia than sucralfate is unresolved, although any difference between these medications would appear to be small. It is recommended that potential adverse effects be considered as part of the economic analysis when an agent is chosen (see Economic analysis). (Strength of evidence = D)

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