ANNALS OF SURGERY
Vol. 220, No. 3, 353–363


# Optimal Therapy for Stress Gastritis

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## Objective

The authors compared the results of sucralfate *versus* $H_2$ blocker ± antacid as prophylaxis for stress ulceration in an intensive care unit patient population.

## Summary Background Data

Stress ulceration carries high morbidity and mortality for the patient who is critically ill. Gastric acid neutralization is an effective prophylaxis. The impact of increased gastric colonization with bacterial pathogens on nosocomial pneumonia after acid neutralization is unclear. The efficacy of sucralfate prophylaxis for stress ulceration and its the effect on the nosocomial pneumonia rate is controversial. The financial implications of sucralfate prophylaxis *versus* $H_2$ blocker-based acid neutralization therapy has not been studied.

## Methods

Ninety-eight injured patients who were critically ill and who required intubation and intensive care unit (ICU) support for at least 72 hours without gastric feeding were randomized and received either maximal $H_2$ blocker infusion therapy (continuous infusion of ranitidine at 0.25 mg/kg/hr after a loading dose of 0.5 mg/kg) plus antacids (for persistent pH < 4) or sucralfate (1 g every 6 hours via nasogastric tube) for stress ulcer prophylaxis. Efficacy in preventing stress ulcer complications was determined. The impact of each therapeutic approach on development of nosocomial pneumonia was evaluated. The charges/cost for each approach was analyzed.

## Results

Heme-positive gastric aspirates occurred in 99% of the patients, whereas 12 (7 in the $H_2$ blocker group and 5 in the sucralfate group) were grossly positive for blood. However, only one from each group required transfusion, and one in the $H_2$ blocker group required operation. Gastric colonization preceded tracheobronchial colonization in five patients in the $H_2$ blocker group and one patient in the sucralfate group; simultaneous gastric/oropharyngeal colonization preceded positive tracheobronchial growth in six patients who received $H_2$ blocker and one patient who received sucralfate. The overall pneumonia rate was 27.5% in the $H_2$ blocker group and 20.8% in the sucralfate group ($p = 0.48$). Days on ventilator were 13.5 *versus* 9.1, ($p = 0.06$), ICU lengths of stay were 14.7 *versus* 10.2 ($p = 0.06$), and hospital lengths of stay were 27.8 *versus* 20.0 ($p = 0.029$) for the $H_2$ blocker group and sucralfate group, respectively. Based on current charges and protocols for optimal $H_2$ blocker and sucralfate prophylaxis, use of sucralfate rather than $H_2$ blockers would decrease the annual cost by more than $30,000 per bed.

## Conclusions

Sucralfate is as efficacious as maximal $H_2$ blocker therapy for stress ulceration prophylaxis, and may have a beneficial effect on the incidence of nosocomial pneumonia. Sucralfate has a major reduction on nursing requirements for stress ulcer prophylaxis and would save approximately $30,000 per ICU bed per year in patient charges.

Aggressive stress gastritis prophylaxis has become the standard of care in the intensive care unit (ICU) setting to prevent the high morbidity and mortality associated with acute gastric hemorrhage, or rarely, perforation in the patient who is critically ill.[1] Routine endoscopy for the patient who is critically ill has documented the nearly ubiquitous occurrence of gastric ulceration that occurs rapidly after admission to the ICU.[1-2] In addition, multiple studies have documented the efficacy of acid neutralization or inhibition of acid release in the prevention of stress ulceration and its associated high morbidity.[3-9] The use of antacids per nasogastric (NG) tube and titrated to maintain a pH greater than 4 has a well-proven track record for prophylaxis.[4-9] However, because of the excessive production of acid in patients who are critically ill, the volume and frequency of antacid dosing commonly is very high. Concerns over aspiration of the large volumes of antacids and the intense nursing requirements to monitor the pH and titrate antacid doses have stimulated interest in alternative methods. Currently, the most popular therapeutic approach is the use of $H_2$ blockers to decrease the production of gastric acid.[10-14] However, because of the excessive acid produced in severe stress states based on clinical trials, $H_2$ blockers at high doses and as a constant infusion are recommended to maintain adequate plasma levels.[11-13,15-18] In fact, many of these patients still require frequent testing of gastric aspirate pH and supplemental antacids to maintain the pH above 4, as recommended for optimal benefit.[5,8,9,11,12]

Another major morbidity in the patient who is critically ill is the development of nosocomial infections, particularly pneumonia.[19] The observation that the pathogens involved in nosocomial pneumonia frequently can be found in gastric aspirates and temporally appear to colonize the stomach before the development of clinical pneumonia have led to several studies supporting the role of gastric colonization in nosocomial infections.[20-22] Studies also have demonstrated an increased rate of gastric colonization when the natural microbicidal activity of gastric acid is prevented by antacids and $H_2$ blockers.[23-24] Although the true impact of bacterial overgrowth in the stomach on nosocomial pneumonia remains controversial, the increased gastric colonization seen when stomach contents are neutralized and the potential for aspiration and tracheobronchial colonization remain significant concerns.

Sucralfate is a recent addition to the ICU armamentarium for care of the patient who is critically ill.[25,26] Sucralfate is a sulfated sucrose moiety that has been proven efficacious in the treatment of multiple gastric acid-induced conditions, including prophylaxis for stress ulceration.[27-31] In addition to directly coating areas of gastric mucosal loss to prevent further injury and permit healing, sucralfate appears to directly promote healing by stimulating the release of cytoprotective agents, in particular prostaglandin $E_2$ ($PGE_2$). Sucralfate also appears to directly inhibit growth of bacterial pathogens that colonize the stomach in the ICU setting. However, although several studies have supported sucralfate as being efficacious, there remains concern that patients who are extremely ill, such as those critically injured, have not been tested extensively, and the need for a nasogastric (NG) tube may increase aspiration complications.[1] In addition, evaluation of the potential beneficial effects of sucralfate in maintaining an acid environment and inhibiting the overgrowth of the stomach with pathogens has led to contradictory results in clinical trials that focus on nosocomial pneumonia rates. Finally, the overall cost impact of prophylaxis with sucralfate in comparison to $H_2$ blockers ± antacids has not been investigated closely.

## METHODS

This study was conducted in a prospective, randomized, open trial at Harborview Medical Center, Seattle, Washington. All intubated patients admitted to the trauma ICU from April 1, 1991 to October 9, 1993 were considered for inclusion in the study. Inclusion criteria were as follows: 1) endotracheal intubation on admission with anticipation of at least 72 hours of ICU care before extubation, 2) presence of an NG tube at the time of admission, and 3) age minimum of 18 years. Patients were enrolled on admission and assigned randomly to receive either sucralfate (1 g as a slurry every 6 hours via NG tube) or hydrochloride (Ranitidine, Glaxo Pharmaceuticals, Research Triangle Park, NC) (continuous infusion at 0.25 mg/kg/hr, after a loading dose of 0.5 mg/kg) combined with antacids (30–60 mL PRN via NG tube for persistent pH < 4). All patients had gastric pH, and Gastroccult (Smith, Kline Diagnostics, Inc., San Jose, CA) checked and recorded at least every 4 to 8 hours while enrolled in the study. Several patients had continuous pH monitoring via NG probe (Sandhill Scientifics, Littleton CO) to compare fluctuations in pH between the two treatment groups.

Cultures of the sputum, gastric fluid (15 mL of NG aspirate) and oropharynx (by oropharyngeal swab) were obtained at the time of study enrollment and again at 72 hours. Subsequent cultures were obtained on Monday, Wednesday, and Friday for 2 weeks or until the patient was extubated or fed via the stomach. Aerobic cultures of the throat swabs and gastric aspirates were performed

Supported in part by grant CDC#R49/CCR002570.
Presented at the 114th Annual Scientific Session of The American Surgical Association; April 7–9, 1994; San Antonio, Texas.
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Accepted for publication April 11, 1994.

by Smith, Kline, Beecham Clinical Laboratories of Seattle, Washington. Swabs of the throat were plated on MacConkey agar and Blood agar. The plates were read daily, and all organisms were identified. Growth was quantitated as scant, light, moderate, or heavy. Gastric aspirates were set up on blood agar and a bi-plate of CNA-MacConkey at a 1:100 dilution. The plates were read daily. All organisms were identified and quantitative results reported as number of colonies per milliliter.

The following clinical variables were recorded daily for each patient during the study period: maximum temperature, white blood cell count, platelet count, results of chest radiographs, and sputum gram stains or cultures. The requirement for and volume of blood transfusions and number and type of operations performed were tracked. The patients were observed for follow-up throughout the study specifically for the development of pneumonia and for gastric bleeding requiring blood transfusion or surgical intervention. The diagnosis of pneumonia was made using criteria previously established by the Centers for Disease Control and included the following: 1) positive sputum gram stain and culture for specific pathogen(s), 2) chest radiograph demonstrating a new focal infiltrate, 3) temperature > 38.5 C or <36.5 C, and 4) a white blood cell count > 15,000. Gastric bleeding was determined on NG aspirates and classified as 1) occult—detected by guaiac only; 2) overt—for gross blood described as "coffee grounds," red/brown fluid, or bright red blood (BRB); and 3) clinically significant—requiring either transfusion of blood or operative intervention.

Informed consent was obtained from each patient or patient representative within 24 hours of study enrollment. The study was approved by the University of Washington Human Subjects Review Board. The data were analyzed using chi square and the unpaired Students t test, where appropriate. Continuous data were analyzed by analysis of variance. A p value of $<0.05$ was considered statistically significant.

## RESULTS

During the study period, 365 intubated patients were admitted to the trauma ICU and screened for entry. Of these, 267 were excluded; the most common causes for exclusion were early extubation in 139, protocol violation in 83, most common of which was incomplete entry data collection, including pretreatment cultures. Other reasons patients were withdrawn from the study were as follows: initiation of gastric feeding, thrombocytopenia in the ranitidine group, death, and inability to obtain consent. Patients were considered evaluable after they had two sets of cultures done within a 72-hour period.

Ninety-eight patients met all criteria for inclusion and were evaluated. Of these, 51 were randomized to ranitidine and 47 to sucralfate prophylaxis. The patient profiles demonstrated the two groups to be closely matched for gender distribution, age, admission APACHE II scores, Injury Severity Score, Revised Trauma Score, and history of smoking, (Table 1). Overall, the patterns of injury were similar in both groups. The study patients were enrolled an average of 4.3 days and an average of 2.3 (range 2–6) samples for culture were obtained during the study. Seventy-two of the 98 patients (73.5%) had two samples, 20 (20.4%) had three samples, 4 (4.1%) had four samples, and 23 (2%) had six samples for culture.

**Table 1. PATIENT PROFILE**

| | Total (n = 98) | Ranitidine (n = 51) | Sucralfate (n = 47) | p Value* |
|---|---|---|---|---|
| Gender | | | | |
| Male | 76/98 (77.5%) | 37/51 (73%) | 39/47 (83%) | 0.21 |
| Female | 22/98 (22.5%) | 14/51 (27%) | 8/47 (17%) | |
| Age | 34.2 ± 14.8 | 34.2 ± 13.3 | 34.2 ± 16.4 | 0.91 |
| APACHE II | | | | |
| Admit | 25.2 ± 7.1 | 25.5 ± 7.3 | 24.8 ± 7.0 | 0.55 |
| ISS | 28.5 ± 9.5 | 28.1 ± 9.1 | 29.0 ± 9.8 | 0.69 |
| RTS (n = 69) | 4.8 ± 2.1 | 4.8 ± 2.1 | 4.8 ± 2.1 | 0.78 |
| Smoking Hx (n = 63) | 29/63 (46%) | 16/33 (48%) | 13/30 (43%) | 0.68 |

* p value for ranitidine vs. sucralfate.

## Gastric Bleeding and pH

Both regimens of stress ulcer prophylaxis were equally effective in preventing overt bleeding. Of the 98 patients enrolled in the study, 97 (99%) had at least one heme positive (occult blood) gastric aspirate during the study period, whereas only 12 (12.2%) had some degree of grossly positive nasogastric tube drainage. Of patients randomized to the ranitidine group, seven (13.7%) had grossly positive drainage, whereas five (10.6%) of the sucralfate group had evidence of gross bleeding, (Table 2).

**Table 2. STRESS GASTRITIS/ULCERATION BLEEDING (n = 98)**

| | Total (%) | Ranitidine (%) (n = 51) | Sucralfate (%) (n = 47) |
|---|---|---|---|
| Occult | 97 (99) | 51 (100) | 46 (98) |
| Gross Blood | 12 (12.2) | 7 (13.7) | 5 (10.6) |
| "Coffee Grounds" | 4 (4.1) | 1 (2.0) | 3 (6.4) |
| Red/Brown | 3 (3.1) | 2 (3.9) | 1 (2.1) |
| BRB | 5 (5.1) | 4 (7.8) | 1 (2.1) |
| Transfusion | 2 (2.0) | 1 (2.0) | 1 (2.1) |
| Operation | 1 (1.0) | 1 (2.0) | 0 |

p value = NS for all.

Only two patients (2.0%), one from each group, had clinically significant bleeding that required blood transfusion. The patient in the sucralfate group required massive blood transfusion for 3 days for a severe coagulopathy secondary to severe trauma with bleeding from every orifice and needle site. The patient in the ranitidine group was noted to have diffuse gastritis on endoscopy and required a 9-unit blood transfusion and ultimately, operative intervention for vagotomy and pyloroplasty with gastrotomy to oversew a focal bleeding site in the fundus.

Gastric pH was measured every 4 to 8 hours in all patients while a nasogastric tube was in place. The pH was <4 for 20.4% (range 2.6–77.8%) of the determinations in patients randomized to the ranitidine group of the study whereas the pH was <4 in 41.1% (range 2.8–91.7%) in the sucralfate group. The pH was <4 in 39.4% of the determinations in patients with "coffee-grounds" in their gastric drainage, 53.5% in patients with red/brown drainage, and only 25.5% in patients with grossly bloody drainage. Patients with continuous pH monitoring via NG probe confirmed the marked, unpredictable fluctuations in pH in both treatment groups, (Fig. 1). Patients treated with ranitidine infusion frequently had prolonged periods with intragastric pH < 4. Patients treated with sucralfate frequently had long episodes of intragastric pH > 5.

## Bacterial Colonization/Pneumonia

In the 98 patients, a total of 232 samples were obtained for microbiologic analyses. Of these 232 samples, colonization of the tracheobronchial tree by pathogenic bacteria from either the oropharynx or stomach occurred in 29 instances in 26 patients, (Table 3). Of these 29 episodes, temporally defined transmission of pathogens occurred most frequently from the oropharynx to the lung in 16, with 7 (43.7%) occurring in the ranitidine group and 9 occurring (56.3%) in the sucralfate group. Of the remaining 13 episodes, 7 demonstrated sequential contamination of simultaneously positive gastric and oropharynx cultures to sputum and 6 had a gastric-to-sputum mode of spread. Of the seven gastric/oropharynx-to-sputum cases, six occurred in the ranitidine group and one occurred in the sucralfate group. The six episodes of gastric-to-sputum dissemination consisted of five in the ranitidine group and one in the sucralfate group. Thus, the overall incidence of pathogen spread to colonize the tracheobronchial tree was similar between the two groups, with 11 in the sucralfate and 18 in the ranitidine group. However, the sucralfate group had only 2 episodes of apparent spread from a gastric or gastric/oropharyngeal source to the lung compared with 11 in the ranitidine group (Table 3).

A diagnosis of clinical pneumonia was made in 24 of the 98 patients (24.5%). Ten of the patients who developed pneumonia were in the sucralfate group (41.7% of patients with pneumonia or 20.8% of patients at risk), and 14 were in the ranitidine group (58.3% of patients with pneumonia and 27.5% of patients at risk; p = 0.48). Of the 24 patients who developed pneumonia, only 9 (37.5%) had transmission of bacteria from oropharynx or gastric sites to the tracheobronchial tree and thus, of

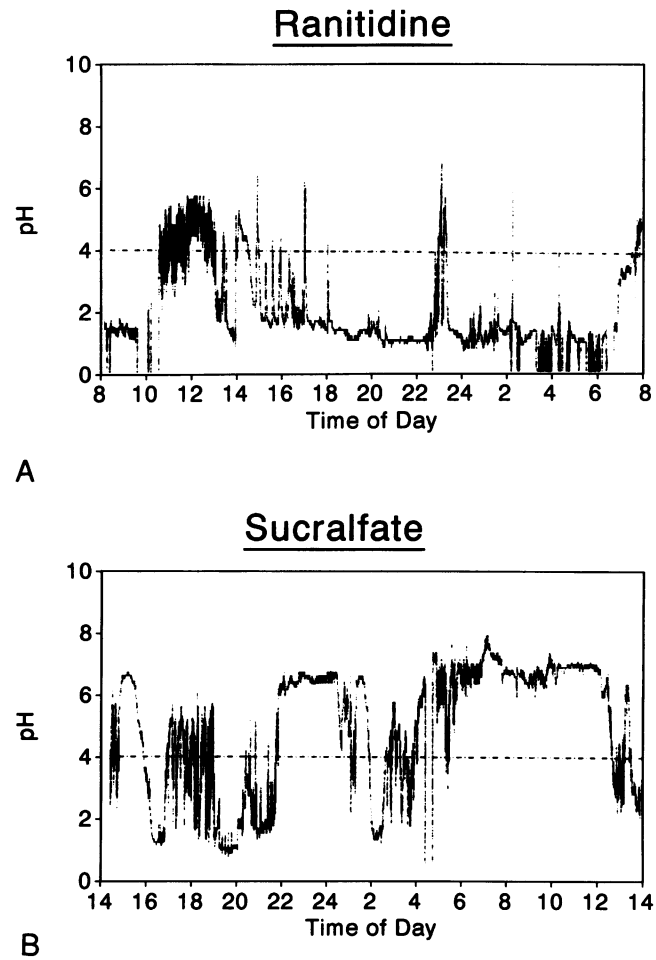


**Figure 1.** Continuous tracing of intragastric pH from two patients demonstrating typical marked fluctuations in pH, ranitidine infusion therapy (A), and sucralfate therapy (B).

**Table 3. TRACHEOBRONCHIAL COLONIZATION**

| Source | Total | Ranitidine | Sucralfate |
|---|---|---|---|
| Oropharynx | 16 (55.2%) | 7 (43.8%) | 9 (56.3%) |
| Gastric | 6 (16.7%) | 5 (83.3%) | 1 (16.7%) |
| Gastric/Oropharynx | 7 (19.4%) | 6 (85.7%) | 1 (14.3%) |
| Total | 29 | 18 (62.1%) | 11 (37.9%) |

**Table 4. TRACHEOBRONCHIAL COLONIZATION AND NOSOCOMIAL PNEUMONIA**

| Source | Total | Ranitidine | Sucralfate |
|---|---|---|---|
| Oropharynx | 16/6 (38%) | 7/2 (29%) | 9/4 (44%) |
| Gastric +/− Oropharyngeal | 13/3 (23%) | 11/3 (27%) | 2/0 |
| Total | 29/9 (31%) | 18/5 (28%) | 11/4 (36%) |

Colonization/pneumonia percent given for each condition and from the various recognized sources.

the 29 episodes of documented transmission of pathogens from oropharynx or stomach to the lung, only 31.0% led to a clinically definable pneumonia. Of the 24 patients with nosocomial pneumonia, only 3 arose from an apparent gastric or simultaneous gastric/oropharyngeal source, and all occurred in the ranitidine group (Table 4).Seventy of the 98 patients were taking antibiotics when entered into the study. The distribution between treatment groups was equal, with 38 in the ranitidine and 32 in the sucralfate groups, respectively. During the period of data collection (ICU length of stay or 2 weeks, whichever occurred first), 82 of the patients (83.7%) received antibiotics—they either began antibiotics for the first time or changed from their original antibiotics to others.

Overall and group outcome data are shown for days on ventilator, ICU length of stay, total hospital length of stay, and mortality (Table 5). Although the sucralfate group had a trend toward improvement in outcome for days on ventilator (0.06) and ICU length of stay (0.06) in comparison with the ranitidine group, only overall hospital length of stay (0.03) reached statistical significance for the sucralfate group.

## Charges

Stress ulcer prophylaxis was implemented in all patients admitted to the ICU. The charges for stress ulceration prophylaxis in the ICU using ranitidine includes the cost of the drug, pharmacy charges for mixing the infusion bags, cost for disposables, rental fees for constant infusion pumps, and cost-shared nursing time to initiate and maintain the infusion. The average daily dose of ranitidine was 517 mg per patient. The cost of the drug per day ($23.02) plus pharmacy charges ($25.00, which includes infusion bag cost, pharmacy preparation time, and estimated nursing time) adds up to $48.02 per day. The daily infusion pump charge ($31.25) and the cost of the infusion set and tubing ($18.00) are added to this charge. Thus, the total charges per day are $97.27 per patient, or $35,503.55 per bed per year. The charges for sucralfate include 4 doses at $0.48 per g plus $1.25 per dose for pharmacy charges. The total daily charge is $6.92 per patient or $2,525.80 per bed per year. The difference in charges between the two modes of therapy is $90.35 per patient per day or $32,977.75 per bed per year.

The ability to generate accurate cost data is difficult because of cost center shifting and lack of line itemization, particularly for manpower efforts. However, if one excludes work effort and prorates, a possible estimate can be generated. At our institution, costs for ranitidine therapy include drug (517 mg/d = $23.02), infusion pump daily cost ($2.98) and infusion set ($6.00) for a total of $42.00/day/patient. The cost for sucralfate at 1g 96h is $1.92/day/patient. The annual savings per bed for cost of drug and supplies/equipment alone would be $14,629.20.

**Table 5. OUTCOME**

| | Ranitidine (n = 51) | Sucralfate (n = 47) | Total (n = 98) | p Value* |
|---|---|---|---|---|
| Days on ventilator | 13.5 ± 12.7 | 9.1 ± 9.9 | 11.4 ± 11.6 | 0.06 |
| ICU LOS | 14.7 ± 12.5 | 10.2 ± 9.6 | 12.6 ± 11.4 | 0.059 |
| Hospital LOS | 27.8 ± 20.0 | 20.0 ± 13.7 | 24.1 ± 17.6 | 0.029 |
| Mortality | 11/51 (22%) | 6/47 (13%) | 17/98 (17.3%) | 0.22 |

* p value for ranitidine vs. sucralfate.

## DISCUSSION

In the current study, several potential benefits of using sucralfate as stress ulcer prophylaxis were compared with attempts at aggressive neutralization of gastric acidity using $H_2$ blockers ± antacids. The patient population chosen was a group of patients who were severely injured who required intubation and intensive ICU support. This population was chosen in an attempt to compare stress ulcer prophylaxis regimens in a fairly uniform and extremely high-risk patient group.[1,19] The patient profiles demonstrate that this was achieved. Overall associated risks and patterns of injury, such as chest trauma and pulmonary contusion, also were matched equally.

To fairly compare the two therapeutic approaches, optimal treatment guidelines were employed. Ranitidine was chosen as the $H_2$ blocker of choice based on several clinical trials documenting its comparability, if not superiority, to cimetidine.[32,33] Ranitidine has been shown to be superior to placebo similar to antacids and cimetidine for stress ulcer prophylaxis.[33,34] Similar to cimetidine, fixed bolus injections generally have been inconsistent in their ability to maintain intragastric pH above 4.0.[34,35] However, when given as a constant infusion, ranitidine

has been shown to maintain pH levels above 4.0. In comparison with cimetidine, ranitidine is more potent, has a longer half life, has less troughing after boluses, and has demonstrated similar but less significant side effects and drug interactions. Studies have documented the frequent breakthrough in acid production that occurs when $H_2$ blockers are given as an intermittent bolus. Therefore, ranitidine was given as a constant infusion after an initial bolus to reach and maintain a maximal recommended dose. However, our data confirm that even at this very high dose of ranitidine, there was frequent breakthrough, with a pH of less than 4 in more than 20% of the measurements (Fig. 1).

These frequent episodes of acid breakthrough have two major implications. One is that $H_2$ blocker infusion therapy does not truly eliminate the normal acid environment. Unless constant pH monitoring is employed with supplemental antacids, the pH will not be kept above 4.0 for optimal therapy (Fig. 1). Also, the ability of the stomach acid to control or limit overgrowth of pathogenic bacteria will not be inhibited. Studies based on the assumption of infusion $H_2$ blocker therapy causing a neutral intragastric condition without on-line monitoring will lead to potentially invalid conclusions regarding pathogen overgrowth and impact on nosocomial pneumonia. Second, the need for constant nursing intervention for both gastric aspirate pH testing and supplementation with antacids is not avoided by using the recommended optimal high-dose constant infusion of $H_2$ blockers. Thus, any purported savings of infusion therapy in manpower requirements are not achieved if optimal neutralization of intragastric pH to above 4 is the therapeutic goal.

The efficacy in prevention of stress ulceration complications was equal for the two regimens. Similar to other studies, the finding of at least one heme-positive NG aspirate during the study period confirms the high incidence of mucosal damage in the patient who is critically ill and the need for stress ulceration prophylaxis.[1-9] Although some argue that, because of enhanced overall care and resuscitation of the ICU patient with preservation of gastric mucosal blood flow, a specific gastric prophylaxis is not necessary,[36] it is unlikely that waiting for patients to develop grossly positive aspirates for directed therapy will optimize outcome in these patients who are critically ill.[37] In previous studies confirming the efficacy of $H_2$ blockers, placebo control groups frequently demonstrated a 15% to 20% clinically significant gastric hemorrhage,[4,5,13] which is consistent with our incidence of grossly positive aspirate in 12.2% of the overall population. However, our significant bleed rate of one (2%) in each group is consistent with several other studies demonstrating a similar efficacy for $H_2$ blockers and traditional antacid trials.[1-14] Thus, even in this critically ill population of severely injured patients, sucralfate is demonstrated to provide stress ulceration prophylaxis comparable with optimal therapy with $H_2$ blockers ± antacids or with older antacid therapy results.

The impact of each form of therapy on nosocomial pneumonia is difficult to assess. This is because of several complicating, interactive processes that help to explain the conflicting data reported from previous trials. It is well accepted that gastric acidity functions as a natural antibacterial host defense that normally keeps levels of pathogenic organisms in the stomach at extremely low concentrations. Conversely, neutralization of gastric contents frequently leads to overgrowth with pathogenic bacteria that is directly proportional to the intragastric pH.[23,24] However, the contribution of this bacterial overgrowth during iatrogenic gastric neutralization in the ICU to the incidence of nosocomial pneumonia is strongly debated. Several studies have noted a possible association between elevated intragastric pH and subsequent development of nosocomial pneumonia.[21-24] Because sucralfate maintains the low intragastric pH, it has been advocated to decrease the incidence of nosocomial pneumonia. However, others have been unable to confirm a lower nosocomial pneumonia rate in randomized trials using sucralfate, $H_2$ blockers, or antacids.[27,28,31] In addition, further analysis of the studies showing a decrease in nosocomial pneumonia with sucralfate appears to implicate use of antacids (and presumed increased aspiration) rather than $H_2$ blockers and increased intragastric pH as the etiology. In our series, only 7 of the 51 patients (13.7%) received antacids, and 2 (28.6%) developed pneumonia. This rate is very similar to the overall pneumonia rate of 27.5% in the ranitidine group and the 27.3% in the ranitidine group who did not receive antacids. Thus, although the numbers are small, the addition of antacids did not appear to influence the occurrence of nosocomial pneumonia.

Our data provide several other insights into the debate of etiology of nosocomial pneumonia. In several studies, it has been assumed that optimal $H_2$ blocker therapy will neutralize the stomach and thus, permit bacterial overgrowth. However, unless pH is monitored closely and supplemented with antacids, neutralization may not be achieved. Although our NG aspirates were more likely to have a pH $< 4$ in the sucralfate group (40% of all tests), there was a significant percentage (20% overall) of aspirates with a low pH in the $H_2$ blocker group. Thus, determining whether gastric neutralization contributes to nosocomial infection is not being tested in several of these studies. Similarly, other studies have monitored gastric cultures and presumed that colonization of the stomach preceded and contributed to the nosocomial pneumonia if similar pathogens are isolated. As we demonstrate with close, serial monitoring of gastric, sputum and oropharyngeal cultures, the per cent of episodes in which gastric colonization precedes tracheobronchial

colonization is very small. More frequently, it appears that the stomach and lung are both colonized from an oropharyngeal source.[38] Any impact of gastric acid manipulation on nosocomial pneumonia could only be expected to influence the small number caused by the gastric-to-lung route. In our series, this represented only 12.5% of the cases of nosocomial pneumonia. Thus, use of the overall pneumonia rate as the only outcome measure of various therapies is unlikely to demonstrate a difference. Ideally, one would monitor the effect of gastric neutralization *versus* non-neutralization on the incidence of pneumonia directly linked to a gastric etiology.

Our data, using serial source-specific cultures, support the theory that use of $H_2$ blockers and antacids do, in fact, increase the number of nosocomial infections in this patient population. However, the number of patients that would be required to prove a statistical benefit makes the definitive study impossible. In addition in our data, through this decrease in pneumonia, sucralfate-treated patients have a beneficial trend for days on the ventilator ($p = 0.06$), in the ICU ($p = 0.06$), and of total hospital stay ($p = 0.03$, Table 5). Finally, because our data demonstrate that the source of the majority of colonization linked nosocomial pneumonias arise from the oropharynx, specific control of bacterial overgrowth in the oropharynx may be beneficial as proposed by others.[39,40] As documented by Johanson,[38] the rapid colonization of the oropharynx and tracheobronchial tree is of major importance to the outcome in the critically ill. Hopefully, future studies focusing on selected potential sources for seeding of the lung will impact on the major morbidity of nosocomial pneumonia in the ICU.

The charges for stress ulcer prophylaxis include the cost of the drug used; pharmacy charges, which include pharmacy preparation time; cost of disposables, such as intravenous bags; and an estimate of nursing time as cost-center sharing. In addition, any equipment required to deliver the agent and additional disposals also are included in daily charges. In the current study, the difference in charges for the two approaches to therapy is $90.35 per day or $32,977.75 per bed per year; constant infusion ranitidine therapy is more than 13 times more expensive when compared with sucralfate. As the number of and need for ICU beds increases in our institutions, this differential becomes increasingly significant. In our institution, the trauma ICU alone has an average length of stay of 4 days, with an average census (in this 8-bed unit) of 6.5 patients. Thus, with a shift to sucralfate as the routine for stress ulcer prophylaxis, this one unit will reduce charges by approximately $200,000 per year. Similarly, although determination of costs is extremely inaccurate at the present time, estimation of costs to the institution for these two forms of therapy indicate that the cost of ranitidine therapy is approximately $42.00 per day, whereas for sucralfate, the cost is $1.92. These estimates do not include the costs for manpower in pharmacy or nursing to provide this care. Thus, although a significant underestimate, savings to the institution under a capitation form of reimbursement would exceed $40.00 per patient per day or $14,600.00 per bed per year. Again, in this one small unit, using our average occupancy, the institution will save in excess of $100,000/yr on this one drug alone. As we enter a new era of medical care delivery, the need to cost-analyze therapeutic options of equal efficacy will become increasingly pertinent to protect the highest quality of care for our patients.

## Acknowledgments

The authors thank Wilma Hoffman, R.N., for her tireless efforts in maintaining the clinical trial and collecting much of the data, and Susie O'Brien for her expertise in preparing this manuscript.

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## Discussion

DR. ANTHONY A. MEYER (Chapel Hill, North Carolina): I'd like to congratulate the authors and Dr. Maier in particular for his presentation.

Stress gastritis is a problem that we have often thought as being solved and it's been relegated to the back burner. It does remain a potentially formidable problem and its treatment can be improved upon with respect to efficacy, complications, and cost, and this study raises these issues very well. I have two general questions.

First of all, with respect to your pH data, what percentage of patients on ranitidine tended to stay below or above the four level and what percentage of time did your sucralfate patients stay below the four level?

Secondly, the differences in days on the ventilator, hospital length of stay and ICU stay are not generally appreciated as to be affected by intragastric treatment to reduce acid production. Do you think that these are related to underlying problems such as sepsis which are associated with increased gastric acid production or are they related to some other factor?

And, if indeed these things are benefits to be achieved by using this type of treatment, the cost savings per bed per day would be much greater since you seem to have gotten about a 25 to 30% reduction in ICU stay with the attendant costs.

DR. CHARLES L. RICE (Chicago, Illinois): Dr. Maier and his co-authors are to be congratulated for bringing this important topic to our attention.

The prophylaxis for stress gastritis is undoubtedly the most frequently employed prophylactic treatment in critical care units in this country. The reason is because of theprimordial dread of most surgeons who cared for critically ill patients, particularly in the 1960s and '70s, who encountered the phenomenon of erosive gastritis.

I think the authors have shown convincingly that both treatments that they tested are equally effective. They make an argument that given equal efficacy, sucralfate is superior because it's cheaper, requires less monitoring, and is less likely to leave the patient with unprotected intervals. An additional advantage that Dr. Maier did not dwell on is that sucralfate is not