

A COMPARISON OF SUCRALFATE AND RANITIDINE FOR THE PREVENTION OF UPPER GASTROINTESTINAL BLEEDING IN PATIENTS REQUIRING MECHANICAL VENTILATION

DEBORAH COOK, M.D., GORDON GUYATT, M.D., JOHN MARSHALL, M.D., DAVID LEASA, M.D., HUGH FULLER, M.B., RICHARD HALL, M.D., SHARON PETERS, M.D., FRANK RUTLEDGE, M.D., LAUREN GRIFFITH, M.Sc., ALLAN McLELLAN, M.D., GORDON WOOD, M.D., AND ANN KIRBY, M.D., FOR THE CANADIAN CRITICAL CARE TRIALS GROUP*

ABSTRACT

Background Critically ill patients who require mechanical ventilation are at increased risk for gastrointestinal bleeding from stress ulcers. There are conflicting data on the effect of histamine H₂-receptor antagonists and the cytoprotective agent sucralfate on rates of gastrointestinal bleeding, ventilator-associated pneumonia, and mortality.

Methods In a multicenter, randomized, blinded, placebo-controlled trial, we compared sucralfate with the H₂-receptor antagonist ranitidine for the prevention of upper gastrointestinal bleeding in 1200 patients who required mechanical ventilation. Patients received either nasogastric sucralfate suspension (1 g every six hours) and an intravenous placebo or intravenous ranitidine (50 mg every eight hours) and a nasogastric placebo.

Results The patients in the two groups had similar base-line characteristics. Clinically important gastrointestinal bleeding developed in 10 of 596 (1.7 percent) of the patients receiving ranitidine, as compared with 23 of 604 (3.8 percent) of those receiving sucralfate (relative risk, 0.44; 95 percent confidence interval, 0.21 to 0.92; P=0.02). In the ranitidine group, 114 of 596 patients (19.1 percent) had ventilator-associated pneumonia, as compared with 98 of 604 (16.2 percent) in the sucralfate group (relative risk, 1.18; 95 percent confidence interval, 0.92 to 1.51; P=0.19). There was no significant difference between the groups in mortality in the intensive care unit (ICU) (23.5 percent in the ranitidine group and 22.8 percent in the sucralfate group) or the duration of the stay in the ICU (median, nine days in both groups).

Conclusions Among critically ill patients requiring mechanical ventilation, those receiving ranitidine had a significantly lower rate of clinically important gastrointestinal bleeding than those treated with sucralfate. There were no significant differences in the rates of ventilator-associated pneumonia, the duration of the stay in the ICU, or mortality. (N Engl J Med 1998;338:791-7.)

©1998, Massachusetts Medical Society.

PROPHYLAXIS against stress ulcers has traditionally been recommended for the prevention of upper gastrointestinal bleeding in critically ill patients.¹⁻³ Recent natural-history studies have documented a very low incidence of bleeding,⁴ however, suggesting that universal prophylaxis may not be warranted.⁵⁻⁷ Respiratory failure

and coagulopathy are the strongest risk factors for clinically important gastrointestinal bleeding.⁸⁻¹¹

Randomized trials of prophylaxis against stress ulcers, as compared with no prophylaxis, indicate that histamine H₂-receptor antagonists and antacids prevent clinically important gastrointestinal bleeding.¹² Observational studies have suggested, however, that a higher gastric pH is associated with gastric microbial growth,¹³ tracheobronchial colonization,¹⁴ and nosocomial pneumonia.¹⁵ In randomized trials, the cytoprotective agent sucralfate, which does not alter the gastric pH, has been associated with a trend toward a lower incidence of ventilator-associated pneumonia, both as compared with histamine H₂-receptor antagonists and antacids¹⁶ and as compared with H₂-receptor antagonists alone.¹⁷⁻³⁰

The need to evaluate patients at highest risk for both bleeding and pneumonia³¹ and the need to blind care givers and research personnel to the treatment assignments, in order to minimize inflated treatment effects,³² prompted us to evaluate the rates of clinically important gastrointestinal bleeding, ventilator-associated pneumonia, and mortality in a randomized trial of 1200 patients who required mechanical ventilation and who were assigned to receive either ranitidine or sucralfate.

METHODS

Enrollment

From October 1992 to May 1996, we screened consecutive patients admitted to 16 participating intensive care units (ICUs) to identify adults who were projected to require mechanical ventilation for at least 48 hours. Criteria for exclusion were a diagnosis of gastrointestinal bleeding or pneumonia on admission, gastrectomy, a prognosis considered to be hopeless, previous randomization in this or another trial, or receipt of two or more previous doses of open-label prophylactic therapy. The protocol was ap-

From McMaster University, Hamilton, Ont. (D.C., G.G., H.F., L.G., A.M.); the University of Toronto, Toronto (J.M.); the University of Western Ontario, London (D.L., F.R., A.K.); Dalhousie University, Halifax, N.S. (R.H.); Memorial University, St. John's, Newf. (S.P.); and Queen's University, Kingston, Ont. (G.W.) — all in Canada. Address reprint requests to Dr. Cook at the Department of Medicine, St. Joseph's Hospital, 50 Charlton Ave., Hamilton, ON L8N 4A6, Canada.

Other authors were Martin Tweeddale, M.D., University of British Columbia, Vancouver; Joe Pagliarello, M.D., University of Ottawa, Ottawa, Ont.; and Richard Johnston, M.D., University of Alberta, Edmonton.

*Other study investigators are listed in the Appendix.

proved by the institutional review boards of all the participating centers, and the patients or their proxies gave informed consent.

Randomization

Patients were randomly assigned to study groups in blocks of six, with stratification according to center, by means of a computer-generated random-number table prepared at the McMaster University Methods Center and managed by the ICU study pharmacist at each site who administered the coded drugs. All care givers and other research personnel were unaware of the randomization schedule and the block size.

Blinding

The patients, research nurses, and all ICU care givers were unaware of the treatment assignments for the duration of the study. Therefore, clinicians did not monitor gastric pH. The radiologists, outcome adjudicators, all investigators, and the study statistician were also blinded until all events had been adjudicated and the analyses completed.

Drug Preparation, Dispensing, and Administration

The bags of ranitidine (Zantac, Glaxo Wellcome; prepared by Baxter) and ranitidine placebo were identical in appearance. The sucralfate (Sulcrate, Hoechst Marion Roussel) and sucralfate placebo slurries were identical in color, taste, and consistency. From coded ranitidine bags and sucralfate bottles stored in each ICU pharmacy, study pharmacists dispensed either active ranitidine (50 mg every eight hours) and sucralfate placebo or active sucralfate (1 g every six hours) and ranitidine placebo.

Ranitidine was administered in intravenous bolus form, with the dose adjusted for renal failure as follows: standard dose, 50 mg every 8 hours; dose for patients with an estimated creatinine clearance rate of 25 to 50 ml per minute, 50 mg every 12 hours; dose for patients with an estimated creatinine clearance rate below 25 ml per minute, 50 mg every 24 hours; and dose for patients dependent on dialysis, 50 mg every 12 hours. Sucralfate suspension was given through a nasogastric tube or orally. We followed all patients until they died or were discharged from the ICU.

Demographic Characteristics of the Patients

We documented each patient's age, sex, admitting diagnosis, location before admission to the ICU, score on the Acute Physiology and Chronic Health Evaluation (APACHE II) scale (range of scores, 0 to 71, with higher scores indicating more severe illness),³³ and multiple-organ-dysfunction (MOD) score (range, 0 to 24, with higher scores indicating more severe organ dysfunction).³⁴

Gastrointestinal Bleeding

We monitored patients for signs of overt gastrointestinal hemorrhage, including hematemesis, nasogastric aspirate containing blood or coffee-ground material, melena, or hematochezia. The decision to perform endoscopy was left to the discretion of the intensive care specialist. Two physicians from the study's bleeding-adjudication committee examined all relevant clinical and diagnostic documents related to possible bleeding episodes in duplicate and independently, using previously defined criteria.³⁵ We defined clinically important bleeding as overt bleeding plus one of the following four features, in the absence of other causes: a spontaneous drop of 20 mm Hg or more in the systolic or diastolic blood pressure within 24 hours after upper gastrointestinal bleeding; an increase in the pulse rate of 20 beats per minute and a decrease in the systolic blood pressure of 10 mm Hg on the patient's assuming an upright position; a decrease in the hemoglobin concentration of at least 2 g per deciliter in 24 hours and the transfusion of 2 units of packed red cells within 24 hours after bleeding; or failure of the hemoglobin concentration (in grams per deciliter) to increase after transfusion by at least the number

of units transfused minus 2 (i.e., if 4 units of packed cells were transfused, the bleeding would be considered clinically important if the hemoglobin concentration did not rise by at least 2 g per deciliter).

Ventilator-Associated Pneumonia

Attending intensivists at each center used a modified version of the criteria of the Centers for Disease Control and Prevention (CDC)³⁶ to identify patients in whom pneumonia was suspected on clinical grounds. These criteria were a new radiographic infiltrate that had persisted for at least 48 hours (as interpreted by designated study radiologists blinded to the patients' treatment assignments) plus at least two of the following: a temperature above 38.5°C or below 35.0°C, a leukocyte count of more than 10,000 per cubic millimeter or less than 3000 per cubic millimeter, purulent sputum, or isolation of pathogenic bacteria from an endotracheal aspirate.

Patients in whom ventilator-associated pneumonia was suspected on clinical grounds underwent bronchoalveolar lavage or protected brush-catheter sampling by the study bronchoscopist.^{37,38} Two members of the pneumonia-adjudication committee examined all relevant clinical and diagnostic documents related to possible cases of pneumonia in duplicate and independently, classifying patients according to several different methods. One method used was the modified CDC criteria described above³⁶; another was the Clinical Pulmonary Infection Score devised by Pugin et al. (range, 0 to 12, with pneumonia defined by a score of 7 or higher).³⁹ In addition, adjudicators used the criteria of the Memphis Ventilator-Associated Pneumonia Consensus Conference for definite ventilator-associated pneumonia (if there was radiographic evidence of abscess and a positive needle aspirate, or if there was histologic proof of pneumonia at biopsy or autopsy) and probable ventilator-associated pneumonia (if bronchoalveolar lavage or protected brush-catheter sampling yielded positive quantitative or semiquantitative cultures, if there was a positive blood culture of an organism found within 48 hours of isolation in the sputum, if there was a positive pleural-fluid culture of an organism found within 48 hours of isolation in the sputum, or if histologic examination showed formation of an abscess or consolidation with polymorphonuclear-cell infiltration).⁴⁰ To make a final decision as to whether each patient had ventilator-associated pneumonia, adjudicators made a summary judgment based on all available information; disagreement was resolved through discussion. We determined a priori that the adjudication committee's consensus rate of pneumonia would be used for the primary analysis and that other definitions would be used in the secondary analyses.

Statistical Analysis

Since ventilator-associated pneumonia has been considered an important potential adverse effect of gastric pH-altering prophylaxis against stress ulcers and because previous trials did not examine pneumonia as rigorously as gastrointestinal bleeding, we designed our trial to have the statistical power to detect a difference in the rates of pneumonia. On the basis of data published through 1991, when our study was designed, we anticipated a 25 percent incidence of pneumonia and identified a 25 percent reduction in the risk of pneumonia associated with sucralfate as being plausible and clinically important. This led to the calculation of a sample size of 1200 patients as necessary to give the study 75 percent power to detect such a difference, assuming a two-sided significance test at the 0.05 level. We analyzed all patients in the groups to which they were randomly assigned, according to the intention-to-treat principle. We compared means using Student's *t*-test and compared proportions using the chi-square test, with two-tailed *P* values.⁴¹ We used Fisher's exact test when the number of data points was small. For the length of the stay in the ICU, we report data as medians and interquartile ranges.

We conducted analyses both with and without adjustment for the following variables, treated categorically: age (<65 or ≥65

years), sex, location before admission to the ICU (emergency room, operating room, hospital ward, or other ICU), medical or surgical (elective or emergency) status, APACHE II score (<25 or ≥ 25), MOD score (<5 or ≥ 5), and medical center (of which there were 16).⁴²

RESULTS

Enrollment

Of 7986 patients admitted to ICUs, 6786 were excluded for the following reasons: mechanical ventilation was expected to be needed for less than 48 hours (3754 patients), the prognosis was considered hopeless (481), the patient had pneumonia (988) or gastrointestinal bleeding (432) at admission, gastrectomy had been performed (41), the patient had previously undergone randomization in this or another trial (565), two or more previous doses of open-label prophylaxis had been received (230), the patient had undergone mechanical ventilation in another ICU (38), the patient or proxy was unable or unwilling to give informed consent (184), an administrative error occurred (44), the physician declined to have the patient enrolled (14), or another reason (15). Excluded patients were a mean (\pm SD) of 60.8 ± 15.3 years of age and had a mean APACHE II score of 21.4 ± 7.9 .

We randomly assigned 1200 patients to the sucralfate or ranitidine group. Demographic and baseline physiologic characteristics were similar in the two groups (Table 1).

Protocol Violations, Compliance, and Nonstudy Prophylaxis

No patient received active drug instead of the assigned placebo, or vice versa. Of the scheduled doses of ranitidine and sucralfate, 94.2 percent and 91.7 percent, respectively, were administered. Among patients who missed doses, the mean number of doses missed was 2.3 (median, 3; interquartile range, 2 to 3) for ranitidine and 2.9 (median, 4; interquartile range, 1 to 4) for sucralfate.

Fourteen patients in the ranitidine group (2.3 percent) and 16 in the sucralfate group (2.6 percent) received an additional drug as prophylaxis against stress ulcers outside of the study protocol ($P = 0.74$). Most patients received enteral nutrition (70.3 percent and 71.8 percent, respectively; $P = 0.55$). Enteral feeding was started a median of three days (interquartile range, two to four) after admission to the ICU.

Gastrointestinal Bleeding

In the ranitidine group, 10 of 596 patients (1.7 percent) had clinically important gastrointestinal bleeding, as compared with 23 of 604 (3.8 percent) in the sucralfate group (relative risk, 0.44; 95 percent confidence interval, 0.21 to 0.92; $P = 0.02$); the absolute reduction in the risk of bleeding was 2.1 percent (95 percent confidence interval, 0.29 to 3.97).

TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY PATIENTS.*

CHARACTERISTIC	RANITIDINE GROUP (N=596)	SUCRALFATE GROUP (N=604)
Age — yr	58.8 \pm 18.1	58.7 \pm 18.7
Female sex — no. (%)	227 (38.1)	250 (41.4)
APACHE II score	24.7 \pm 7.1	24.6 \pm 7.3
MOD score	6.7 \pm 3.2	6.8 \pm 3.4
Reason for admission — no. (%)		
Medical	369 (61.9)	355 (58.8)
Elective surgery	93 (15.6)	105 (17.4)
Emergency surgery	134 (22.5)	144 (23.8)
Primary diagnosis — no. (%)		
Cardiovascular, medical	94 (15.8)	77 (12.7)
Cardiovascular, surgical	83 (13.9)	89 (14.7)
Respiratory, medical	96 (16.1)	83 (13.7)
Respiratory, surgical	8 (1.3)	15 (2.5)
Gastrointestinal, medical	16 (2.7)	18 (3.0)
Gastrointestinal, surgical	46 (7.7)	51 (8.4)
Central nervous system, medical	73 (12.2)	75 (12.4)
Central nervous system, surgical	26 (4.4)	23 (3.8)
Sepsis	37 (6.2)	39 (6.5)
Trauma	66 (11.1)	92 (15.2)
Burns	9 (1.5)	3 (0.5)
Transplantation	10 (1.7)	9 (1.5)
Other	32 (5.4)	30 (5.0)

*Plus-minus values are means \pm SD. APACHE II denotes the Acute Physiology and Chronic Health Evaluation scale (range of scores, 0 to 71; higher scores indicate more severe illness); MOD denotes multiple-organ dysfunction (range of scores, 0 to 24; higher scores indicate more severe organ dysfunction).

The results of the analysis in which we adjusted for other factors were similar (relative risk, 0.45; 95 percent confidence interval, 0.22 to 0.92; $P = 0.03$).

Seventeen patients underwent upper gastrointestinal endoscopy; additional diagnostic tests included laparotomy (in four), angiography (three), sigmoidoscopy (three), and red-cell scanning (one); two patients were examined at autopsy. One patient in the sucralfate group had bleeding from a gastroduodenal anastomosis, and another in the same group had bleeding from an aortic graft-enteric fistula. The source of bleeding was unclear for 8 patients in the ranitidine group and for 11 patients in the sucralfate group. Table 2 lists the 14 patients who had bleeding from gastric, esophageal, or duodenal erosions or discrete ulcers along with their study group, indication of bleeding, and diagnostic tests or procedures (Table 2). Post hoc subgroup analysis of patients with documented esophageal, gastric, or duodenal ulcers or erosions generated results consistent with our main findings (relative risk of bleeding in the ranitidine group as compared with the sucralfate group, 0.41; 95 percent confidence interval, 0.13 to 1.29; $P = 0.22$).

Ventilator-Associated Pneumonia

Among 596 patients receiving ranitidine, 114 (19.1 percent) had ventilator-associated pneumonia, as compared with 98 of 604 (16.2 percent) in the sucralfate group (relative risk, 1.18; 95 percent confidence interval, 0.92 to 1.51; $P=0.19$); the absolute difference in risk was 2.9 percent (95 percent confidence interval, -1.4 to 7.2). Results of the adjusted analysis were similar (relative risk, 1.14; 95 percent confidence interval, 0.91 to 1.44; $P=0.26$).

Table 3 presents the rates of pneumonia when different diagnostic criteria were used. As the definition of pneumonia became more strict, the overall rate decreased, although the difference between the two groups persisted. Table 4 shows the organisms isolated from endotracheal aspirates from patients with pneumonia. There was no significant difference in the types of isolates between the groups.

Duration of Patients' Stay in the ICU

All patients were included in the analysis. The median length of the ICU stay was 9 days (interquartile

range, 5 to 15) in the ranitidine group and 9 days (interquartile range, 5 to 17) in the sucralfate group ($P=0.27$). The duration of intubation was 7 days (interquartile range, 4 to 13) in the ranitidine group and 8 days (interquartile range, 4 to 15) in the sucralfate group ($P=0.25$).

Mortality in the ICU

Mortality in the ICU was similar among patients receiving ranitidine (140 of 596 [23.5 percent]) and those receiving sucralfate (138 of 604 [22.8 percent]; relative risk, 1.03; 95 percent confidence interval, 0.84 to 1.26; $P=0.79$).

DISCUSSION

We found that patients receiving ranitidine had a significantly lower risk of gastrointestinal bleeding than patients receiving sucralfate (relative risk, 0.44; 95 percent confidence interval, 0.21 to 0.92). This finding appears to contrast with the results of a recent meta-analysis, which suggested that the drugs' effect on bleeding was equivalent (relative risk, 0.95;

TABLE 2. EROSIVE OR ULCERATIVE CONDITIONS AFFECTING THE ESOPHAGUS, STOMACH, OR DUODENUM IN THE TWO STUDY GROUPS.*

PATIENT NO.	INDICATION OF BLEEDING	FEATURES PRESENT	TESTS OR PROCEDURES PERFORMED	SOURCE OF BLEEDING
Sucralfate group				
1	Melena	3, 4	Endoscopy	Gastric erosions
2	Melena	1, 3	Endoscopy	Gastric ulcer
3	Melena	1	Endoscopy	Gastric erosions
4	Melena	4	Endoscopy	Gastric erosions
5	Blood and coffee-grounds material in nasogastric aspirate	4	Endoscopy	Gastric erosions
6	Hematemesis, blood and coffee-grounds material in nasogastric aspirate	3, 4	Endoscopy	Gastroesophageal ulcer, gastric erosions, duodenal erosions
7	Melena	4	Endoscopy, computed tomography	Gastric ulcer, duodenal ulcer, aortic graft-enteric fistula
8	Coffee-grounds material in nasogastric aspirate, melena	1, 4	Endoscopy	Gastric erosions
9	Melena	1	Endoscopy	Esophageal ulcer, gastric erosions
10	Melena	1, 4	Endoscopy	Esophageal erosions, gastric ulcer
Ranitidine group				
11	Blood and coffee-grounds material in nasogastric aspirate, melena, hematochezia	3	Red-cell scanning, angiography, surgery	Gastric erosions
12	Hematemesis, melena, hematochezia	1	Endoscopy	Gastric erosions
13	Coffee-grounds material in nasogastric aspirate, melena	3	Endoscopy	Esophageal ulcer, duodenal ulcer
14	Melena	1	Endoscopy	Esophageal erosions, esophageal ulcer, gastric erosions

*The 14 patients listed are those who had clinically important gastrointestinal bleeding with erosions or ulcers of the esophagus, stomach, or duodenum.

†Clinically important bleeding was defined as overt bleeding plus one of the following four features, in the absence of other causes: (1) a spontaneous drop of 20 mm Hg or more in the systolic or diastolic blood pressure within 24 hours after upper gastrointestinal bleeding; (2) an increase in the pulse rate of 20 beats per minute and a decrease in the systolic blood pressure of 10 mm Hg on the patient's assuming an upright position; (3) a decrease in the hemoglobin concentration of at least 2 g per deciliter in 24 hours and the transfusion of 2 units of packed red cells within 24 hours after bleeding; or (4) failure of the hemoglobin concentration (in grams per deciliter) to increase after transfusion by at least the number of units transfused minus 2 (i.e., if 4 units of packed cells were transfused, the bleeding would be considered clinically important if the hemoglobin concentration did not rise by at least 2 g per deciliter).

TABLE 3. PATIENTS WITH VENTILATOR-ASSOCIATED PNEUMONIA.*

DIAGNOSTIC CRITERIA USED	RANITIDINE GROUP	SUCRALFATE GROUP	DIFFERENCE IN RISK (95% CI)†	RELATIVE RISK (95% CI)	P VALUE
	no.	no.	%		
Adjudication rate	114	98	2.9 (-1.4 to 7.2)	1.18 (0.92 to 1.51)	0.19
Bedside clinicians' assessment	153	133	3.7 (-1.2 to 8.5)	1.17 (0.95 to 1.43)	0.14
CDC	140	120	3.6 (-1.0 to 8.3)	1.18 (0.95 to 1.47)	0.13
Clinical suspicion	132	107	4.4 (-0.1 to 9.0)	1.25 (0.95 to 1.57)	0.06
Probable pneumonia	58	54	0.8 (-2.5 to 4.1)	1.09 (0.77 to 1.55)	0.64
Definite pneumonia	5	0	0.8 (0.1 to 1.6)	Undefined	0.03

*CI denotes confidence interval, adjudication rate the consensus of the study's pneumonia-adjudication committee, CDC the modified criteria of the Centers for Disease Control and Prevention,³⁶ clinical suspicion a Clinical Pulmonary Infection Score ≥ 7 (range of scores, 0 to 12),³⁹ probable pneumonia probable ventilator-associated pneumonia according to the criteria of the Memphis Consensus Conference,⁴⁰ and definite pneumonia definite ventilator-associated pneumonia according to the same criteria.⁴⁰

†The absolute percent difference shown is the rate in the ranitidine group minus that in the sucralfate group.

95 percent confidence interval, 0.17 to 5.36)¹²; however, the confidence limits around these two estimates overlap widely, and the difference could be attributable to chance. We found no significant difference in the incidence of pneumonia between patients receiving an H₂-receptor antagonist and those receiving sucralfate (relative risk, 1.18; 95 percent confidence interval, 0.92 to 1.51), a finding that is consistent with pooled data from previous randomized trials (relative risk, 1.19; 95 percent confidence interval, 0.98 to 1.44).¹²

The strengths of our trial include the measures taken to conceal the patients' treatment assignments; the blinding of care givers, research personnel, and analysts; the high rates of compliance; the adjudication of outcomes according to rigorous criteria; and the examination of the relation between prophylaxis and the incidence of ventilator-associated pneumonia defined according to a variety of criteria, given the absence of a well-accepted reference standard. Our study was limited by uncertainty about the causes of gastrointestinal bleeding; even in patients whose condition was stable enough for them to undergo endoscopy or other diagnostic tests, a site of bleeding could not always be identified. The source of bleeding remained unknown for 19 of 33 patients. Moreover, although our sample was large, the confidence intervals around key estimates were wide.

Previous randomized trials indicate that H₂-receptor antagonists substantially lower the incidence of overt and clinically important bleeding as compared with no prophylaxis.¹² Our findings show that rates of bleeding are lower among patients given H₂-receptor antagonists than among those given sucralfate. The incidence of bleeding in the sucralfate

TABLE 4. ORGANISMS ASSOCIATED WITH VENTILATOR-ASSOCIATED PNEUMONIA IN THE STUDY PATIENTS.*

ORGANISM	RANITIDINE GROUP (N=596)	SUCRALFATE GROUP (N=604)
	no. (%)	
Gram-negative bacilli		
<i>Escherichia coli</i>	9 (1.5)	9 (1.5)
Klebsiella	10 (1.7)	11 (1.8)
Serratia	3 (0.5)	4 (0.7)
Pseudomonas	20 (3.4)	21 (3.5)
Other	49 (8.2)	41 (6.8)
All types	80 (13.4)	61 (10.1)
Gram-positive cocci		
<i>Streptococcus pneumoniae</i>	9 (1.5)	10 (1.7)
<i>Staphylococcus aureus</i>	44 (7.4)	36 (6.0)
Other	5 (0.8)	7 (1.2)
All types	52 (8.7)	48 (7.9)
Gram-positive bacilli	0	3 (0.5)
Gram-negative cocci	6 (1.0)	6 (1.0)
Candida	19 (3.2)	11 (1.8)
Other	36 (6.0)	26 (4.3)
No growth	2 (0.3)	5 (0.8)

*Organisms shown are those isolated from endotracheal aspirates from patients with ventilator-associated pneumonia; the total number of organisms is more than the number of patients because several patients had more than one isolate.

group in this trial (3.8 percent) approximates the 3.7 percent incidence observed among untreated patients receiving mechanical ventilation in our natural-history study.¹¹ Previous trials comparing sucralfate with no prophylaxis have found a significantly lower rate of overt bleeding with sucralfate^{23,29,43,44}; however, in the single trial from which data on clin-

ically important bleeding events could easily be extracted,²⁹ 1 of 30 patients in the control group and 1 of 24 patients in the sucralfate group had clinically important bleeding. Given all this evidence, it is plausible that sucralfate has no effect on clinically important bleeding.

Although we found no significant difference in the rates of pneumonia between the two groups, the relative risk suggests a trend toward a lower rate of pneumonia among patients receiving sucralfate. It is possible that sucralfate appears to have a small protective effect against pneumonia because stress-ulcer prophylactic medications that increase the gastric pH themselves increase the incidence of pneumonia. This contention is supported by direct comparisons of trials of H₂-receptor antagonists with no prophylaxis, which show a trend toward higher rates of pneumonia among the patients receiving H₂-receptor antagonists (odds ratio, 1.25; 95 percent confidence interval, 0.78 to 2.00).¹² Furthermore, the relative effects of sucralfate and no prophylaxis against stress ulcers on the incidence of pneumonia is unclear. Among the 226 patients enrolled in two randomized trials, there was a trend toward a higher incidence of pneumonia among those receiving sucralfate than among those given no prophylaxis (odds ratio, 2.11; 95 percent confidence interval, 0.82 to 5.44).^{23,44}

Previous cost-effectiveness studies and practice guidelines have appropriately considered not only the base-line risk of bleeding and the effectiveness of prophylaxis against stress ulcers, but also the clinical and economic consequences of different preventive approaches.⁴⁵⁻⁴⁷ The direct and indirect costs of medicines for prophylaxis vary among health care organizations — a fact that highlights the need to appraise economic evaluations critically to determine their applicability to specific settings. The incremental number of days in the ICU attributable to clinically important upper gastrointestinal bleeding is estimated to be seven, and the attributable risk of mortality is about 12.5 percent.⁴⁸ The trend toward a lower rate of nosocomial pneumonia among patients receiving sucralfate rather than H₂-receptor antagonists¹² has been considered in some policy documents about the prophylactic treatment of stress ulcers. The development of ventilator-associated pneumonia may lead to an additional 13 days in the ICU,⁴⁹ although the effect of this type of pneumonia on mortality is less certain.^{49,50}

The patients at highest risk for clinically important bleeding are those who require mechanical ventilation for more than 48 hours and those with coagulopathy.⁸⁻¹¹ The estimated number of critically ill patients undergoing ventilation who would need to receive prophylaxis with ranitidine rather than sucralfate to prevent one clinically important upper gastrointestinal hemorrhage is approximately 48.

Supported by the Medical Research Council of Canada and Hoechst Marion Roussel. Drugs were supplied by Glaxo Wellcome, Baxter, and Hoechst Marion Roussel. Dr. Cook is a Career Scientist of the Ontario Ministry of Health.

We are indebted to the members of the Canadian Critical Care Trials Group for their help, particularly the research nurses who participated in this study, and to Drs. Thomas Todd, Thomas Noseworthy, Timothy Winton, and Michael Tryba for their support and advice.

APPENDIX

In addition to the authors, the study investigators and institutions were as follows: B. Plumstead and L. Frighetto, Vancouver General Hospital, Vancouver, B.C.; T. Noseworthy, E. Konopad, S. Bishop, M.L. Derko, and K. Horon, Royal Alexandra Hospital, Edmonton, Alta.; D. Stollery, M. Goers, and R. Jarman, Grey Nun's Hospital, Edmonton, Alta.; D. Roberts, T. Ostrusniuk, and J. Studney, Winnipeg Health Sciences Center, Winnipeg, Man.; T. Winton, D. Foster, D. Baptiste, M. Steinberg, and M. Lee, Toronto Hospital, General Division, Toronto; G. Darling, M. Culham, and V. Bobiwash, Wellesley Hospital, Toronto; M. Lefcoe (study radiologist), D. McCormack (study bronchoscopist), L. McCarthy, and C. Gawlik, London Health Sciences Center (Victoria Campus), London, Ont.; S. Langdon, M. Johnson, and C. Charters, London Health Sciences Center (University Campus), London, Ont.; M.K. Scott and S. Jansen, St. Joseph's Health Center, London, Ont.; E. McDonald, T. Dinh, and S. Toner, St. Joseph's Hospital, Hamilton, Ont.; S. Salama, Henderson Hospital, Hamilton, Ont.; A. Taite and P. Newman, Kingston General Hospital, Kingston, Ont.; M. Loewen, Ottawa Civic Hospital, Ottawa, Ont.; D. Gibbons, P. Leaman, and G. Gibbons, Health Sciences Center, St. John's, Newf.; P. Roy, M. Coffin, and H. Lummis, Victoria General Hospital, Halifax, N.S.; *Methods Center* — P. Austin and S. Troyan (project coordinators), L. Buckingham (data-base manager), and S. Duchesne (data entry); *Adjudication Committees* — D. Heyland, A. Freitag, K. Gough, M. Meade, A. Sarabia, M. Turner, H. Devitt, B. Guslits, M. Heule, R. Jaeschke, and J. Lang.

REFERENCES

- Borrero E, Bank S, Margolis IB, Schulman ND, Chardavoine R. Comparison of antacid and sucralfate in the prevention of gastrointestinal bleeding in patients who are critically ill. *Am J Med* 1985;79:Suppl 2C:62-4.
- Noseworthy TW, Shustack A, Johnston RG, Anderson BJ, Konopad E, Grace M. A randomized clinical trial comparing ranitidine and antacids in critically ill patients. *Crit Care Med* 1987;15:817-9.
- Shuman RB, Schuster DP, Zuckerman GR. Prophylactic therapy for stress ulcer bleeding: a reappraisal. *Ann Intern Med* 1987;106:562-7.
- Zandstra DF, Stoutenbeck CP. The virtual absence of stress-ulceration related bleeding in ICU patients receiving prolonged mechanical ventilation without any prophylaxis: a prospective cohort study. *Intensive Care Med* 1994;20:335-40.
- Schuster DP. Stress ulcer prophylaxis: in whom? With what? *Crit Care Med* 1993;21:4-6.
- Tryba M. Stress ulcer prophylaxis — quo vadis? *Intensive Care Med* 1994;20:311-3.
- Navab F, Steingrub J. Stress ulcer: is routine prophylaxis necessary? *Am J Gastroenterol* 1995;90:708-12.
- Kamada T, Fusamoto H, Kawano S, Noguchi M, Hiramatsu K. Gastrointestinal bleeding following head injury: a clinical study of 433 cases. *J Trauma* 1977;17:44-7.
- Schuster DP, Rowley H, Feinstein S, McGue MK, Zuckerman GR. Prospective evaluation of the risk of upper gastrointestinal bleeding after admission to a medical intensive care unit. *Am J Med* 1984;76:623-30.
- LaCroix J, Nadeau D, Laberge S, Gauthier M, Lapierre G, Farrell CA. Frequency of upper gastrointestinal bleeding in a pediatric intensive care unit. *Crit Care Med* 1992;20:35-42.
- Cook DJ, Fuller HD, Guyatt GH, et al. Risk factors for gastrointestinal bleeding in critically ill patients. *N Engl J Med* 1994;330:377-81.
- Cook DJ, Reeve BK, Guyatt GH, et al. Stress ulcer prophylaxis in critically ill patients: resolving discordant meta-analyses. *JAMA* 1996;275:308-14.
- Atherton ST, White DJ. Stomach as source of bacteria colonising respiratory tract during artificial ventilation. *Lancet* 1978;2:968-9.
- du Moulin GC, Paterson DG, Hedley-White J, Lisbon A. Aspiration of gastric bacteria in antacid-treated patients: a frequent cause of postoperative colonisation of the airway. *Lancet* 1982;1:242-5.
- Craven DE, Kunches LM, Kilinsky V, Lichtenberg DA, McCabe BJ, McCabe WR. Risk factors for pneumonia and fatality in patients receiving continuous mechanical ventilation. *Am Rev Respir Dis* 1986;133:792-6.
- Driks MR, Craven DE, Celli BR, et al. Nosocomial pneumonia in in-

- tubated patients given sucralfate as compared with antacids or histamine type 2 blockers: the role of gastric colonization. *N Engl J Med* 1987;317:1376-82.
17. Laggner AN, Lenz K, Graninger W, et al. Stressblutungprophylaxe auf einer internen Intensivstation: Sucralfat versus Ranitidin. *Anaesthesist* 1988;37:704-10.
 18. Prodhom G, Leuenberger PH, Blum AL, et al. Effect of stress ulcer prophylaxis on nosocomial pneumonia in ventilated patients: a randomized comparative study. In: Program and abstracts of the 31st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, September 29–October 2, 1991. Washington, D.C.: American Society for Microbiology, 1991.
 19. Pickworth KK, Falcone RE, Hoogbeem JE, Santanello SA. Incidence of nosocomial pneumonia in mechanically ventilated trauma patients: a comparison of sucralfate and ranitidine. *Crit Care Med* 1992;20:Suppl:S95. abstract.
 20. Garcia-Labattut A, Rodriguez-Muñoz S, Gobernado-Serrano M, et al. Sucralfate versus cimetidine in the stress bleeding prophylaxis. *Intensive Care Med* 1990;16:Suppl 1:S19. abstract.
 21. Eddleston JM, Vohra A, Scott P, et al. A comparison of the frequency of stress ulceration and secondary pneumonia in sucralfate or ranitidine-treated intensive care unit patients. *Crit Care Med* 1991;19:1491-6.
 22. Cannon LA, Heiselman DE, Gardner WG, Jones J. Prophylaxis of upper gastrointestinal tract bleeding in mechanically ventilated patients: a randomized study comparing the efficacy of sucralfate, cimetidine, and antacids. *Arch Intern Med* 1987;147:2101-6.
 23. Ben-Menachem T, Fogel R, Patel RV, et al. Prophylaxis for stress-related gastric hemorrhage in the medical intensive care unit: a randomized, controlled, single-blind study. *Ann Intern Med* 1994;121:568-75.
 24. Ryan P, Dawson J, Teres D, Celoria G, Navab F. Nosocomial pneumonia during stress ulcer prophylaxis with cimetidine and sucralfate. *Arch Surg* 1993;128:1353-7.
 25. Fabian TC, Boucher BA, Croce MA, et al. Pneumonia and stress ulceration in severely injured patients: a prospective evaluation of the effects of stress ulcer prophylaxis. *Arch Surg* 1993;128:185-91.
 26. Levy MM, Corson R, Miyasaki A, Tom R. Randomized trial: continuous infusion H2 blockers: bolus H2 blockers or carafate bid for the prophylaxis of stress ulcers in the ICU. *Crit Care Med* 1993;21:Suppl:S181. abstract.
 27. Mustafa NA, Akturk G, Ozen I, et al. Acute stress bleeding prophylaxis with sucralfate versus ranitidine and increase of secondary pneumonia in intensive care unit patients. *Intensive Care Med* 1995;21:287. abstract.
 28. Thomason M, Reeves R, Payseur E, Maddox A, Hakenewerth A, Norton J. Nosocomial pneumonia in ventilated trauma patients during stress ulcer prophylaxis with sucralfate, ranitidine and antacid. *Crit Care Med* 1995;23:Suppl:A93. abstract.
 29. Ruiz-Santana S, Ortiz E, Gonzalez B, Bolanos J, Ruiz-Santana AJ, Manzano JL. Stress-induced gastroduodenal lesions and total parenteral nutrition in critically ill patients: frequency, complications, and the value of prophylactic treatment: a prospective, randomized study. *Crit Care Med* 1991;19:887-91.
 30. Simms HH, DeMaria E, McDonald L, Peterson D, Robinson A, Burdard KW. Role of gastric colonization in the development of pneumonia in critically ill trauma patients: results of a prospective randomized trial. *J Trauma* 1991;31:531-6.
 31. Peterson WL. Prevention of upper gastrointestinal bleeding. *N Engl J Med* 1994;330:428-9.
 32. Schulz KF, Chalmers I, Hayes RJ, Altman D. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273:408-12.
 33. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818-29.
 34. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Crit Care Med* 1995;23:1638-52.
 35. Cook DJ, Pearl RG, Cook RJ, Guyatt GH. Incidence of clinically important bleeding in mechanically ventilated patients. *J Intensive Care Med* 1991;6:167-74.
 36. CDC definitions for nosocomial infections, 1988. *Am Rev Respir Dis* 1989;139:1058-9.
 37. Wimberley N, Faling LJ, Bartlett JG. A fiberoptic bronchoscopy technique to obtain uncontaminated lower airway secretions for bacterial culture. *Am Rev Respir Dis* 1979;119:337-43.
 38. Meduri GU, Chastre J. The standardization of bronchoscopic techniques for ventilator-associated pneumonia. *Chest* 1992;102:Suppl 1:557S-564S.
 39. Pugin J, Auckenthaler R, Mili N, Janssens JP, Lew PD, Suter PM. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. *Am Rev Respir Dis* 1991;143:1121-9.
 40. Pingleton SK, Fagon JY, Leeper KV Jr. Patient selection for clinical investigation of ventilator-associated pneumonia: criteria for evaluating diagnostic techniques. *Chest* 1992;102:Suppl 1:553S-556S.
 41. Fleiss JL. Statistical methods for rates and proportions. 2nd ed. New York: John Wiley, 1981.
 42. Aitkin M, Anderson D, Francis B, Hinde J. Statistical modelling in GLIM. Oxford, England: Clarendon Press, 1989.
 43. Labattut AG, Santolalla PM, De Andres AP, Ortigosa AM, Del Mar Gobernado Serrano M, Gimeno OL. Efficacy of sucralfate in the prevention of upper gastrointestinal stress bleeding in intensive care patients: comparison vs a control group. *Clin Intensive Care* 1992;3:Suppl:S19-S25.
 44. Eddleston JM, Pearson RC, Holland J, Tooth JA, Vohra A, Doran BH. Prospective endoscopic study of stress erosions and ulcers in critically ill adult patients treated with either sucralfate or placebo. *Crit Care Med* 1994;22:1949-54.
 45. Schumock GT, Lam NP, Winkler SR, Kong SX. Pharmacoeconomic analysis of stress ulcer prophylaxis for critically ill patients. *Pharmacoeconomics* 1996;9:455-65.
 46. Ben-Menachem T, McCarthy BD, Fogel R, et al. Prophylaxis for stress-related gastrointestinal hemorrhage: a cost effectiveness analysis. *Crit Care Med* 1996;24:338-45.
 47. Erstad BL, Camamo JM, Miller MJ, Webber AM, Fortune J. Impacting cost and appropriateness of stress ulcer prophylaxis at a university medical center. *Crit Care Med* 1997;25:1678-84.
 48. Heyland DK, Gafni A, Griffith L, et al. The clinical and economic consequence of clinically important gastrointestinal bleeding in critically ill patients. *Clin Intensive Care* 1996;7:121-5.
 49. Fagon JY, Chastre J, Hance AJ, Montravers P, Novara A, Gibert C. Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. *Am J Med* 1993;94:281-8.
 50. Papazian L, Bregeon F, Thirion X, et al. Effect of ventilator-associated pneumonia on mortality and morbidity. *Am J Respir Crit Care Med* 1996;154:91-7.