

— Clinical Investigations —

## Continuous intravenous cimetidine decreases stress-related upper gastrointestinal hemorrhage without promoting pneumonia

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**Objectives:** To determine whether a continuous iv infusion of cimetidine, a histamine-2 (H<sub>2</sub>) receptor antagonist, is needed to prevent upper gastrointestinal (GI) hemorrhage when compared with placebo and if that usage is associated with an increased risk of nosocomial pneumonia. Due to the importance of this latter issue, data were collected to examine the occurrence rate of nosocomial pneumonia under the conditions of this study.

**Design:** A multicenter, double-blind, placebo-controlled study.

**Interventions:** Patients were randomized to receive cimetidine (n = 65) as an iv infusion of 50 to 100 mg/hr or placebo (n = 66).

**Setting:** Intensive care units in 20 institutions.

**Patients:** Critically ill patients (n = 131), all of whom had at least one acute stress condition that previously had been associated with the development of upper GI hemorrhage.

**Measurements and Main Results:** Samples of gastric fluid from nasogastric aspirates were collected every 2 hrs for measurement of pH and were examined for the presence of blood. Upper GI hemorrhage was defined as bright red blood or persistent (continuing for >8 hrs) "coffee ground material" in the nasogastric aspirate. Baseline chest radiographs were performed and sputum specimens were collected from all patients, and those patients without clear signs of pneumonia (positive chest radiograph, positive cough, fever) at baseline were followed prospectively for the development of pneumonia while receiving the study medication.

Cimetidine-infused patients experienced significantly (p = .009) less upper GI hemorrhage than placebo-infused patients: nine (14%) of 65 cimetidine vs. 22 (33%) of 66 placebo patients. Cimetidine patients demonstrated significantly (p = .0001) higher mean intragastric pH (5.7 vs. 3.9), and had intragastric pH values at >4.0 for a significantly (p = .0001) higher mean percentage of time (82% vs. 41%) than placebo patients. Differences in pH variables were not found between patients who had upper GI hemorrhage and those patients who did not, although there was no patient in the cimetidine group who bled with a pH <3.5 compared with 11 such patients in the placebo group. Also, the upper GI hemorrhage rate in patients with one risk factor (23%) was similar to that rate in patients with two or more risk factors (25%). Of the 56 cimetidine-infused patients and 61 placebo-infused patients who did not have pneumonia at baseline, no cimetidine-infused patient developed pneumonia while four (7%) placebo-infused patients developed pneumonia.

**Conclusions:** The continuous iv infusion of cimetidine was highly effective in controlling

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**intra-gastric pH and in preventing stress-related upper GI hemorrhage in critically ill patients without increasing their risk of developing nosocomial pneumonia. While the number of risk factors and intra-gastric pH may have pathogenic importance in the development of upper GI hemorrhage, neither the risk factors nor the intra-gastric pH was predictive. Therefore, short-term administration of continuously infused cimetidine offers benefits in patients who have sustained major surgery, trauma, burns, hypotension, sepsis, or single organ failure. (Crit Care Med 1993; 21:19-30)**

**KEY WORDS: gastrointestinal hemorrhage, prevention; cimetidine; infusions, intravenous; pneumonia; randomized controlled trials; intensive care units; critical care; severity of illness index; cross infection; histamine H<sub>2</sub>-receptor blockers; abdominal emergencies**

Endoscopic examination of the gastric mucosa of patients admitted to ICUs after trauma, surgery, or life-threatening medical illnesses demonstrates that at least 80% of patients develop superficial erosive gastritis, more commonly referred to as stress ulceration (1, 2). Skillman et al. (3) reported in 1969 that 5% of their patients who required ICU care developed massive hemorrhage from stress ulcers, which contributed to death in 88% of these patients. This research group also demonstrated that prophylactic treatment with antacids significantly reduced the occurrence rate of bright red blood or prolonged "coffee ground" material aspirated from the nasogastric tube when compared with no treatment (4). Even though prophylactic treatment with antacids to prevent hemorrhage from stress ulcers did not change the overall mortality rate in critically ill patients (4), treatment with agents that increased intra-gastric pH became a standard of care in ICUs because this treatment decreased the number of patients who developed massive gastrointestinal (GI) hemorrhage.

In 1987, Driks et al. (5) reported that 6% of mechanically ventilated ICU patients, all of whom received some form of prophylaxis to prevent hemorrhage from stress ulcer, demonstrated bright red blood or "coffee ground" material in nasogastric aspirates, including one patient who died after massive GI hemorrhage. These authors also reported that patients receiving agents that increased gastric pH had a higher occurrence rate of nosocomial pneumonia than patients who received an agent that did not increase gastric pH. Although this study (5) did not show a statistically

significant association between the development of pneumonia and individual treatment regimens that increased gastric pH, these data prompted editorial comment (6) suggesting that agents that increase gastric pH should no longer be used to prevent the development of hemorrhage from stress ulcers. Such comment has led physicians to reconsider all aspects of prophylactic treatment for GI hemorrhage, and there is no longer a consensus on which patients should receive prophylactic treatment. Intensive care medicine has undergone a major evolution since the mid 1960s when Skillman et al. (3) documented GI hemorrhage in association with multiple organ failure. Massive hemorrhage from stress ulcers is no longer a common occurrence. However, many major medical centers still treat several such patients each year for massive hemorrhage from stress ulcers (L. F. Martin, F. V. McCl Booth, unpublished data). In our experience, massive hemorrhage usually results from a failure to provide stress ulcer prophylaxis for patients who develop unexpected postoperative complications (7).

Nosocomial pneumonia is a more common problem in the ICU, with numerous etiologies in these critically ill patients (8). In a recent study, Martin et al. (9) documented that 20% of intubated, postoperative patients who showed evidence of hypotension and/or sepsis developed diffuse stress ulcers (ten or more lesions), even when they received stress ulcer prophylaxis. In this study (9), the risk of developing evidence of GI hemorrhage or pulmonary complications was similar, and the development of either problem was significantly associated with death. The authors recommended that patients who appear to be at risk for developing multiple system organ failure receive stress ulcer prophylaxis. Forty-one percent of their patients developed additional gastric lesions despite prophylaxis, and the number of lesions correlated with their risk of developing GI hemorrhage.

In the present study, we examined patients who had at least one risk factor known to be associated with the development of stress ulcers (10) to determine whether these patients still needed to receive stress ulcer prophylaxis. We chose to examine the continuous iv infusion of the histamine-2 (H<sub>2</sub>) receptor antagonist, cimetidine, as our prophylactic agent, since this route of administration is convenient (does not require nasogastric manipulation or frequent change in dose/medication), and several studies (11, 12) suggested that continuous infusion more reliably maintains the gastric pH >4.0 than intermittent injection (which fails at least 25% of critically ill patients) (13). A placebo-controlled trial was used to evaluate whether the risk of developing GI bleeding was still a consideration in patients not requiring prolonged ICU admissions.

addition, we collected data to examine the occurrence rate of nosocomial pneumonia with the short-term administration of cimetidine.

## MATERIALS AND METHODS

**Study Population.** One hundred thirty-one patients were enrolled by 23 investigators into this multicenter, randomized, double-blind trial between September 1988 and March 1989. This protocol had been reviewed and approved by each investigator's Institutional Review Board.

Signed informed consent was obtained from the patient or legal guardian before randomization. Eligible patients were males or nonlactating, nonpregnant females,  $\geq 16$  yrs of age, with a nasogastric tube in place, who were admitted to the ICU for a minimum anticipated treatment period of 36 hrs and who had at least one of the following risk factors for upper GI hemorrhage: a) major surgery; b) multiple trauma to head, chest, abdomen, solid organs, or limbs; c) hypotension defined as a decrease in BP of  $>30/20$  mm Hg (systolic/diastolic) when the patient was placed in a semierect position; d) hypovolemic shock, defined clinically as a syndrome of inadequate tissue perfusion characterized by a systolic BP of  $<90$  mm Hg (or a decrease of 30 mm Hg in previously hypertensive patients) and metabolic acidosis; e) sepsis, including patients with peritonitis, confirmed bacteremia, or the complex of fever, increased WBC count, and hypotension with a bacteriologically determined source of infection; f) acute respiratory failure, defined as one of the following criteria: 1) the need for assisted mechanical ventilation, 2) severe hypoxemia with an oxygen deficit great enough to require an  $F_{iO_2}$  of 0.31 by mask or at least 2 L/min of oxygen by nasal prongs, or 3) acute hypoventilation resulting in an arterial blood pH of  $<7.34$  that was associated with an arterial blood  $P_{CO_2}$  of  $>46$  torr ( $>6.1$  kPa) for  $>24$  hrs; g) jaundice with a plasma total bilirubin concentration of  $>513$   $\mu\text{mol/L}$  ( $>30$  mg/dL) (acute hepatic failure only); or h) burns involving  $\geq 30\%$  of the body surface area.

Patients were excluded from the study for the following reasons: a) if  $>24$  hrs had elapsed since they had become eligible for enrollment into the study; b) if patients had been intubated for  $>24$  hrs (thus eliminating chronically intubated patients); c) if ICU admission followed esophageal, gastric, or duodenal surgery; or d) if patients had a history of gastrectomy or upper GI lesions that were likely to bleed. Patients were also excluded if they had received  $H_2$ -receptor antagonists within 12 hrs of admission to the study or treatment within 24 hrs before admission to the study with omeprazole, anticoagulants (except low-dose heparin),

aspirin, nonsteroidal anti-inflammatory agents, or treatment with an investigational drug within 30 days before entry. Patients were allowed to receive enteral feedings through a tube that traversed the pylorus into the small bowel (e.g., Dobhoff tube) or through a jejunostomy tube.

Additionally, during the screening phase, patients were excluded from the study if either of the two gastric aspirates (at least 30 mins apart) demonstrated bright red blood, coffee ground material, or a strongly positive test for occult blood. Although it is possible that this requirement did not exclude all patients with asymptomatic lesions, this procedure resulted in the exclusion of 40 otherwise eligible patients.

**Upper Gastrointestinal Hemorrhage Criteria.** Because this study was a blinded, placebo-controlled trial, it was considered essential by the investigators to set the threshold at which bleeding was defined at a sufficiently sensitive level to ensure patient safety. Clinically significant upper GI hemorrhage was defined as: a) hematemesis or bright red blood that did not clear after nasogastric tube adjustment and a 5- to 10-min lavage; or b) persistent coffee ground material (eight consecutive hours) that were Gastrocult (Smith Kline Diagnostics, Sunnyville, CA) positive, not clearing with a 100-mL lavage, and/or accompanied by a 5% decrease in hematocrit. Any patient meeting either criterion was considered to have failed to respond to prophylactic therapy; they were removed from the study and treated at the discretion of the primary physician.

**Treatment.** Baseline gastric pH was obtained before randomization. All patients received a one-time, 50-mL loading dose of coded medication (cimetidine or placebo) in 5% dextrose in water that was infused over a 20-min period. This loading dose was followed immediately by a continuous infusion of coded medication (cimetidine or placebo) in 5% dextrose in water at a rate of approximately 10.4 mL/hr, using an infusion pump. Patients randomized to receive cimetidine were infused with 300 mg of drug in the loading dose and 50 mg/hr thereafter; those randomized to receive placebo had a similar volume (8 mL) of matching placebo solution (normal saline, buffer and preservative) added to 5% dextrose in water.

The study medication dose was reduced by 50% in patients with severe renal failure (creatinine clearance  $<0.50$  mL/sec or  $<30$  mL/min); the volume of infusion was not altered. If the pH of the nasogastric aspirate was  $<4.0$  on two occasions 1 hr apart, the infusion rate was increased to 20.8 mL/hr (100 mg/hr, or 50 mg/hr in renally impaired patients), where it remained throughout the trial. To prevent bias in the interpretation of end-points and safety data, each institution designated

one investigator to monitor pH data and a second investigator, blinded to the pH determinations, to monitor signs and symptoms of upper GI hemorrhage, pneumonia, and other safety parameters.

**Data Collection.** Each patient's demographic characteristics, diagnosis on admission, underlying disease, vital signs, medications, laboratory values, and gastric aspirate information were recorded prospectively. All patients received a severity of illness score at baseline and daily while receiving study medication, using the Acute Physiology and Chronic Health Evaluation (APACHE II) scoring system of Knaus and Zimmerman (14). The physiologic values furthest from normal for each 24-hr period were used to calculate the APACHE II scores.

Nasogastric aspirates were obtained every 2 hrs and examined for bleeding and pH. The pH measurements were obtained using a portable, digital pH meter with a gel-filled combination electrode (pH pen, Nester Instruments, North Wales, PA). Patients were also observed for other signs of bleeding every 2 hrs.

Transfusion data were monitored daily. In those patients who met the criteria for upper GI hemorrhage, transfusion monitoring was continued for an additional 24 hrs after the study medication was discontinued.

The study was completed for any of the following reasons: if the nasogastric tube was permanently removed because it was no longer needed (patient eating) or no longer medically desirable (e.g., signs of sinusitis); if protocol-defined upper GI hemorrhage occurred; or if 7 days of study medication had been administered.

**Nosocomial Pneumonia Criteria.** At least two chest radiographs were obtained; a baseline radiograph was obtained within 24 hrs of admission to the study and an exit radiograph was obtained 48 hrs after the study medication was discontinued. If patients developed signs and symptoms of pneumonia while in the study or after their exit chest radiograph was done (if still requiring ICU management), additional chest radiographs were obtained. The diagnosis of pneumonia required a new and persistent (at least 24 hrs) infiltrate on the chest radiograph that was consistent with pneumonia, and sputum that showed, on Gram stain, >25 leukocytes and <10 squamous cells per low-power field and numerous bacteria per oil immersion field, and a positive sputum culture.

**Data Monitoring Board.** To ensure patient protection, SmithKline Beecham Pharmaceuticals requested the establishment of an independent Data Monitoring Board to be available for consultation on medical issues at any time. The Data Monitoring Board was composed

of a biostatistician (Jay Herson, PhD, Applied Logic Associates, Houston, TX), who served as Chairman and three physicians (Frederick Ognibene, MD, National Institutes of Health, Bethesda, MD; David Peura, MD, Walter Reed Army Medical Center, Washington, DC; and William Silen, MD, Beth Israel Hospital, Boston, MA). The Data Monitoring Board was authorized to analyze the trial, and to recommend termination of the trial, if appropriate. Although no treatment-related safety concerns were found, the Data Monitoring Board recommended that the study be discontinued based on the statistically significant reduction in bleeding for patients treated with cimetidine. Immediately on receipt of the recommendation of the Data Monitoring Board, the study was terminated. At the time of termination, a total of 131 patients had been enrolled in the study.

**Statistical Analysis.** This study was designed as a multicenter trial with 200 randomized patients. The sample size was derived from the assumption that the population failure rate for placebo-infused patients would be 20% vs. 5% for cimetidine-infused patients. Thus, 100 patients per group (200 patients total) would be required to provide a power of 90%, with a two-sided, type-1 error of 0.05. The external Data Monitoring Board served to analyze the data in a group-sequential fashion. There were to be two analyses performed after 100 and 200 patients completed the study. The trial was to terminate at the first analysis if the descriptive significance level for the difference in upper GI hemorrhage between treatment groups was <.025. The final significance level was to be set at .034. This set of decision rules would maintain an overall power  $\geq 90\%$  (based on the assumption above) and an overall type-1 error rate of 0.05 (15, 16). The trial was terminated subsequent to the interim analysis, based on the results of 104 patients.

At the time the decision was made to terminate the trial, a total of 131 patients had been randomized. Since the estimates of treatment differences for the "104 patient group" were nearly identical to the "104 patient group," the total group of 131 patients was used in the analyses presented here.

The primary analysis was performed on the pooled data from all centers and included an evaluation of treatment by investigator interaction. Since only one patient was declared ineligible, the analyses presented in this study are those analyses based on all patients (intent to treat).

The primary efficacy variable was the occurrence rate of clinically important upper GI hemorrhage. This variable was evaluated using appropriate chi-square methods. Time to occurrence (in hrs) of each bleeding event was also recorded and evaluated using

Kaplan-Meier estimation approach and the log-rank test.

The collected data were also evaluated to examine the occurrence rate of nosocomial pneumonia during and after the trial. The estimated difference between treatments was calculated using PROC CATMOD in Statistical Analysis Systems (SAS) (17). Applying the continuity correction, the occurrence rate of death within 30 days after randomization was also examined. Secondary analyses were performed to examine the number of patients whose dose of cimetidine was increased to maintain a gastric pH of >4.0 and to look for possible relationships between gastric pH, age, APACHE II score, and the development of upper GI hemorrhage. These analyses were performed using Fisher's exact test. To examine the effect of baseline characteristics on the occurrence rate of clinical events such as upper GI hemorrhage and death, a categorical model (PROC CATMOD in SAS [17]) and the Cox proportional hazards model (PROC LIFETEST in SAS [17]) were used. All significance levels cited in this paper are two-sided; mean  $\pm$  SD values are presented.

## RESULTS

There were a total of 198 patients screened from 20 institutions by the 24 investigators participating in this study. Of these patients, 67 did not meet the entry criteria. The most common reason for exclusion was prestudy GI bleeding ( $n = 40$ ) followed by no written consent ( $n = 33$ ) and expected treatment <36 hrs ( $n = 15$ ). The other patients fell randomly into the other exclusion criteria, ranging from two to nine patients in each category. Six investigators admitted ten or more patients while the rest of the investigators admitted between one and nine patients. There was no investigator interaction.

Of the 131 study patients, 65 received cimetidine and 66 received placebo. The two treatment groups were similar in terms of demographic and clinical characteristics at baseline, including age, sex, race, type, and number of risk factors for bleeding, and intragastric pH (Tables 1 and 2). The baseline APACHE II score was an exception, with cimetidine-infused patients having a higher mean APACHE II score than placebo-infused patients ( $p = .05$ ). The baseline gastric pH values were >4.0 in approximately 75% of the patients; this value was approximately 5.0 for both treatment groups.

The average time in the ICU, before, during and after the study for the patient population was  $9.7 \pm 17.7$  days. The median time was 4 days for cimetidine (range to 91) and 4 days for placebo (range 1 to 133). Although

**Table 1.** Demography of patients enrolled in study

	Cimetidine (n = 65)	Placebo (n = 66)
Age (yr)		
<18	2 (3) <sup>a</sup>	1 (2)
18-50	16 (25)	17 (26)
51-64	20 (31)	14 (21)
>64	27 (42)	34 (52)
Mean age $\pm$ SD	59 $\pm$ 19	60 $\pm$ 17
Sex (M/F)	41 (63)/24 (37)	48 (73)/18 (27)
Race		
White	50 (77)	52 (79)
Black	11 (17)	18 (20)
Other	4 (6)	1 (2)
Height (cm)		
Mean $\pm$ SD	170 $\pm$ 10	173 $\pm$ 10
Range	152-198	137-188
Weight (kg)		
Mean $\pm$ SD	75 $\pm$ 17	76 $\pm$ 16
Range	38-123	43-118

<sup>a</sup>Values in parentheses are percentages.

**Table 2.** Clinical characteristics on admission to study

	Cimetidine (n = 65)	Placebo (n = 66)
<i>Stress Condition</i>		
Major Surgery	40 (62)	49 (74)
Elective/emergent	30/10	32/17
Multiple trauma	16 (25)	15 (23)
Hypotension	6 (9)	1 (2)
Respiratory failure	14 (22)	12 (18)
Hypovolemic shock	5 (8)	2 (3)
Sepsis	4 (6)	6 (9)
Jaundice	0 (0)	1 (2)
Burns	1 (2)	0 (0)
<i>Number of Conditions</i>		
One	50 (77)	49 (74)
Two	11 (17)	14 (21)
Three or more	4 (6)	3 (5)
<i>APACHE II Scores<sup>a</sup></i>		
$\leq 11$	20 (31)	15 (23)
11-15	14 (22)	23 (35)
15-20	11 (17)	18 (27)
>20	20 (31)	10 (15)
Mean $\pm$ SD	16.9 $\pm$ 7.8 <sup>b</sup>	15.1 $\pm$ 5.8
<i>Baseline pH</i>		
<2	5 (8)	1 (2)
2-3.9	13 (20)	14 (21)
4-5.9	18 (28)	23 (35)
6-7.9	23 (35)	24 (36)
Not available	6 (9)	4 (6)
Mean $\pm$ SD	5.0 $\pm$ 1.9	5.1 $\pm$ 1.7
<i>Pneumonia Present</i>		
Pretreatment	9 (14)	5 (8)

<sup>a</sup>APACHE, Acute Physiology and Chronic Health Evaluation; For complete explanation of variables in score, see reference 14; <sup>b</sup> $p = .05$ ; Student's *t*-test of the differences between cimetidine and placebo groups. Values in parentheses are percentages.

enteral feedings through a jejunostomy or Dobhoff-like tube in the small bowel were permitted, only five patients received these feedings. Of the four cimetidine patients receiving such a feeding, one experienced protocol-defined bleeding. The one placebo-infused patient experienced mild bleeding that did not meet the protocol definition.

**pH Results.** The mean pH decreased over time in the placebo-infused group, but did not decrease in the cimetidine-infused group (Fig. 1). Mean intragastric pH while receiving study medication was 5.7 for cimetidine-infused and 3.9 for placebo-infused patients ( $p = .0001$ ). Patients who received cimetidine had a pH of  $>4.0$  approximately 82% of the time, while patients receiving placebo had a pH of  $>4.0$  approximately 41% of the time ( $p = .0001$ ). Overall, 52 (79%) placebo patients and 32 (49%) cimetidine patients received a dosage adjustment because of low pH. Only eight cimetidine-infused patients failed to maintain a mean pH of  $>4.0$  on the adjusted dose.

**Occurrence Rate of Upper Gastrointestinal Hemorrhage.** The proportion of patients with upper GI hemorrhage was significantly ( $p = .009$ ) less in the cimetidine group (nine [14%] of 65 patients) than in the placebo group (22 [33%] of 66 patients). These results are nearly identical to those results that prompted the Data Monitoring Board to recommend early termination of the study (seven of 50 cimetidine-infused vs. 20 of 54 placebo-infused patients;  $p = .007$ ).

Analysis of the cumulative bleeding rates using life-table methodology, which accounts for varying durations of drug exposure, demonstrated a significant (log rank test  $p = .015$ ) difference between treatment groups in the time to upper GI hemorrhage (Fig. 2). Among patients who required study medication for  $>3$  days, bleeding occurred in five of 18 patients who were

treated with placebo and in none of 14 patients who were treated with cimetidine.

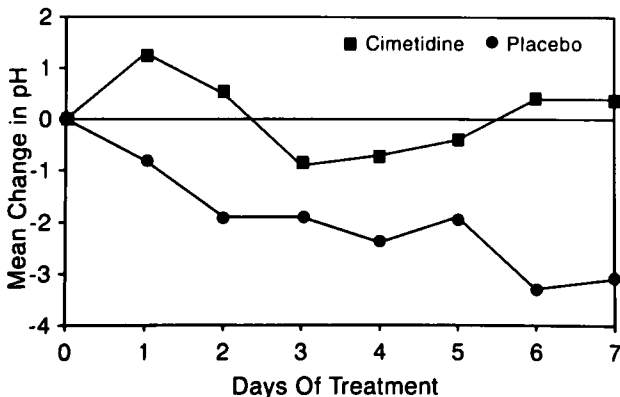
Table 3 presents the clinical characteristics of patients who met the criteria for upper GI hemorrhage. There was no significant difference between patients with upper GI hemorrhage and those patients without upper GI hemorrhage in mean age (57.4 vs. 59.6 yrs) or mean baseline pH (5.40 vs. 5.05). The occurrence rate of upper GI hemorrhage was 23% (23/99) in patients presenting with one acute stress condition and 25% (32/128) in patients with two or more stress conditions.

Five of the cimetidine-infused patients who bled had adequate control of their gastric fluid pH, as defined by the protocol, with the initial medication dosage (50 mg/hr,  $n = 4$ ; 25 mg/hr,  $n = 1$ ), while four patients required a dosage adjustment to 100 mg/hr.

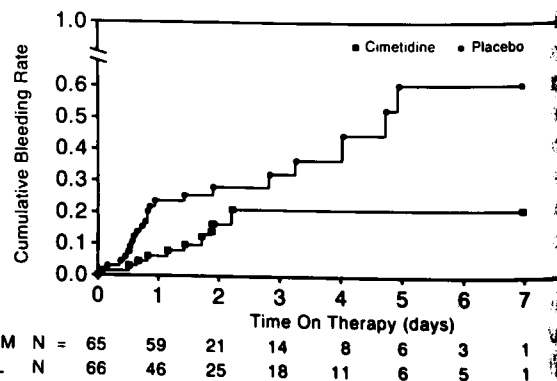
The occurrence rate of upper GI hemorrhage by APACHE II score is shown in Table 4. There was a trend for both treatment groups toward a higher occurrence rate of upper GI hemorrhage with increasing APACHE II scores. However, cimetidine-infused patients experienced less upper GI hemorrhage than placebo-infused patients did across all APACHE II score quartiles.

The baseline pH did not predict the subsequent occurrence of upper GI hemorrhage. The occurrence rate of upper GI hemorrhage in the placebo-infused patients was 33% (5/15) for those patients whose baseline pH was  $<4.0$  and 33% (17/51) for those patients whose baseline pH was  $\geq 4.0$ . The occurrence rate of upper GI hemorrhage in cimetidine patients was 17% (3/18) for those patients whose baseline pH was  $<4.0$  and 13% (6/47) for those patients whose baseline pH was  $\geq 4.0$ .

Similarly, the mean pH of patients receiving study medication did not predict the occurrence of upper GI hemorrhage (Table 5). The occurrence rate of upper GI hemorrhage in the placebo-infused patients was 33%



**Figure 1.** Mean change in the gastric fluid pH values from baseline for all patients remaining in the study for the first 7 days of treatment.



**Figure 2.** A life-table analysis of the time from study admission to the time when criteria for upper gastrointestinal hemorrhage were met. CIM, cimetidine-infused patients; PL, placebo-infused patients.

**Table 3. Patients demonstrating upper gastrointestinal hemorrhage**

Risk Factor(s)	APSII	Age (yr)	Time to UGIH <sup>a</sup> (hr)	Gastric Fluid		Type of UGIH	Blood Trans <sup>b</sup> (mL)
				Baseline pH	Mean pH		
<i>Cimetidine Patients</i>							
TR	29	36	37.5	6.0	4.4	CG	1321
SU	9	62	16.0	—	7.4	CG	0
SU	21	69	1.5	4.4	4.0	BRB	250
SU, HY, HS, SE, RF	26	55	45.4	7.3	7.4	BRB	0
HY, RF	16	74	20.0	7.0	6.1	CG	0
SU	18	69	45.5	2.1	3.9	CG	0
TR	14	16	60.5	4.0	4.7	BRB	0
TR, RF	24	22	12.5	3.9	6.5	BRB	655
HS, SE, RF	38	78	31.5	1.7	6.7	BRB	625
<i>Placebo Patients</i>							
SU	12	77	14.0	5.4	3.9	CG	250
SU	9	73	24.0	4.3	2.7	CG	1200
SE	16	29	11.1	4.5	2.1	CG	0
SU, TR	18	42	75.0	6.0	3.2	CG	600
TR	18	31	10.0	3.3	2.8	CG	0
RF	16	65	1.0	—	6.6	CG	0
SU	11	69	18.1	4.3	3.4	CG	0
SU	14	79	37.5	—	8.1	CG	0
SU	18	67	12.0	7.2	6.2	BRB	250
SU, RF	18	71	6.9	6.9	6.3	BRB	0
SU, TR, HY	15	38	122.0	5.0	3.5	CG	1000
RF	35	55	19.5	2.0	1.6	CG	0
SU	17	54	16.0	1.8	1.7	CG	0
SU	4	23	21.3	6.1	4.0	CG	0
SU	12	56	45.8	5.8	4.6	BRB	0
TR	21	60	116.4	2.0	4.5	CG	0
SU	21	80	82.2	5.8	2.9	CG	0
SU	14	83	20.0	3.2	2.1	CG	0
SU	12	68	13.0	6.7	4.2	CG	0
SU, SE, RF	12	34	112.0	7.1	3.0	CG	750
RF	26	80	20.0	4.0	4.6	CG	0
SU	13	66	14.8	5.6	3.4	CG	0

UGIH, upper gastrointestinal hemorrhage; APSII, baseline Acute Physiology and Chronic Health Evaluation Score; TR, trauma; CG, coffee ground material; SU, surgery; BRB, bright red blood; HY, hypotension; HS, hypovolemic shock; SE, sepsis; RF, respiratory failure.

Each line represents a separate patient.

<sup>a</sup>Relative to initiation of coded medication; <sup>b</sup>Volume of whole blood or packed RBCs transfused on the day of bleeding and over the next 24 hrs.

**Table 4. Frequency of upper gastrointestinal hemorrhage by Acute Physiology and Chronic Health Evaluation (APACHE II) score (APSII)**

APACHE II Score <sup>a</sup>	Cimetidine	Placebo
<11	1/20 (5)	3/15 (20)
11-15	1/14 (7)	9/23 (35)
15-20	2/11 (18)	6/18 (33)
>20	5/20 (25)	4/10 (40)

Values in parentheses are percentages.

<sup>a</sup>APACHE II score intervals based on quartiles.

**Table 5. Frequency of upper gastrointestinal hemorrhage in patients categorized by their mean gastric pH while on study medication**

Mean pH	Cimetidine	Placebo
>6.0	5/33 (16)	4/10 (40)
5.0-5.9	0/13 (0)	0/5 (0)
4.0-4.9	3/11 (27)	5/11 (46)
3.5-3.9	1/4 (25)	2/6 (33)
<3.5	0/4 (0)	11/34 (34)

Values in parentheses are percentages.

(9/26) for those patients with a mean pH of  $\geq 4.0$  and 33% (13/40) for those patients with a mean pH of  $< 4.0$ .

In the cimetidine-infused patients, the occurrence rate was 14% (8/57) for those patients with a mean pH of

$\geq 4.0$  and 13% (1/8) for those patients with a mean pH of  $< 4.0$ . In each category, the occurrence rate was less in the cimetidine-infused patients than in the placebo-infused patients. However, bleeding associated with a low gastric fluid pH was practically abolished in the cimetidine group. Only one cimetidine patient in the entire group ( $n = 65$ ) bled with a mean pH of  $< 4.0$  and none bled at all with a mean pH of  $< 3.5$ , compared with 13 placebo-infused patients (of the entire group of 66 patients) who bled with a mean pH of  $< 4.0$  and 11 patients with a mean pH of  $< 3.5$ .

**Nosocomial Pneumonia.** Baseline chest radiographs and sputum examinations identified 14 (11%) of 131 patients who entered the study with pneumonia. Investigators indicated pneumonia as a presenting condition for only two of these patients. Nine patients were randomized to the cimetidine group, and five patients were randomized to the placebo group (Table 2). While receiving the study medication, 0 (0%) of the 56 remaining cimetidine patients and four (7%) of the 61 remaining placebo patients developed pneumonia. The estimated difference between treatments was  $-6.4\%$  with a 95% confidence interval of  $-13.4\%$  to  $0.6\%$ .

Investigators were asked to follow patients after study medication was discontinued, and four (4%) of 113 additional patients developed pneumonia between 3 and 6 days after the study. Two of these patients had received cimetidine during the study, and two had received placebo. None of these patients received cimetidine after the study medication was discontinued.

Sputum culture results can be found in Table 6. Investigators obtained culture results through the normal procedures of their individual institutions. In all patients who had baseline and follow-up sputum cultures performed, three (27%) of 11 cimetidine-infused patients and three (30%) of ten placebo-infused patients developed colonization of one or more of the following: *Acinetobacter*, *Enterobacter*, *Pseudomonas*, *Klebsiella*, *Serratia*, and *Staphylococcus aureus*.

**Safety Parameters.** Table 7 shows the number of patients in each treatment group who died or survived, by bleeding status and with associated APACHE II scores. Cimetidine patients who died were more severely ill than placebo patients who died. Mortality rates within 30 days of randomization were nearly identical for cimetidine-infused (8/65, 12%) and placebo-infused (7/66, 11%) patients. The difference in the mortality rates between treatment groups was 1.7%, with a 95% confidence interval of  $-9.2\%$  to  $12.6\%$ . Although no death was attributed to upper GI hemorrhage, four deaths occurred among placebo patients with upper GI hemorrhage vs. one death among cimetidine patients with upper GI hemorrhage (Table 6). The elapsed time between bleeding and death was 2 to

**Table 6.** Patients who developed pneumonia while receiving medication and after study medication was stopped

Study Medication	Causative Pathogen
<i>During Study</i>	
Placebo	<i>Pseudomonas aeruginosa</i>
Placebo	<i>Serratia marcescens</i>
Placebo	<i>S. marcescens</i>
Placebo	<i>Pseudomonas</i>
<i>Poststudy</i>	
Placebo	(Gram-negative rods)
Placebo	( <i>Hemophilus</i> ; <i>Staphylococcus aureus</i> )
Cimetidine	<i>Candida albicans</i>
Cimetidine	<i>Acinetobacter anitratus</i>

**Table 7.** Survival data by mean baseline Acute Physiology and Chronic Health Evaluation Score (APACHE II) and bleeding status

	Bleeding Patients (n = 31)		Nonbleeding patients (n = 100)	
	Died	Survived	Died	Survived
Cimetidine	38% (n = 1)	19.6 $\pm$ 6.7 (n = 8)	26.0 $\pm$ 8.6 (n = 7)	14.7 $\pm$ 6.0 (n = 4)
Placebo	13.5 $\pm$ 2.8 (n = 4)	16.3 $\pm$ 6.83 (n = 18)	18.0 $\pm$ 7.0 (n = 3)	14.4 $\pm$ 5.5 (n = 4)

\*Mean baseline APACHE II scores for each group with the number of patients in the group listed below the mean  $\pm$  SD.

5 days for the placebo-infused patients and 7 days for the cimetidine-infused patient.

Overall, the frequency rates of adverse events that were considered by investigators as related or possibly related to the study medication were similar for the two treatment groups (25% for cimetidine-infused vs. 20% for placebo-infused patients). For example, mental status changes (agitation, confusion, disorientation) and lethargy were reported in five cimetidine-infused patients and four placebo-infused patients. Serum chemistry results showed no significant differences between the two treatment regimens. Compared with prestudy values, there was an increased occurrence rate in both treatment groups for decreases in hemoglobin, hematocrit, and platelet count. These increases were comparable between the groups.

No adverse drug interactions were reported among cimetidine patients despite the concomitant use of phenytoin (six patients), diazepam or chlordiazepoxide (ten patients), xanthines or lidocaine (ten patients), and propranolol (two patients).

## DISCUSSION

Stress-related upper GI bleeding represents a potentially serious complication in critically ill patients.

although overt exsanguination is uncommon. Schuster et al. (18) noted a 64% mortality rate in critically ill patients with GI bleeding as opposed to a 9% mortality rate in patients without such bleeding. It is well recognized that the reported occurrence rate of stress-related GI bleeding is dependent on the sensitivity of the methods used to detect bleeding. Almost all patients can be shown to have some bleeding if very sensitive methods are used, but many clinicians and investigators discount the clinical importance of occult bleeding. However, even occult bleeding is a harbinger of more serious bleeding in some patients (19). One of the goals of this study was to determine if stress ulcer prophylaxis had become obsolete due to improvements in intensive care medicine. The data from the placebo group in the present study demonstrate that stress-related bleeding, as defined by the strictest criteria possible in a placebo-controlled trial, continues to be a common occurrence (33%) despite advances in ICU techniques. This occurrence rate of upper GI hemorrhage is consistent with rates reported in other studies in the literature (1).

Even in these "moderately ill" patients who were "typical" ICU patients, the blood transfusion requirement was similar regardless of type of bleeding; "coffee ground" bleeding and hemorrhagic bleeding. Six patients experiencing  $\geq 8$  hrs of continuing "coffee ground" bleeding required transfusions which averaged approximately 850 mL per patient. The four patients with the appearance of bright red blood requiring lavage which did not immediately clear) received approximately 450 mL per patient. Thus, preventing both types of bleeding are important if transfusion is to be avoided.

The continuous intravenous infusion of cimetidine used in this study resulted in statistically and clinically important reductions in stress-related upper GI hemorrhage over placebo, such that the external Data Monitoring Board recommended early termination of the placebo-controlled study. The significant prophylactic effect of the cimetidine regimen was achieved despite cimetidine patients having a higher mean APACHE II score than placebo patients at baseline (Table 2). Cimetidine was effective in reducing upper GI hemorrhage regardless of the severity of illness, as shown by the analysis of upper GI hemorrhage by APACHE II score (Table 4). This analysis also suggested a trend toward increasing upper GI hemorrhage with increasing severity of illness, while the more traditional analysis of hemorrhage by number of risk factors failed to show a significant relationship in this patient population.

The occurrence rate of upper GI hemorrhage in this study is consistent with the rates reported in the

literature (1) from studies that are now 10 yrs old. A recent study (2), which examined patients with risk factors that were similar to the risk factors in this study, and which used endoscopy to count stress ulcers, found that  $>60\%$  of patients who were admitted to ICUs postoperatively developed lesions, even while receiving prophylaxis. Another recent study (9) examined postoperative patients who had already developed postoperative complications but who had  $<10$  stress ulcers at study entry. Forty percent of these patients developed additional stress ulcers, even after stress ulcer prophylaxis was initiated. Bleeding rates correlated with the total number of lesions that developed (9). Eight percent of this group of patients who were receiving prophylaxis developed upper GI hemorrhage, even though they had no lesions at a time when other complications were present (9). Collectively, these studies (2, 9) suggested that prophylaxis is still important in all patients who have experienced major surgery, operations, burns, hypotension, sepsis, or developed organ failure.

The continuous infusion of cimetidine was chosen to provide a more consistent effect on gastric fluid pH. Ostro et al. (11) compared the continuous infusion of cimetidine with an intermittent dosing regimen in critically ill patients. They (11) confirmed prior reports (10, 13) that 300 mg of cimetidine given intravenously every 6 hrs maintained a gastric pH of  $\geq 4.0$  in only about 25% of patients, while the same dose given as a continuous infusion maintained a pH of  $\geq 4.0$  in 87% of their patients. Kingsley (12) compared cimetidine and antacid as intermittent and continuous regimens in ICU patients and found that both continuous regimens (i.e., cimetidine or antacids) were superior to the intermittent regimens in preventing stress-related bleeding.

The cimetidine regimen provided an effective gastric pH increase, as shown by the cimetidine group having an intragastric pH of  $\geq 4.0$  for 82% of the study time compared with 41% of the study time for the placebo group. Although cimetidine reduced upper GI hemorrhage and increased intragastric pH relative to placebo, the intragastric pH variables analyzed here did not predict bleeding. In each treatment group, the mean baseline intragastric pH and both the mean intragastric pH and the amount of time (%) pH was  $\geq 4.0$  while receiving study medication were similar in patients with and without upper GI hemorrhage. That these pH parameters were not predictive for upper GI hemorrhage may be related to the variability of gastric pH or to the difficulty in choosing the appropriate sampling interval for analysis. Alternatively, pH may be one of several important pathogenic factors, such as gastric blood flow and gastric mucosal barrier

integrity, which are affected by cimetidine (20–25), and may thereby influence the development of stress-related upper GI hemorrhage.

The importance of pathogenetic factors other than acid (e.g., ischemia) is apparent from the fact that the pH was high in many patients in this study at baseline (the mean baseline pH being  $\geq 5.0$ ) and upper GI hemorrhage occurred in 17 patients whose mean pH remained  $>4.0$ . As demonstrated in the placebo-infused group, the return of acid secretory capability in some patients was manifested by a gradual decrease in the mean pH of the group (Fig. 1).

Nevertheless, 11 of the 22 placebo-infused patients bled with a mean pH  $\geq 3.5$ , i.e., without "free acid" present. It is not clear to what extent smaller amounts of acid (i.e., producing pH values between 4.0 and 6.0) contribute to bleeding, but it is clear that at least some bleeding is not pH dependent and one would not expect bleeding in those cases to be affected greatly by measures affecting pH alone.

There is no obvious way to determine what proportion of the bleeding in the cimetidine group was due to these relatively pH-insensitive factors and what proportion may have been due to inadequate pH control. In the placebo group, 32 patients failed to produce enough acid to lower the pH to  $<3.5$  and 11 of these patients bled. Thus, one would have expected a similar number of cimetidine patients to bleed with a pH of  $\geq 3.5$  (11 patients), whether or not cimetidine had been administered. Nine such cases were observed, and these cases accounted for all of the bleeding in the cimetidine group; no bleeding was associated with a mean pH of  $<3.5$ . One interpretation of these results is that cimetidine, when given as in this study, can prevent bleeding associated with "free acid" (pH  $<3.5$ ), but may be less effective at a higher pH, when pathogenetic factors other than acid assume more importance. This interpretation does not preclude some additional effect of cimetidine in these patients based on other mechanisms of action (20–27) and it would not be logical to assume that there is any threshold pH above which cimetidine would be ineffective.

This study was not designed to detect an effect of the prophylaxis of bleeding on mortality. For ethical reasons, sample sizes were based on bleeding end-points rather than on mortality. Bleeding end-points and monitoring intervals were chosen to permit early intervention with every available modality, thus minimizing the potential for bleeding to affect morbidity and mortality. Nevertheless, mortality rates were greater among the patients who bled (five [16%] of 31 patients) than among the nonbleeding patients (ten [10%] of 100). Furthermore, of the five patients who bled and died, four were in the placebo group and

one was in the cimetidine group. This mortality was temporally associated with bleeding, occurring between 2 and 7 days of the hemorrhage. While this finding suggests that mortality rates due to bleeding may be decreased with cimetidine, the total number of patients dying in association with bleeding in this study was too small to clearly demonstrate this interpretation.

This study, like the majority of studies, excluded admitted patients who, despite the presence of risk factors, had not developed upper GI hemorrhage before entry. Forty patients were excluded from this study because they had evidence of upper GI hemorrhage at screening, and thus, the population actually studied may have been relatively hemorrhage resistant. Patients who have mild bleeding at the time when their need for intensive care is determined are probably at an even greater risk for developing serious hemorrhage. In future studies, either earlier entry or the inclusion of patients with minimal bleeding at entry should be used to evaluate the ability of this treatment regimen to prevent serious hemorrhage.

The risk for developing nosocomial pneumonia in the ICU setting ranges from 15% to 70% and is generally higher than the risk in other hospital areas. Rodriguez et al. (28) reported that the mean time to the development of nosocomial pneumonia in trauma patients was 6.1 days. The mean ICU length of stay for the present patient population (including time before, during, and after receiving the study medication) was 9.7 days and resulted in an overall occurrence rate of nosocomial pneumonia of 15%. The relatively low overall occurrence rate of nosocomial pneumonia observed in this study may be due to the exclusion of chronically intubated patients from the study population and the inclusion of a large number of surgical and trauma patients without numerous predisposing medical conditions.

It has been postulated (5) that cimetidine, by depressing gastric acidity, might promote gastric overgrowth of Gram-negative enteric bacteria, which can then colonize the respiratory tract and result in nosocomial pneumonia. During the medication phase of this study, four (7%) placebo-infused patients and zero (0%) cimetidine-infused patients developed new pneumonias, even though the mean intragastric pH in the cimetidine patients was 5.7. The lower overall incidence of new pneumonia relative to the overall occurrence rate cited above is consistent with the lower mean duration of treatment in the study (5.7 days) relative to the mean duration of treatment in the ICU (9.7 days).

Thus, in this prospective, placebo-controlled evaluation, there was no evidence that cimetidine increased

the incidence of nosocomial pneumonia. Possibly, the reduction in the volume of gastric secretion afforded by cimetidine was more important than the reduction in gastric acidity in determining whether nosocomial pneumonia developed in these patients. Also, cimetidine has been shown to have immunopotentiating effects (25, 26) that could be beneficial in this setting.

Finally, doubt is growing that suppression of gastric acidity influences respiratory tract colonization rates or that manipulation of this type of flora in critically ill patients changes mortality rates. Cioffi et al. (29) compared sucralfate with antacid/cimetidine treatment in 67 patients who sustained burns to >20% of body surface area. Although nosocomial pneumonia developed in approximately 30% of the patients, there was no significant difference in colonization rates of the upper airway (sucralfate 88%, antacid/cimetidine 97%), the gastric contents (sucralfate 69%, antacid/cimetidine 85%) or pneumonia (sucralfate 33%, antacid/cimetidine 29%). The rate of colonization of the upper airway with Gram-negative bacteria was also not different (76% for both), although the sucralfate group had a slightly lower rate of Gram-negative colonization in their gastric specimens (54% vs. 76%;  $p = .07$ ). Seven patients in each group died.

Perhaps more importantly, Gastinne et al. (30) examined whether selective decontamination of the digestive tract with nonabsorbable antibiotics affected nosocomial pneumonia rates or mortality rates in intubated critically ill patients. Nosocomial pneumonia rates (13%) and mortality rates (32%) were nearly identical, although treated patients had significantly fewer episodes of pneumonia due to Gram-negative bacteria and a trend toward more episodes due to staphylococcus ( $p = .06$ ). These studies (29, 30) suggested that manipulation of gastric flora in critically ill patients does not contribute to rates of nosocomial pneumonia or mortality.

In summary, the continuous iv infusion of 50 to 100 mg/hr of cimetidine significantly reduced the occurrence rate of upper GI hemorrhage in patients who were at risk for developing stress-related gastric mucosal damage and subsequent hemorrhage with no increased risk for the development of nosocomial pneumonia during 1 wk of treatment. There are, at present, insufficient data to abandon the practice of prophylaxis against stress-induced upper GI hemorrhage in the ICU patient. On the contrary, the present results affirm the utility of this approach, regardless of initial or subsequent intragastric pH in patients who have sustained major surgery, trauma, burns, hypotension, sepsis, or organ failure. Additional studies to delineate predictors of bleeding are needed before a policy of selective prophylaxis can be applied.

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