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RISK FACTORS FOR GASTROINTESTINAL BLEEDING IN CRITICALLY ILL PATIENTS

DEBORAH J. COOK, M.D., HUGH D. FULLER, M.B., GORDON H. GUYATT, M.D., JOHN C. MARSHALL, M.D., DAVID LEASA, M.D., RICHARD HALL, M.D., TIMOTHY L. WINTON, M.D., FRANK RUTLEDGE, M.D., THOMAS J.R. TODD, M.D., PETER ROY, M.D., JACQUES LACROIX, M.D., LAUREN GRIFFITH, M.S., AND ANDREW WILLAN, PH.D., FOR THE CANADIAN CRITICAL CARE TRIALS GROUP*

Abstract *Background.* The efficacy of prophylaxis against stress ulcers in preventing gastrointestinal bleeding in critically ill patients has led to its widespread use. The side effects and cost of prophylaxis, however, necessitate targeting preventive therapy to those patients most likely to benefit.

Methods. We conducted a prospective multicenter cohort study in which we evaluated potential risk factors for stress ulceration in patients admitted to intensive care units and documented the occurrence of clinically important gastrointestinal bleeding (defined as overt bleeding in association with hemodynamic compromise or the need for blood transfusion).

Results. Of 2252 patients, 33 (1.5 percent; 95 percent confidence interval, 1.0 to 2.1 percent) had clinically important bleeding. Two strong independent risk factors for bleeding were identified: respiratory failure (odds ratio, 15.6) and coagulopathy (odds ratio, 4.3). Of 847 patients who had one or both of these risk factors, 31 (3.7 percent; 95 percent confidence interval, 2.5 to 5.2 percent) had clinically important bleeding. Of 1405 patients without these risk factors, 2 (0.1 percent; 95 percent confidence interval, 0.02 to 0.5 percent) had clinically important bleeding. The mortality rate was 48.5 percent in the group with bleeding and 9.1 percent in the group without bleeding ($P<0.001$).

Conclusions. Few critically ill patients have clinically important gastrointestinal bleeding, and therefore prophylaxis against stress ulcers can be safely withheld from critically ill patients unless they have coagulopathy or require mechanical ventilation. (N Engl J Med 1994;330: 377-81.)

GASTROINTESTINAL bleeding due to stress ulceration is an important complication in critically ill patients.[1,2] Prophylactic measures such as neutralization of gastric acid, reduction of gastric acid secretion, or cytoprotection are commonly recommended, on the basis of the positive results of randomized trials.[3-15] A recent meta-analysis reported a 50 percent reduction in the relative risk of clinically important bleeding among patients receiving prophylaxis.[16]

From the Faculty of Health Sciences, McMaster University, Hamilton, Ont. (D.J.C., H.D.F., G.H.G., L.G., A.W.); Toronto General Hospital and the University of Toronto, Toronto (J.C.M., T.L.W., T.J.R.T.); University Hospital and the University of Western Ontario, London, Ont. (D.L.); Victoria General Hospital and Dalhousie University, Halifax, N.S. (F.R.); Victoria General Hospital and the University of Western Ontario, London, Ont. (R.H., P.R.); and Hôpital Ste.-Justine and the Université de Montréal, Montreal (J.L.) — all in Canada. Address reprint requests to Dr. Cook at the Department of Medicine, Division of Critical Care, St. Joseph's Hospital, 50 Charlton Ave. E., Hamilton, ON L8N 4A6, Canada.

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*In addition to the authors, the participants in the Canadian Critical Care Trials Group were as follows: *Project Group* — H. Fuller and P. Powles, Hamilton, Ont., J. Lacroix, Montreal, J. Marshall, Toronto, T. Noseworthy, Edmonton, Alta., and L. Oppenheimer, Winnipeg, Man.; *Outcome Review Committee* — D. Cook, H. Fuller, J. Hewson, J. Lang, H. Lee, and P. Powles, Hamilton, Ont., B. Guslits, Detroit, M. Heule and T. Noseworthy, Edmonton, Alta., J. Lacroix, Montreal, and J. Marshall and T. Todd, Toronto; *Data Monitoring* — P. Powles, Hamilton, Ont.

Prophylaxis against stress ulcers, however, is expensive[17] and may have adverse effects,[18] and the risk of clinically important bleeding has decreased during the past decade independently of the use of prophylaxis.[1,19-21] We undertook this prospective study to determine the incidence of clinically important gastrointestinal bleeding in a heterogeneous group of critically ill patients and to identify patients at sufficiently low risk of bleeding to obviate the need for prophylaxis.

METHODS

Study Design

Consecutive patients more than 16 years old who were hospitalized between June 1990 and July 1991 at four university-affiliated medical–surgical intensive care units were considered for enrollment. Patients were ineligible if they had upper gastrointestinal bleeding (hematemesis, a nasogastric aspirate containing gross blood or "coffee grounds" material, hematochezia, or melena) within 48 hours before or 24 hours after admission, previous total gastrectomy, facial trauma or epistaxis, brain death, or a hopeless prognosis or if they died or were discharged within 24 hours after admission. Limited resources at three centers forced us to enroll subgroups of patients chosen by random allocation and to close enrollment on weekends during part of the study period.

We encouraged the attending physicians to withhold prophylaxis against stress ulcers in all patients[21] except those with head injury, burns over more than 30 percent of the body-surface area, organ transplants, an endoscopic or radiographic diagnosis of peptic ulcer

or gastritis in the preceding six weeks, or upper gastrointestinal bleeding three days to six weeks before admission. Prophylaxis against stress ulcers was defined as the administration of two or more doses of histamine H_2-receptor antagonists, antacids, sucralfate, prostaglandin analogues, or omeprazole.

We recorded the age, sex, admitting diagnosis, and score on the Acute Physiology and Chronic Health Evaluation (APACHE II)[22] scale of all eligible patients within 24 hours after admission. Daily evaluations included assessment for sepsis (defined as the presence of a core temperature >38.5°C [>101.3°F] or <35.0°C [<95.0°F], a white-cell count >15,000 per cubic millimeter or <3000 per cubic millimeter, and a positive blood culture); hypotension (either a systolic blood pressure <80 mm Hg for 2 hours or more or a decrease of ≥30 mm Hg in the systolic blood pressure); renal failure (a creatinine clearance rate <40 ml per minute, oliguria [<500 ml of urine per day], or a serum creatinine concentration >2.8 mg per deciliter [248 μmol per liter]); coagulopathy (a platelet count <50,000 per cubic millimeter, an International Normalized Ratio of >1.5 [i.e., prothrombin time >1.5 times the control value], or a partial-thromboplastin time >2.0 times the control value); hepatic failure (any two of the following: a serum bilirubin concentration >8.8 mg per deciliter [150 μmol per liter], a serum aspartate aminotransferase level >500 U per liter, a serum albumin level <41 g per liter, and clinical signs and symptoms of hepatic coma); the presence of a Glasgow coma score <5; administration of heparin or warfarin sodium, glucocorticoids (>200 mg of hydrocortisone or the equivalent per day), aspirin, or another nonsteroidal antiinflammatory drug; respiratory failure (a need for mechanical ventilation for at least 48 hours); the use of active enteral feeding; and the use of prophylaxis against stress ulceration (two or more doses).

The end points we studied[16,21] were overt bleeding (defined as hematemesis, gross blood or "coffee grounds" material in a nasogastric aspirate, hematochezia, or melena) and clinically important bleeding. Clinically important bleeding was defined as overt bleeding complicated by one of the following within 24 hours after the onset of bleeding (in the absence of other causes): a spontaneous decrease of more than 20 mm Hg in the systolic blood pressure; an increase of more than 20 beats per minute in the heart rate, or a decrease of more than 10 mm Hg in the systolic blood pressure measured on sitting up; or a decrease in the hemoglobin level of more than 2 g per deciliter (1.2 mmol per liter) and subsequent transfusion, after which the hemoglobin did not increase by a value defined as the number of units transfused minus 2 g per deciliter. These criteria were applied independently by three outcome adjudicators who were not involved in patient care; disagreements were resolved by repeated reviews or by a fourth adjudicator.

Statistical Analysis

We conducted a forward stepwise logistic-regression analysis of the 12 potential risk factors evaluated daily, plus the following variables: age; APACHE score; head injury; multiple trauma; receipt of a transplant; status one week or less after a cardiovascular, thoracic, abdominal, pelvic, orthopedic, neurosurgical, or peripheral vascular procedure; surface burn; peptic ulcer or gastritis within six weeks of admission to the intensive care unit; and upper gastrointestinal bleeding three days to six weeks before admission. Variables that were significantly associated ($P<0.05$) with clinically important bleeding in a simple regression analysis were entered into a multiple logistic-regression analysis and tested for interaction. The analysis was repeated for the subgroup of patients who did not receive prophylaxis. All statistical tests were two-tailed.

Results

Of the 3241 patients admitted to intensive care units during the study, 413 were ineligible. Among these 413 patients, 227 had upper gastrointestinal bleeding (77 had hematemesis, 77 had grossly bloody nasogastric aspirates, 37 had nasogastric aspirates containing "coffee grounds" material, 18 had hematochezia, and 18 had melena), 25 had previously undergone total gastrectomy, 32 had facial trauma, 6 had epistaxis, 10 were brain-dead, and 113 had a hopeless prognosis. An additional 538 patients were admitted when resources were insufficient to enroll all patients; among them 299 were admitted on a weekend. Another 38 patients died or were discharged from the intensive care unit within 24 hours after admission. The characteristics of the remaining 2252 eligible patients are shown in Table 1.

Table 1. Characteristics of 2828 Eligible Patients Admitted to an Intensive Care Unit.*

Characteristic	Enrolled (N = 2252)	Not Enrolled† (N = 576)
Age — yr	60±15	60±16
Male sex — %‡	66.4	62.7
Primary diagnosis — no. (%)§		
Cardiovascular disease	141 (6.3)	59 (10.2)
Cardiovascular surgery	1093 (48.5)	195 (33.9)
Respiratory disease	273 (12.1)	67 (11.6)
Gastrointestinal disease	221 (9.8)	68 (11.8)
Genitourinary disease	89 (4.0)	17 (3.0)
Central nervous system disease	89 (4.0)	41 (7.1)
Head injury	28 (1.2)	6 (1.0)
Multiple trauma	18 (0.8)	12 (2.1)
Sepsis	36 (1.6)	19 (3.3)
Organ transplant	108 (4.8)	44 (7.6)
Other	156 (6.9)	48 (8.3)
APACHE score	21±9	—
Length of stay (days)	5±9	—
Mortality — %	9.7	—

*Plus–minus values are means ±SD.

†A total of 538 patients were not enrolled because of limited resources; another 38 died or were discharged within 24 hours after admission.

‡$P<0.001$ for the comparison between the enrolled and the unenrolled patients.

§Because of rounding, percentages for the unenrolled patients do not total 100. $P<0.001$ for the comparison of the distribution of diseases in the two groups.

Of these 2252 patients, 674 received prophylaxis against stress ulcers. Their sex distribution and APACHE scores were similar to those of the other 1578 patients, but they were slightly younger (59 vs. 60 years, $P = 0.02$), had longer stays in the intensive care unit (eight vs. three days, $P<0.001$), and had higher mortality (16.8 percent vs. 6.7 percent, $P<0.001$). The indications for prophylaxis against stress ulcers are shown in Table 2. The prophylactic treatment was an H_2-receptor antagonist in 71.8 percent of the cases, sucralfate in 7.0 percent, antacids in 4.9 percent, a prostaglandin in 0.6 percent, omeprazole in 0.3 percent, and a combination of drugs in 15.4 percent. The median number of days of prophylaxis was as follows: H_2-receptor antagonists, 2 days; sucralfate, 3 days; antacids, 2 days; prostaglandin, 1 day; omeprazole, 1 day; and multiple agents, 10 days. Of the 23 patients who bled while receiving prophylactic treatment, 3 bled within three days, 7 between three and seven days, and 13 more than one week after prophylaxis was started.

Of the 2252 patients, 100 had overt bleeding episodes (4.4 percent; 95 percent confidence interval, 3.6 to 5.6 percent); 87 of these 100 patients were receiving

Table 2. Indications for Prophylaxis against Stress Ulcer in 674 Patients Admitted to an Intensive Care Unit.*

INDICATION	PROPHYLACTIC AGENT	
	SINGLE	MULTIPLE
No. of patients	453	221
	no. (%) of patients	
Gastrointestinal		
Previous gastrointestinal diagnosis†	59 (13.0)	44 (19.9)
Constipation	14 (3.1)	66 (29.9)
Nongastrointestinal		
Drugs‡	84 (18.5)	31 (14.0)
Prophylaxis prescribed before admission	75 (16.6)	37 (16.7)
High-risk surgery§	30 (6.6)	21 (9.5)
Head injury	3 (0.7)	1 (0.5)
Trauma	2 (0.4)	2 (0.9)
Low gastric pH	1 (0.2)	10 (4.5)
Other¶	55 (12.1)	60 (27.1)
Not specified	84 (18.5)	103 (46.6)
Treatment-related		
Current gastrointestinal symptoms‖	25 (5.5)	54 (24.4)
Overt bleeding	25 (5.5)	44 (19.9)

*Many patients had more than one indication for prophylaxis. The total number of indications was 457 among the patients given single agents and 473 among those given combination therapy.

†Previous gastrointestinal diagnoses were peptic ulcer disease and gastritis.

‡Drugs that increased the risk of bleeding included anticoagulants, glucocorticoids, aspirin, other nonsteroidal antiinflammatory drugs, and dipyridamole.

§Includes urgent surgery, reoperations, and complicated procedures.

¶Includes pulmonary hypertension, burns, possible transplantation, psychiatric problems, error, refusal by physician, patient, or family, or patient's incapacity to consent.

‖Includes heartburn and abdominal pain.

prophylaxis. Thirty-three patients had clinically important bleeding (1.5 percent; 95 percent confidence interval, 1.0 to 2.1 percent); 23 of them (69.7 percent) were receiving prophylaxis. Gastrointestinal bleeding occurred a mean (±SD) of 14±12 days after admission to the intensive care unit. The age, sex distribution, and APACHE scores were similar in the patients who had clinically important bleeding and those who did not (Table 3). The mortality rate among the patients with clinically important bleeding was 48.5 percent, as compared with 9.1 percent for all other patients ($P<0.001$) (Table 3). Agreement among the adjudicators on the presence of overt as opposed to clinically important bleeding was 81 percent after the first review and 100 percent after the second review. Agreement was 100 percent on the sources of bleeding.

Among the 33 patients with clinically important bleeding, 19 had endoscopic documentation of the site of bleeding, and the site was seen at surgery in 3 other patients. The sources of bleeding in the 22 patients in whom a cause was identified were esophageal erosions (3 patients) or gastric erosions (8 patients, 3 of whom also had esophageal erosions); esophageal (1 patient), gastric (9 patients), or duodenal (7 patients) ulcers (a total of 11 patients had ulcers); esophageal and gastric varices (1 patient); Dieulafoy's vascular anomaly (1 patient); and an ileostomy anastomosis (1 patient). No upper gastrointestinal source was identified in 11 patients. Stress ulceration was present in the stomach and esophagus in four of eight patients in whom another bleeding site was identified.

The risk factors for clinically important bleeding are shown in Table 4. The only independent risk factors identified in the multiple regression analysis were respiratory failure requiring mechanical ventilation for more than 48 hours (odds ratio, 15.6) and coagulopathy (odds ratio, 4.3). Among the 33 patients with clinically important bleeding, 22 had both respiratory failure and coagulopathy, 8 had respiratory failure alone, 1 had coagulopathy alone, and only 2 patients had neither (Table 5). These two factors were predictive both in patients receiving prophylaxis (odds ratios, 18.2 and 2.6, respectively) and in those not receiving prophylaxis (odds ratios, 8.9 and 7.7, respectively). The incidence of bleeding was 3.4 percent in the group receiving prophylaxis and 0.6 percent in the group that did not receive prophylaxis, suggesting that physicians were able to identify patients at higher risk for bleeding. That the proportion of patients who had one or more risk factors was 58.0 percent among those receiving prophylaxis and 28.9 percent among those not receiving prophylaxis supports this inference.

Of 847 patients at high risk (i.e., those who had respiratory failure or a coagulopathy), 31 had clinically important bleeding (3.7 percent; 95 percent confidence interval, 2.5 to 5.2 percent). In contrast, only 2 of 1405 patients at low risk (those with neither risk factor) had clinically important bleeding (0.1 percent; 95 percent confidence interval, 0.02 to 0.5 percent).

DISCUSSION

The incidence of clinically important bleeding was less than 2 percent among the 2252 patients in this study. In the only other study known to us that prospectively evaluated clinically important bleeding in critically ill adults, the incidence was 2.0 percent in a group of high-risk patients undergoing mechanical ventilation.[21] In addition, our results are consis-

Table 3. Characteristics of 2252 Patients Admitted to an Intensive Care Unit, According to the Presence or Absence of Clinically Important Bleeding after Admission.*

CHARACTERISTIC	BLEEDING (N = 33)	NO BLEEDING (N = 2219)
Age (yr)	62±15	60±15
Male sex (%)	66.7	66.4
APACHE score	23±9	21±8
Mortality (%)	48.5	9.1†

*Plus–minus values are means ±SD.

†$P<0.001$ for the comparison with the patients who had clinically important bleeding.

tent with the estimate of 2.6 percent derived from 27 randomized trials.[16]

The value of previous attempts to identify risk factors for bleeding caused by stress ulceration in critically ill patients was limited by their use of chart review without documentation of reproducibility[23,24] and without comparison with a control group.[25,26] Furthermore, although three prospective cohort studies[20,27,28] and six randomized trials[4,6,29-32] sought risk factors for either occult or overt bleeding, the relative risk associated with individual variables was not quantified. In only three studies in adults[20,21,28] and one in children[33] was the independent contribution of individual risk factors explored, and as in this study, the results indicated that coagulopathy[20,21,28,33] and respiratory failure[20,28,33] were associated with the risk of gastrointestinal bleeding.

The most important finding of our study is that a simple decision rule predicts the risk of bleeding and allows more selective use of prophylaxis against stress ulcers, thus avoiding the unnecessary exposure of patients to potential adverse effects. Patients who did not undergo mechanical ventilation for more than 48 hours and who had no coagulopathy, who made up 62 percent of the study group, were at extremely low risk of clinically important bleeding (0.1 percent or, at worst, 0.5 percent when the upper limit of the confidence interval is considered). Of the 1405 patients in this group, 283 (20.1 percent) received prophylaxis. A conservative estimate, based on a synthesis of the available data,[16] is that if none of these patients had received prophylaxis, twice the number of patients (or, at worst, 1 percent) might have had bleeding. If prophylaxis reduces this risk by 50 percent, one would need to administer prophylaxis to more than 900 low-risk patients to prevent one episode of bleeding.[34] These results support the view that the risk of bleeding in patients without these two risk factors is low enough that prophylaxis can be safely withheld. A decision to restrict prophylaxis to patients with at least one risk factor for bleeding would substantially reduce the use of prophylactic agents in the critically ill.

On the other hand, our results support the use of prophylaxis in the subgroup of patients in the intensive care unit who have a coagulopathy or undergo ventilation for more than 48 hours. The risk of bleeding among these patients was 3.7 percent, despite the fact that more than half received prophylactic therapy of some type. Again applying the results of the meta-analysis, which showed a reduction of approximately 50 percent in the risk of clinically important bleeding with prophylaxis,[16] and assuming that this benefit applies to all relevant subgroups, we estimate that almost twice as many of these patients would have bled if prophylaxis had been withheld, and that only about 30 high-risk patients would have to receive prophylaxis to prevent one episode of clinically important bleeding.

We think that the large heterogeneous cohort of critically ill patients that we studied, the reproducible classification of clinically important bleeding, and the precision of our estimates should provide confidence that the conclusions of this study can be applied to most critically ill patients.

Table 4. Risk Factors for Clinically Important Bleeding among 2252 Patients Admitted to an Intensive Care Unit.

Risk Factor	Simple Regression		Multiple Regression	
	Odds Ratio	P Value	Odds Ratio	P Value
Respiratory failure	25.5	<0.001	15.6	<0.001
Coagulopathy	9.5	<0.001	4.3	<0.001
Hypotension	5.0	0.03	3.7	0.08
Sepsis	7.3	<0.001	2.0	0.17
Hepatic failure	6.5	<0.001	1.6	0.27
Renal failure	4.6	<0.001	1.6	0.26
Enteral feeding	3.8	<0.001	1.0	0.99
Glucocorticoid administration	3.7	<0.001	1.5	0.26
Organ transplantation	3.6	0.006	1.5	0.42
Anticoagulant therapy	3.3	0.004	1.1	0.88

Table 5. Clinically Important Gastrointestinal Bleeding among 2252 Patients Admitted to an Intensive Care Unit, According to the Presence or Absence of Respiratory Failure and Coagulopathy.

Patient Group and Risk Factor	Bleeding	No Bleeding	Percent with Bleeding*
All patients			
Neither	2	1403	0.1
Respiratory failure	8	384	2.0
Coagulopathy	1	191	0.5
Both	22	241	8.4
Total	33	2219	1.5
Patients who received prophylaxis			
Neither	1	282	0.4
Respiratory failure	6	157	3.7
Coagulopathy	0	64	0.0
Both	16	148	9.8
Total	23	651	3.4
Patients who did not receive prophylaxis			
Neither	1	1121	0.1
Respiratory failure	2	227	0.9
Coagulopathy	1	127	0.8
Both	6	93	6.1
Total	10	1568	0.6

*The percentage of the total number of patients in each risk-factor category.

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