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Clinically significant gastrointestinal bleeding in critically ill patients with and without stress-ulcer prophylaxis

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Abstract *Objective:* To compare the rates of clinically significant gastrointestinal bleeding and the number of blood units and endoscopies required for gastrointestinal hemorrhage between patients receiving or not receiving stress-ulcer prophylaxis. *Design:* Historical observational study comparing two consecutive periods: with (phase 1) and without stress-ulcer prophylaxis (phase 2). *Design and setting:* A 17-bed intensive care unit in a university teaching hospital. *Patients:* In phase 1 there were 736 patients and in phase 2 737. Those in the two phases were comparable in age and reason for admission; clinically significant gastrointestinal bleeding rates did not differ between the two phases, but patients in phase 2 were more severely ill. *Measurements and results:* Comparable numbers of blood units were transfused per bleeding patient in the two phases, especially for patients with significant gastrointestinal bleeding. During each phase 19 fibroscopies were performed for significant bleeding, and two patients required surgery. The clinically significant gastrointestinal bleeding rate and outcome did not differ in patients with at least one risk factor. Total expenditures directly related to gastrointestinal bleeding were similar during the two phases; the total cost incurred by stress-ulcer prophylaxis was estimated at € 6700. *Conclusions:* Our results suggest that stress-ulcer prophylaxis does not influence the clinically significant gastrointestinal bleeding rate in intensive care unit patients or the cost of its management.

Keywords Stress-ulcer prophylaxis · Gastrointestinal bleeding · Intensive care · Blood transfusion · Upper gastrointestinal endoscopies · Ventilator-associated pneumonia

Introduction

During the past two decades the rate of stress-related gastrointestinal bleeding has declined in critical care probably due to improved management of acutely ill patients including prevention of mucosal hypoperfusion and enteral feeding [1, 2, 3, 4, 5]. Reported frequencies of clinically significant gastrointestinal bleeding vary from 0.6% to 6% [6, 7, 8] in absence of stress-ulcer prophylaxis and reached 1.5% in the large, prospective, multicenter cohort study conducted by Cook and colleagues [9]. Two independent risk factors for bleeding were identified in that study: acute respiratory failure requiring mechanical ventilation for more than 48 h and coagulopathy [9]. The same group [10] showed that for patients requiring mechanical ventilation, renal failure, absence of enteral nutrition, and absence of stress-ulcer prophylaxis with H_2-receptor antagonists were independently associated with an increased risk of clinically significant gastrointestinal bleeding. However, Lam and colleagues [11] underlined the lack of rationale for stress-ulcer prophylaxis use in routine practice among

North American clinicians. Moreover, unnecessary stress-ulcer prophylaxis could erode the economic benefit of preventing gastrointestinal bleeding [12, 13].

Despite conflicting results concerning the outcome of and need for surgery in patients with clinically significant gastrointestinal bleeding among meta-analyses conducted during the past decade [8, 14, 15, 16, 17, 18, 19] both H_2-receptor antagonists and sucralfate are still recommended for stress-ulcer prophylaxis [8, 14, 18]. Moreover, no recent study has compared active prophylaxis with a placebo group [19]. Likewise, controversy persists concerning the possible relationship between H_2-receptor antagonists or sucralfate use and increased risk of ventilator-associated pneumonia [20, 21, 22]. Most side effects attributed to sucralfate are minor but occur in as many as 15% of patients, and sucralfate is known to reduce absorption and bioavailability of many drugs [23]. Moreover, sucralfate is not recommended in conjunction with enteral nutrition because of the risk of bezoar, and patients with impaired gastric motility due to disease or surgery may be at increased risk of bezoar formation.

The aim of our study was to determine the impact of the systematic use or nonuse of stress-ulcer prophylaxis on the frequencies and management of gastrointestinal bleeding.

Patients and methods

Design

We conducted a historical, observational study comparing two consecutive periods: 15 months with stress-ulcer prophylaxis (phase 1) followed by 15 months without prophylaxis (phase 2). During phase 1 stress-ulcer prophylaxis was systematically given according to the recommendations of the Stress-Ulcer Prophylaxis Consensus Committee organized by the Société de Réanimation de Langue Française [24]. Phase 2 was carried out in agreement with the Therapeutic and Pharmacy Committee of our hospital. Major endpoints were: occurrence of clinically significant gastrointestinal bleeding, blood units required for gastrointestinal hemorrhage, and endoscopies performed for suspected or recurrent gastrointestinal bleeding. Gastrointestinal hemorrhage rates in patients with risk factors for clinically significant gastrointestinal bleeding (prolonged mechanical ventilation, coagulopathy or acute renal failure as defined by Cook and colleagues [9]) were also analyzed. Because of the observational and retrospective design of our study no local institutional review board authorization was needed according to the French Bioethics Law.

Patients

The charts of all patients admitted to the medical intensive care unit (ICU) of Boucicaut Hospital were analyzed retrospectively over a 30-month period (phase 1 from January 1996 to March 1997; phase 2 from April 1997 to June 1998). Patients admitted for gastrointestinal bleeding were excluded from the analysis. A total of 1514 admissions were analyzed: 761 in phase 1 and 753 in phase 2. Twenty-five patients in phase 1 and 16 in phase 2 were excluded from the analysis because of gastrointestinal hemorrhage at the time of ICU admission. Finally, 1473 patients (736 in phase 1 and 737 in phase 2) were eligible for analysis. Characteristics of patients in the two phases are summarized in Table 1. As indicated by their higher Simplified Acute Physiology Score II (SAPS II), phase 2 patients were more severely ill at ICU admission than phase 1 patients. A slightly higher percentage of medical patients had hematological failure during phase 2 [1.6% (95% CI: 0.7–2.5) vs. 0.7% (95% CI: 0.1–1.3), n.s.]. Surgical ICU admissions differed significantly only for cervical interventions between phases 1 and 2. Mechanical ventilation was required by 283 phase 1 patients and 326 phase 2 patients [38% (95% CI: 34–42) vs. 44% (95% CI: 40–48), $p=0.02$]. Prolonged mechanical ventilation (>48 h) and acute renal failure occurred more frequently in phase 2 than phase 1 patients [284/737, 39% (95% CI: 35–43) vs. 228/736, 31% (95% CI: 28–34), $p=0.002$, and 116/737, 16% (95% CI: 13–19) vs. 85/736, 11% (95% CI: 9–13), $p=0.02$, respectively]. Coagulopathy affected 90 phase 1 patients [12% (95% CI: 10–14)] and 115 phase 2 patients [16% (95% CI: 13–19)].

Table 1 Characteristics of patients with and without stress-ulcer prophylaxis (*parentheses* 95% CI)

	Prophylaxis (n=736)	No prophylaxis (n=737)
Age (years)	58±21 (57–59)	58±20 (56–59)
SAPS II at ICU admission	31±19 (30–32)*	33±22 (31–35)
Sex (%)		
Male	49 (45–53)	51 (47–55)
Female	51 (47–55)	49 (45–53)
Medical ICU admission (%)	93 (91–95)	94 (92–96)
Acute respiratory failure	40 (36–43)	44 (40–48)
Cardiovascular failure	16 (13–19)	18 (15–21)
Drug overdose	21 (18–24)	18 (15–21)
Neurological failure	7 (5–9)	7 (5–9)
Metabolic disorders	7 (5–9)	6 (4–8)
Other	2 (1–3)	1 (0–2)
Surgical ICU admission (%)	7 (5–9)	6 (4–8)
Obstetric	0.8 (−1 to +3)	2.3 (1–3)
Trauma	1.3 (0–2)	2.7 (1–4)
Cervical	4.9 (3–6)*	1 (0–2)

*$p<0.05$ vs. no prophylaxis

Intervention

During phase 1 stress-ulcer prophylaxis was systematically administered to all patients admitted to our ICU. Prophylaxis consisted of oral sucralfate (1 g, four times daily ;*n*=700,) or ranitidine (150 mg, twice daily, intravenous bolus; *n*=36), when sucralfate was contraindicated or when enteral administration was not possible. Sucralfate was administrated on an empty stomach: 1 h before meals in conscious patients and 1 h after stopping the tube feeding in unconscious patients nourished via a nasogastric tube. Enteral nutrition was restarted 1 h after sucralfate administration. Sucralfate in suspension (1 g/5 ml) was diluted in 45 ml sterile water and administered orally or via a nasogastric tube. No stress-ulcer prophylaxis was given during phase 2.

Enteral nutrition was started as soon as possible for all patients during both phases. It required a functional gastrointestinal tract and hemodynamic stability in patients who had been admitted for shock. Caloric intake was progressively increased over few days to reach the theoretical energy expenditure estimated by the corrected Harris and Benedic's equations. In our Department enteral nutrition was provided exclusively via a nasogastric tube and the gastric position of the tube was checked systematically by radiography before the onset of feeding. When enteral nutrition was not possible or was contraindicated, parenteral nutrition was administered (20 patients during phase 1, 2.7%; 25 patients during phase 2, 3.3%).

Gastrointestinal bleeding

Overt gastrointestinal bleeding and clinically significant gastrointestinal bleeding were defined according to the criteria retained by Cook and colleagues [9, 14]. Presence of hematemesis, bloody gastric aspirate, or melena defined overt gastrointestinal bleeding. Clinically significant gastrointestinal bleeding was defined as the association of overt gastrointestinal bleeding with one of the following criteria: (a) blood pressure drop of 20 mmHg or (b) blood pressure drop of 10 mmHg and heart rate increase of 20 beats/min upon change in the orthostatic position, and (c) hemoglobin level decrease in 20 g/l and transfusion of 2 U blood.

Management of clinically significant gastrointestinal bleeding during phases 1 and 2

When clinically significant gastrointestinal bleeding occurred, units of packed red blood cells were transfused as required (hemoglobin level <70 g/l or occurrence of shock). Transfusions were carried out to maintain hemoglobin values between 70 and 90 g/l according to the restrictive transfusion strategy proposed by Hebert and colleagues [25]. Gastrointestinal endoscopy was systematically performed within 24 h of hemodynamic stabilization to identify the origin of hemorrhage and to stop it when possible. In the case of recurrent bleeding, the same procedure was repeated. Medical treatment included omeprazole (40 mg, four times daily, intravenous bolus) and correction of coagulopathy, when needed. Surgery was required when medical treatment, and iterative endoscopies were unable to stop clinically significant gastrointestinal bleeding.

Extradigestive blood loss during phases 1 and 2

A cause other than gastrointestinal hemorrhage was considered to be confirmed when the origin of bleeding was clearly recognized. When hemoglobin concentrations fell below 70 g/l and the cause of the extradigestive blood loss remained unidentified, bleeding was considered as probable. The transfusion strategy for extradigestive blood loss was the same as that used for gastrointestinal bleeding.

Data collected

We recorded age, sex, type of admission diagnosis (medical or surgical), and the SARS II calculated 24 h after ICU admission according to Le Gall and colleagues [26], length of ICU stay, ICU outcome, presence of acute renal failure (creatinine clearance <40 ml/min, oliguria <500 ml/day or plasma creatinine concentration >250 μmol/l), coagulopathy as defined by Cook and colleagues [9], and invasive mechanical ventilation lasting longer than 48 h. We also recorded overt gastrointestinal bleeding or clinically significant gastrointestinal bleeding, the number of blood units, the number of endoscopies performed for gastrointestinal hemorrhage during the ICU stay, the occurrence of ventilator-associated pneumonia, and complications attributable to stress-ulcer prophylaxis (bezoar, drug interactions, thrombocytopenia, liver dysfunction, atrioventricular block) [23, 27]. Ventilator-associated pneumonia was diagnosed according to the following criteria [22]: new and persistent infiltrates on chest radiography associated with fever above 38.3°C, leukocyte count higher than 12×10^9/ml, or purulent tracheobronchial secretions, and identification of micro-organisms grown from bacteriological sample (positive blood culture or pleural fluid culture, quantitative cultures of protected specimen brush with >10^3 colony forming units/ml or bronchoalveolar lavage with >10^4 colony forming units/ml).

Statistical analyses

Statistical analyses were performed using StatView 4.5 software (Abacus Concept, Berkeley, Calif., USA). Results are expressed as means±standard deviation and 95% confidence intervals (CI) or as percentages and 95% CI. Between-group comparisons were made between their 95% CI. The Mann-Whitney *U* test was used because of the nonnormal distribution of quantitative variables. The χ^2 test with Yate's correction (or bilateral Fisher's test when required) was used for comparison of categorical variables. A difference was considered significant when the α risk was less than 5% (*p*<0.05).

Results

Frequencies and causes of bleeding

Comparing phases 1 and 2, rates of overt gastrointestinal bleeding (14/736 and 12/737, respectively) and clinically significant gastrointestinal bleeding (10/736 and 8/737, respectively) did not differ significantly (Table 2). SAPS II at ICU admission did not differ significantly between phase 1 and phase 2 patients who experienced clinically significant gastrointestinal bleeding [56±20 (95% CI: 44–68) vs. 52±19 (95% CI: 39–65)]. However, patients with clinically significant gastrointestinal bleeding had significantly higher SAPS II at ICU admission than those without gastrointestinal hemorrhage in phase 1 [56±20 (95% CI: 44–68) vs. 30±19 (95% CI: 29–31), *p*=0.0001] and phase 2 [52±19 (95% CI: 39–65) vs. 33±22 (95% CI: 31–35), *p*=0.005]). Confirmed extradigestive hemorrhages were significantly more frequent during phase 2 (*p*=0.0001) than phase 1 while the frequency of probable extradigestive blood loss did not differ between phases (Table 2).

Table 2 Incidence of gastrointestinal bleeding and causes of extradigestive blood loss in patients with and without stress-ulcer prophylaxis: percentages (*parentheses* 95% CI)

*p<0.0001 vs. no prophylaxis

Cause of bleeding	Prophylaxis (*n*=736)	No prophylaxis (*n*=737)
Overt gastrointestinal bleeding	1.9 (0.9–2.9)	1.6 (0.7–2.5)
Clinically significant gastrointestinal bleeding	1.4 (1.5–2.2)	1.1 (0.3–1.8)
Confirmed extradigestive bleeding	4.6 (3.1–6.1)*	9 (7–11)
Probable extradigestive blood loss	2.2 (1.2–3.2)	3 (1.8–4.2)

Table 3 Blood units transfused in patients with and without stress-ulcer prophylaxis. No differences were statistically significant (*parentheses* 95% CI)

Reason for transfusion	Prophylaxis (*n*=736)	No prophylaxis (*n*=737)
Overall transfusion		
Number of patients	60	96
Total number of blood units transfused	292	461
Blood units transfused per patient	5±3 (4–6)	5±7 (3–6)
Clinically significant gastrointestinal bleeding		
Number of patients	10	8
Total number of blood units transfused	69	93
Blood units transfused per patient	7±3 (5–9)	12±17 (0–24)
Confirmed extradigestive bleeding		
Number of patients	34	66
Total number of blood units transfused	159	303
Blood units transfused per patient	5±3 (4–6)	5±5 (3–6)
Probable extradigestive blood loss		
Number of patients	16	22
Total number of blood units transfused	64	65
Blood units transfused per patient	4±3 (3–5)	2±1 (2–3)

Blood transfusions

No significant differences concerning blood transfusion were observed for patients who experienced clinically significant gastrointestinal bleeding in phases 1 and 2 (Table 3). However, the higher overall number of transfusions during phase 2 [96/737, 13% (95% CI: 11–15) vs. 60/736, 8% (95% CI: 6–10) during phase 1, *p*=0.003], suggests that more of these patients required blood transfusion for extradigestive bleeding (Table 3). Pertinently, the total number of blood units used and number of blood units transfused per patient did not differ significantly between the two phases regardless of the cause of bleeding (Table 3).

Endoscopies and surgery to diagnose and control gastrointestinal bleeding

During each phase 19 endoscopies were performed for gastrointestinal bleeding, and two patients required surgery.

Ventilator-associated pneumonia and stress-ulcer prophylaxis-related complications

Thirty-four episodes of ventilator-associated pneumonia developed in 283 mechanically ventilated phase 1 patients and 55 in 326 ventilated phase 2 patients [12% (95% CI: 8–16) vs. 17% (95% CI: 13–21), n.s.). No complication attributed to stress-ulcer prophylaxis was diagnosed during phase 1.

Outcome

Overall ICU mortality [88/736 phase 1 patients, 12% (95% CI: 10–14) vs. 96/737 phase 2 patients, 13% (95% CI: 11–15)] and length of ICU stay [8±9 days (95% CI: 7–9) vs. 8±12 days (95% CI: 7–9), respectively] were similar in phases 1 and 2. In patients with clinically significant gastrointestinal bleeding, ICU mortality [9/10, 90% (95% CI: 88–92) during phase 1 vs. 6/8, 75% (95% CI: 71–79) during phase 2] and length of ICU stay [22±15 days (95% CI: 13–31) vs. 34±35 days (95% CI: 10–59)] were also comparable. ICU mortality was higher in patients with clinically significant gastrointestinal bleeding than those without gastrointestinal hemorrhage

Table 4 Characteristics, frequencies of clinically significant gastrointestinal bleeding (*CSGB*) and outcome of patients with risk factors for bleeding treated with and without stress-ulcer prophylaxis (*parentheses* 95% CI)

Risk factors for CSGB	Prophylaxis (*n*=736)	No prophylaxis (*n*=737)
MV >48 h		
Number of patients	228*	284
Age (years)	65±17 (63–68)	65±18 (63–67)
SAPS II	43±19 (41–46)	46±20 (44–48)
CSGB (%)	4.4 (2–7)	2.8 (1–5)
Length of ICU stay (days)	13±12 (11–15)	14±18 (12–16)
ICU mortality (%)	32 (26–38)	32 (27–37)
Coagulopathy		
Number of patients	90*	115
Age (years)	62±20 (58–66)	64±18 (61–67)
SAPS II	42±24 (37–47)	47±27 (42–52)
CSGB (%)	5.5 (1–10)	3.5 (0–7)
Length of ICU stay (days)	9±7 (7–10)	11±19 (9–15)
ICU mortality (%)	31 (21–40)	32 (23–40)
Acute renal failure		
Number of patients	85*	116
Age (years)	70±17 (66–74)	69±17 (66–72)
SAPS II	53±25 (47–58)	57±18 (54–60)
CSGB (%)	3.5 (0–7)	3.4 (0–7)
Length of ICU stay (days)	8±6 (6–9)	11±15 (8–14)
ICU mortality (%)	43 (32–53)	56 (47–65)
MV >48 h + coagulopathy		
Number of patients	50*	77
Age (years)	61±18 (56–66)	66±16 (63–70)
SAPS II	52±26 (45–59)	55±28 (49–61)
CSGB (%)	10 (7–12)	4 (0–8)
Length of ICU stay (days)	9±8 (6–12)	15±22 (10–20)
ICU mortality (%)	46 (39–53)	45 (34–56)
MV >48 h +coagulopathy + acute renal failure		
Number of patients	20*	42
Age (years)	65±18 (57–73)	66±16 (61–71)
SAPS II	71±27 (60–83)	68±28 (60–77)
CSGB (%)	10 (−3 to +23)	7 (−1 to +15)
Length of ICU stay (days)	7±6 (5–10)	14±20 (8–20)
ICU mortality (%)	85 (69–100)	69 (55–83)

*$p<0.05$ vs. no prophylaxis

in phases 1 and 2 [9/10, 90% (95% CI: 88–92) vs. 79/726, 11% (95% CI: 9–13), $p<0.0001$; and 6/8, 75% (95% CI: 71–79) vs. 90/729, 12% (95% CI: 10–14); $p<0.0001$, respectively].

Patients with high-risk factors for gastrointestinal bleeding

When the analysis was restricted to patients with at least one risk factor for clinically significant gastrointestinal bleeding (prolonged mechanical ventilation, coagulopathy, or acute renal failure) in each stress-ulcer prophylaxis subgroup, the clinically significant gastrointestinal bleeding rates and ICU outcomes did not differ significantly between phases 1 and 2 for any parameter assessed (Table 4).

Costs due to stress-ulcer prophylaxis and gastrointestinal bleeding

We calculated the expenditures required by stress-ulcer prophylaxis use in our patients (cost of daily administration of sucralfate or ranitidine ×length of ICU stay) and costs directly associated with clinically significant gastrointestinal bleeding management (medical treatments, blood units, transfusions and endoscopies). During phase 1 the total stress-ulcer prophylaxis cost was € 6,800, and total expenditures directly incurred by clinically significant gastrointestinal bleeding were € 17,100 (total 23,900 or 1,710 per patient) while the latter cost was € 17,200 (2,150 per patient) during phase 2. Thus the higher cost associated with stress-ulcer prophylaxis was estimated to be € 6,700 (23,900–17,200) during phase 1.

Discussion

This historical observational study comparing two periods with and without stress-ulcer prophylaxis found that prevention of gastrointestinal bleeding had no significant impact on the clinically significant gastrointestinal bleeding rate and outcomes of patients admitted to a medical ICU. Within a few hours after their admission most critically ill patients have gastrointestinal mucosal erosions and subepithelial hemorrhage [9, 20, 28, 29]. It has been shown that stress-ulcer prophylaxis decreases the rate of upper gastrointestinal ulceration [30]. However these lesions have a wide spectrum of clinical presentations, including occult, overt gastrointestinal bleeding, and clinically significant gastrointestinal bleeding. Clinically significant gastrointestinal hemorrhage is defined as decreased hemodynamic performance and/or requirement of blood transfusions or surgery [18]. To be useful, prophylaxis of stress-ulcer hemorrhage should affect the clinical outcome of the ICU patients. It has been shown that clinically significant gastrointestinal bleeding is associated with increased ICU morbidity and mortality [9]. In our study, mortality among patients who experienced clinically significant gastrointestinal bleeding was six or seven times higher than that for the overall ICU population. However, the significantly higher SAPS II at ICU admission of patients with clinically significant gastrointestinal bleeding, regardless of the phase, suggests that the higher mortality rate of patients with significant gastrointestinal hemorrhage results in most cases from their primary disease and not directly from the gastrointestinal bleeding [7, 9, 31]. We observed a clinically significant gastrointestinal bleeding rate less than 1.5% with or without stress-ulcer prophylaxis. Cook et al. [9] for the Canadian Critical Care Trials Group reported an incidence of clinically significant gastrointestinal bleeding less than 2% in 2,252 ICU patients. These authors showed that coagulopathy and prolonged respiratory failure (especially when associated with acute renal failure) were risk factors for gastrointestinal bleeding. They suggested that prophylaxis against stress-related gastrointestinal bleeding should be reserved for ICU patients with such risk factors [8, 9, 10]. Moreover, according to their model of stress-ulcer prophylaxis cost-effectiveness analysis, Ben-Menachem and colleagues [12] showed that the prevention cost was prohibitive for patients at low risk for gastrointestinal bleeding, and they pointed out the low efficacy of prophylaxis in patients with risk factors. Erstad and colleagues [32] conducted a prospective study on 543 patients and reported that clinically significant gastrointestinal bleeding rates were similar for patients with risk factor(s) for bleeding receiving inappropriate stress-ulcer prophylaxis and those with appropriate prevention. In agreement with these data, we found that the absence of prophylaxis did not modify the clinically significant gastrointestinal bleeding rate for patients with risk factors as defined by Cook et al. [9, 10], thus putting in doubt the usefulness of stress-ulcer prophylaxis in these patients.

Based on their prospective cohort of 183 patients receiving prolonged mechanical ventilation Zandstra and Stoutenbeek [2] reported gastrointestinal bleeding in fewer than 1% of 167 patients without stress-ulcer prophylaxis on admission to the ICU. All patients included in that study received aggressive fluids resuscitation and catecholamines for shock, infection prevention with selective decontamination of the digestive tract, stress-ulcer prophylaxis, and suppression of generalized inflammation with corticosteroids and vasodilatators to improve gastrointestinal microcirculation, suggesting that stress-ulcer bleeding is a part of the multiple organ failure syndrome [33]. Indeed, prolonged hypoxemia of gastrointestinal tissues could be involved in the pathophysiology of this syndrome [33]. During the past two decades improved microcirculation and tissue oxygenation in critically ill patients have led at least in part to a dramatically lower clinically significant gastrointestinal bleeding rates [4, 14]. These data suggest that routine stress-ulcer prophylaxis for critically ill patients should be reconsidered. We did not systematically use selective digestive decontamination or administer corticosteroids or vasodilatators to enhance the gastrointestinal microcirculation. We used simple standardized procedures of care for all patients admitted to our ICU. Among these procedures, early enteral feeding could play a major role in the preventive strategy of gastrointestinal bleeding [10, 33]. In a retrospective analysis, Raff and colleagues [34] demonstrated that early (within 12 h posttrauma) enteral nutrition was at least as effective as H_2-receptor antagonists and/or antacids as stress-ulcer prophylaxis in a cohort of 526 severely burned patients. However, a recent meta-analysis of prospective randomized trials of early vs. late enteral nutrition in critically ill patients showed that early feeding decreased only infectious complications and length of stay [35]. These results must be interpreted with caution because of the wide heterogeneity among selected studies. More generally, conclusions drawn based on prospective studies evaluating the role of enteral feeding as stress-ulcer prophylaxis are limited by their poor design [36]. Protective effects of enteral feeding may involve direct mechanisms of cytoprotection of the gastrointestinal mucosa and alkalinization of gastric juices [10, 36, 37]. Pertinently, parenteral nutrition alone could be effective as stress-ulcer prophylaxis [38]. Finally, our results suggest that standard care procedures for stress-related gastrointestinal hemorrhage prevention are as effective as sucralfate or H_2-blockers, even for patients with risk factors for bleeding.

We established that the absence of stress-ulcer prophylaxis did not affect the need for blood units, endoscopies, or surgery in patients who experienced clinically significant gastrointestinal bleeding or the ICU length of

stay and ICU mortality. Clinically significant gastrointestinal bleeding is associated with prolonged hospital stay and increased costs, but the latter are usually consequences of the primary disease [31, 32]. Direct comparisons of costs incurred by clinically significant gastrointestinal bleeding management between patients with and without stress-ulcer prophylaxis are lacking in the literature. Our cost analysis suggests that the absence of stress-ulcer prophylaxis does not increase the total costs engendered by gastrointestinal bleeding. Prophylaxis with H_2-blockers raising gastric pH might increase the risk of nosocomial pneumonia and affect costs and outcome [18]. However, the real risk of nosocomial pneumonia attributable to stress-ulcer prophylaxis with pH-altering drugs remains controversial [18, 22, 39, 40]. In a multicenter randomized trial Cook and colleagues [8] found no difference between the ventilator-associated pneumonia rates in patients treated with H_2-blockers and those who received sucralfate, but these rates were lower than would be expected a priori, thereby suggesting that this study lacked statistical power. Including the latter study, Messori and colleagues [19] conducted a meta-analysis to evaluate the incidence of nosocomial pneumonia with ranitidine vs. sucralfalte and reported that ranitidine might increase the risk. More recently the results of the French ARDS Study Group's nonrandomized prospective multicenter study showed sucralfate use to be significantly associated with an increased risk of ventilator-associated pneumonia during acute respiratory distress syndrome [41]. However, the respective potential advantages of sucralfate and absence of prophylaxis remain unclear [22]. Stress-ulcer prophylaxis had no effect on the ventilator-associated pneumonia rate in our study.

The major limitation of our study is its retrospective design: cointerventions were not noted, and caution is needed before generalizing our results to nonmedical ICU patients or to other stress-ulcer prophylaxis regimens. Prospective observational studies with large patient populations are a valid alternative in situations in which randomized controlled trials are unethical or too difficult to perform [42, 43]. In light of the dramatically declining incidence of stress-ulcer bleeding over the past two decades in the ICU, the unclear effects of stress-ulcer prophylaxis on outcome or need of surgery, and the possible stress-ulcer prophylaxis-related side effects it became necessary to analyze the impact of prophylaxis. We therefore decided to suspend stress-ulcer prophylaxis in accordance with the Therapeutic and Pharmacy Committee of our hospital. Another limitation of our study is the disease-severity bias, as patients without stress-ulcer prophylaxis (phase 2) were more severely ill than those given prophylaxis, and it cannot be excluded that the more aggressive therapy to improve gastrointestinal mucosa microcirculation could be responsible. The higher SAPS II at ICU admission during the period without prophylaxis and study design also could explain in part the concomitant increased rate of confirmed extradigestive bleeding. The reasons for ICU admission were slightly modified between the two study periods: more obstetric, trauma, and hematological patients were admitted during phase 2 while the number of patients admitted after cervical surgery decreased. This modification could suggest that more severe hemorrhagic episodes occurred in patients who experienced clinically significant gastrointestinal bleeding or confirmed extradigestive bleeding during phase 2.

In summary, our results suggest that stress-ulcer prophylaxis does not significantly influence the risk of clinically significant gastrointestinal bleeding in ICU patients, even in those with risk factor(s) for bleeding, and its withdrawal does not induce cost overrun in the management of clinically significant gastrointestinal bleeding. Our findings must be confirmed in different populations of ICU patients and/or by using different prophylactic regimens.

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