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Implementation of a clinical practice guideline for stress ulcer prophylaxis increases appropriateness and decreases cost of care

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Abstract *Objective:* To develop, implement and evaluate a practice guideline for stress ulcer prophylaxis.
Design: Before-after study.
Setting: Ten-bed Intensive Care Unit (ICU) and 4-bed Step-down Unit in a teaching hospital.
Patients and participants: Fifty patients admitted during 1 year before and 50 patients admitted 3–6 months after introduction of the guideline.
Intervention: Introduction of the practice guideline by dissemination of pocket cards, seminars and 'academic detailing'.
Measurements and results: Appropriateness (defined as proportion of days in which the prophylaxis met the criteria in the guideline), incidence of gastrointestinal bleeding and of ventilator-associated pneumonia, length of stay in ICU and in hospital, ventilator days, ICU mortality and medication costs for stress ulcer prophylaxis. After the introduction of the guideline, appropriateness increased from 75.8% to 91.1%, and medication costs decreased from C$2.50/day to C$1.30/day. There were no differences in any clinical outcomes. Predictors of appropriate use or the withholding of prophylaxis were the introduction of the guideline, lack of an indication for prophylaxis and number of days studied.
Conclusions: Introduction of this guideline was associated with an increase in appropriateness of prophylaxis and a decrease in medication costs.

Key words Stress ulcer prophylaxis · Practice guideline · Critical care medicine

Introduction

The incidence of stress-related gastric ulceration in critically ill patients has diminished in recent years, independent of the use of prophylaxis [1–8]. In a recent prospective multi-center cohort study, clinically important stress ulceration (as defined by significant gastrointestinal bleeding) was found in fewer than 2% of patients overall, but in 3.7% of patients who were at increased risk [9]. Although stress ulceration does not contribute to overall mortality [10], it portends a poor outcome [11] because complications of this problem are important contributors to morbidity [6, 12]. Stress ulcer prophylaxis is therefore recommended for critically ill patients [9, 13].

The efficacy of various strategies to prevent bleeding related to stress ulceration has been assessed in a large number of studies, but many of these studies have an inadequate sample size to detect a significant difference in outcome or they differ in definitions of gastrointestinal bleeding [14]. Systematic reviews of the literature have, therefore, been published to clarify the effect of stress ulcer prophylaxis [6, 14–18], but these have produced inconsistent results [13]. A recent systematic review of prospective trials has shown that the risk of overt bleeding can be reduced by 42% and of clinically important

bleeding by 56% with histamine$_2$-receptor antagonists compared to placebo or no therapy [13]. The histamine$_2$-receptor antagonists are superior to antacids, and sucralfate is as effective as antacids and histamine$_2$-receptor antagonists in preventing clinically significant bleeding related to stress ulceration [13]. In addition, the incidence of nosocomial pneumonia is lower in patients who receive sucralfate compared to those who receive histamine$_2$-receptor antagonists [13].

The use of stress ulcer prophylaxis is widely accepted in the Intensive Care Unit (ICU) in our hospital, a 500-bed-tertiary-care teaching hospital in Vancouver, British Columbia, Canada. Based on the reviewed evidence of efficacy of prophylaxis [13, 14, 17, 18] and the identification of patients at high risk for development of clinically significant stress ulceration [9], we developed and implemented a clinical practice guideline for stress ulcer prophylaxis in our ICU. We hypothesized that implementation of this guideline would increase the appropriate use of stress ulcer prophylaxis (based on the criteria in the guideline) and would decrease related medication costs. Further, to study and improve the effect of our implementation strategy, we determined predictors of appropriate use of stress ulcer prophylaxis. Although we also measured clinical outcomes, our main hypothesis did not address these outcomes because clinical trials have already addressed this issue. This study was primarily an evaluation of change in clinical practice and medication use due to a practice guideline program.

Materials and methods

Development and implementation of the clinical practice guideline

This guideline was developed by a multi-disciplinary committee of intensivists, two of whom have expertise in critical appraisal of clinical trials, housestaff and a clinical pharmacist. The mandate of this committee was to identify groups at risk of stress ulceration, determine the preferred approach to prophylaxis, consider exceptions to this preference and to articulate areas of controversy which may be subjects for future research. A literature search using Medline was undertaken to identify systematic reviews on the subject of stress ulcer prophylaxis. The committee appraised these publications, determined appropriate indications for, and preferred form of, prophylaxis and developed a 'seed' guideline. This guideline was then reviewed by ICU medical staff, housestaff, nurses and pharmacists, and feedback from this review was used to develop the final guideline.

The final guideline recommended that prophylaxis should be considered for all critically ill patients at risk for stress ulceration (Fig. 1). The risk factors identified were those found to be significantly associated with stress ulcer-related bleeding in a prospective multi-center cohort study [9]. These included respiratory failure with anticipated need for mechanical ventilation for more than 48 h and coagulopathy (international normalized ratio greater than 1.5 and/or partial thromboplastin time greater than twice normal) not related to anticoagulant therapy. Other indications that have been accepted [2, 9] include head injury, burns over more than 30% of the body surface area, organ transplant recipient, endoscopic or radiographic diagnosis of peptic ulcer or gastritis in the preceding 6 weeks and upper gastrointestinal bleeding 3 days–6 weeks prior to admission. Prolonged hypotension, characterized by a systolic blood pressure less than 80 mm Hg or a 30 mm Hg decline from usual premorbid systolic blood pressure for an individual patient (where known) for at least 2 h, was also considered an indication for prophylaxis, based on the expert opinion of attending intensivists in our ICU.

Based on the systematic reviews of clinical trials in this area [13, 14, 17, 18], the guideline recommended using sucralfate if there was access to the stomach and endoscopy was not planned in the near future. If access to the stomach was not available or endoscopy was planned, intravenous ranitidine was recommended (Fig. 1). Medications were administered as follows: sucralfate 1 g enterally every 6 h; ranitidine 50 mg by intravenous bolus every 8 h (dose adjusted as warranted by renal failure).

A role for enteral nutrition in preventing clinically significant stress ulceration has been postulated in experimental and uncontrolled clinical studies [19–26]. However, the evidence in this area is not clear and there was no consensus among the guideline committee members and staff physicians regarding stress ulcer prophylaxis in patients who are being fed. Therefore, either continuation or discontinuation of prophylaxis in patients who were enterally fed was considered appropriate in this guideline.

The guideline was implemented by dissemination and 'academic detailing' within the ten-bed ICU and four-bed step-down unit. Specifically, laminated pocket cards were distributed to housestaff and attending staff, a copy of the guideline was provided at every bedside, the guideline was included in the housestaff orientation manual, educational sessions to housestaff on this topic were provided with each rotation and a clinical pharmacist was present on daily rounds to remind prescribing physicians about the guideline.

Evaluation of the clinical practice guideline

Appropriate use of stress ulcer prophylaxis, relevant clinical outcomes and medication costs were assessed using a time-series design. A chart review was carried out of 50 patients selected at random who were admitted to the ICU during 1 year before introduction of the guideline and of 50 patients selected at random who were admitted to the ICU from 3 to 6 months after introduction. Each patient was evaluated for a maximum of 10 days from the date of admission to ICU. Each chart was reviewed by the same reviewer (S.P.). Patient descriptors included age, gender, APACHE II score [27] and admission diagnosis. Appropriateness was measured as the proportion of days studied during which stress ulcer prophylaxis was administered or withheld according to the recommendations of the guideline. Clinical outcomes that were assessed included length of stay in the ICU and in hospital, number of days ventilated, ICU mortality, incidence of gastrointestinal bleeding and incidence of ventilator-associated pneumonia.

Gastrointestinal bleeding was based on the definition of Cook and colleagues [9] as one or more of hematemesis or frankly bloody gastric aspirate, coffee ground emesis or gastric aspirate, hematochezia or melena. Overt and clinically significant gastrointestinal bleeding were not differentiated. Ventilator-associated pneumonia was determined on clinical grounds, based on the criteria of Salata and colleagues [28]. Specifically, the diagnosis was based on the presence of a new or progressive infiltrate on chest radiograph without other obvious source, in addition to 1) pleural fluid or blood cultures positive for the same organism isolated from the tracheal aspirate, or radiographic cavitation or histo-

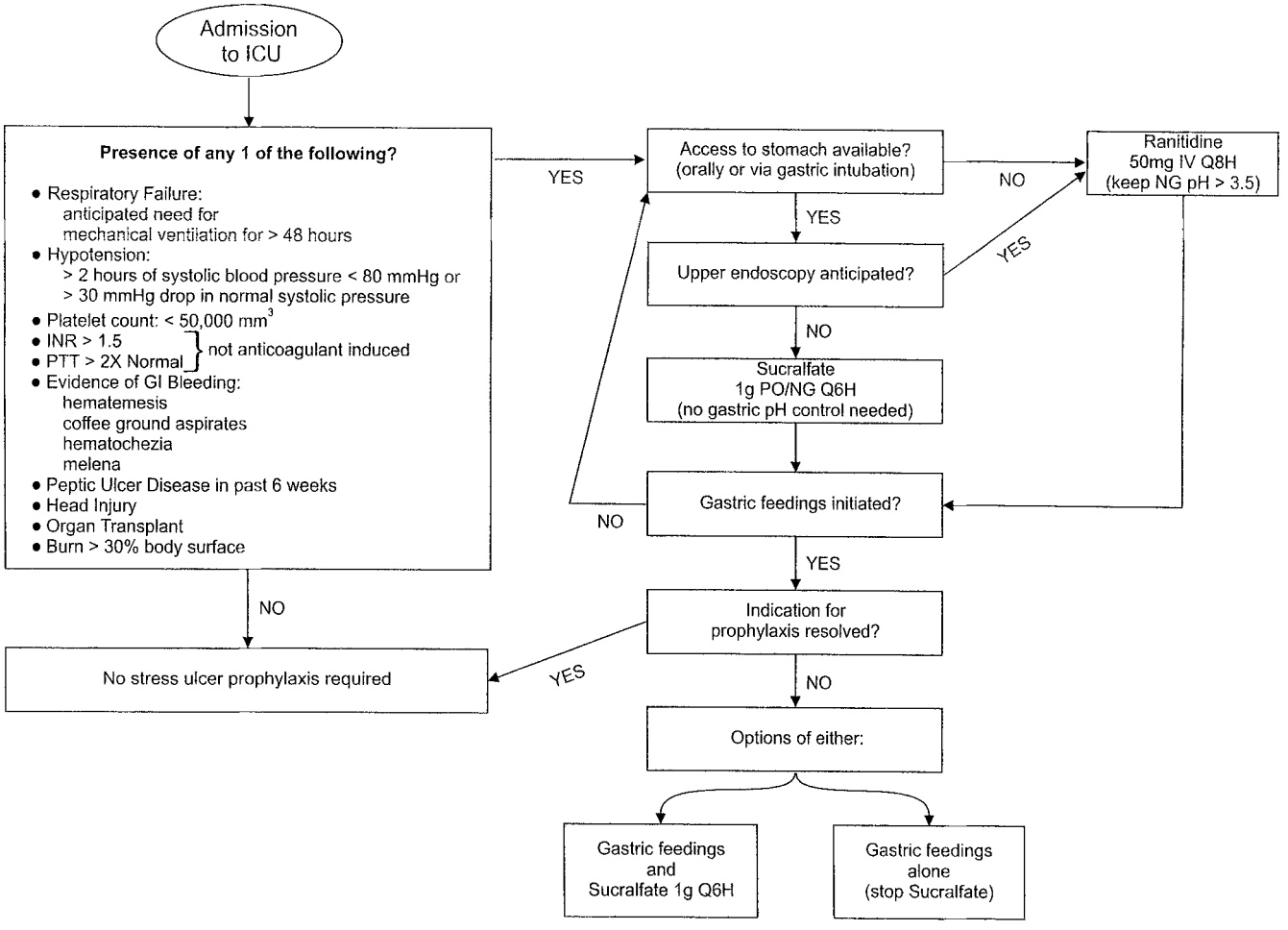

Fig. 1 Algorithm version of the practice guideline for stress ulcer prophylaxis (*INR* international normalized ratio, *PTT* partial thromboplastin time, *PO* by mouth, *NG* nasogastric)

pathologic evidence of pneumonia or 2) at least two of: tracheal aspirates with at least 25 polymorphonuclear leukocytes per high power field; new leukocytosis (more than 10×10^9 cells/l) with an increase of at least 25% over baseline; temperature more than 38.5 °C with increase of at least 1 °C over baseline [28]. The presence of a new or progressive infiltrate on chest radiograph was based on the radiologist's report in the chart.

Costs were calculated in 1995 Canadian dollars from the perspective of the hospital pharmacy. For injectable medications (ranitidine), the costs included each dose administered as well as the syringe used. Enteral medications are usually administered via nasogastric tube using a syringe which can be reused for administration of other medications. Hence, the material cost of enteral administration was not considered. The costs related to the preparation of drug, delivery and related administrative costs were not considered, as these represent fixed costs for the pharmacy that are unchanged by prescription of stress ulcer prophylaxis or the type prophylaxis used. The costs of drugs were as follows: ranitidine 50 mg intravenous C$1.743 per dose plus C$0.063 per syringe for a total of C$5.42 per day at 50 mg every 8 h; ranitidine enterally C$10.26 per 3-day prescription, and sucralfate enterally C$5.60 per 3-day prescription. Enterally administered medication is supplied in prescription form by the pharmacy sufficient for 3 days dosing; any unused drug from this allotment is discarded. Thus the cost of each prescription for enteral medications was used, regardless of the number of doses administered.

The intervention in this study was no different from an accepted practice and the evaluation consisted only of chart review. Therefore, no informed consent was required.

Statistical analysis

Since the proportion of appropriateness was not known before development of the guideline and the primary hypothesis was not based on a difference in clinical outcomes, the sample size was based on convenience. Outcomes before and after introduction of the guideline were compared using a Mann-Whitney U test (for median length of stay and median number of days ventilated) or a two-sample chi-square test of proportions (for appropriate days, ICU mortality, gastrointestinal bleeding and ventilator-associated pneumonia). Average daily drug costs were compared using a Student's *t*-test for two independent samples. Factors felt to be potentially predictive of the appropriate use of stress ulcer prophylaxis were selected by the investigators. Initial analysis of the selected variables was carried out using chi-square and Student's *t*-tests. To investigate the effect of introducing the guideline and the effect of time on appropriateness of prophylaxis, forward stepwise logistic regression [29] was undertaken. All statistical tests were two-tailed and the level of statistical significance used was 0.05.

Table 1 Baseline characteristics of patient cohorts before and after implementation of clinical practice guidelines

Characteristic	Before implementation	After implementation
Number in group	50	50
Gender (% male)	62	58
Median age	62.5	60
Median APACHE II score	15	15.5
Admitting diagnosis:		
Acute respiratory failure	14	20
Sepsis	3	9
Pneumonia	6	4
Cardiac failure	3	2
Acute neurologic event[a]	8	3
Overdose	8	4
Trauma	4	3
Gastrointestinal bleed	1	1
Hepatic or renal failure	1	2
Other[b]	2	1

[a] Acute neurologic event = cerebrovascular accident, cerebral tumor, depressed level of consciousness of uncertain etiology and head injury

[b] Other = drowning/hypothermia, epiglottitis and post-cardiac arrest

Table 2 Comparison of outcomes in patient cohorts before and after implementation of clinical practice guideline

Characteristic	Before implementation	After implementation
Median length of ICU stay (days)	3	5
Median length of hospital stay (days)	12	14
Median number of days ventilated	2	2
ICU mortality (%)	28	20
Gastrointestinal bleeding (%)	2	2
Ventilator-associated pneumonia (%)	8	6

There were no significant differences between groups

Results

The practice guideline was introduced in the ICU on March 6, 1995. Before and after introduction of the guideline, 217 and 271 ICU days, respectively, were studied in two groups of 50 patients. Characteristics of the patients in each group were similar (Table 1). The proportion of days during which stress ulcer prophylaxis was administered or withheld appropriately, according to the guideline, increased from 75.8% (95% confidence intervals (CI) 63.9%–87.7%) in the year before introduction of the guideline to 91.1% (95% CI 83.2%–99.0%) in the 6 months after introduction ($p < 0.001$).

Before introduction of the guideline, five prescriptions of sucralfate were filled for a total of 9 days of therapy. Ranitidine was given on 64 days, on 58 days by the intravenous route and on 6 days enterally. Five prescriptions for enteral ranitidine were filled. After introduction of the guideline, 20 prescriptions of sucralfate were filled for a total of 42 days of therapy. Ranitidine was given on 36 days, mostly by the intravenous route (33 days). Three prescriptions for enteral ranitidine were filled.

There were no differences in clinical outcomes between the groups. The median length of stay in ICU and in hospital and median number of days ventilated was similar in the two groups (Table 2). Mortality in ICU was 28% before introduction of the guideline and 20% afterwards ($p > 0.10$; Table 2). Overt gastrointestinal bleeding occurred in one patient (2%) in each group and was not associated with death in either instance (Table 2). Ventilator-associated pneumonia developed in 8% of patients in the group before introduction of the guideline and in 6% of patients afterwards ($p > 0.10$; Table 2).

Total actual costs for stress ulcer prophylaxis (medications and administration) in these cohorts were C$393.66 before introduction of the guideline and C$321.64 afterwards; this difference is an 18% decrease in total costs. The average daily cost of stress ulcer prophylaxis in the year before and 6 months after introduction of the guideline was C$2.50 ± 2.96 and C$1.30 ± 1.80, respectively (mean ± SD, $p < 0.01$).

Data from 99 patients were available for analysis of predictors associated with appropriateness of stress ulcer prophylaxis. The following variables were considered: gender, age, APACHE II score, length of ICU stay, duration of mechanical ventilation, introduction of the guideline, presence of an indication for stress ulcer prophylaxis according to the guideline, respiratory failure (as an indication), combination of access to the gastrointestinal tract and administration of enteral feeds, and number of days studied. Univariate analysis showed that APACHE II score, ICU length of stay and presence of an indication for stress ulcer prophylaxis were related to appropriateness (data not shown). Subsequently, a logistic regression model was developed to predict the probability of appropriate use of the guideline using the same set of variables. Applying forwards stepwise regression, we found that the introduction of the guideline was a significant predictor of appropriateness (odds ratio 3.37; 95% CI 2.04, 5.55; $p = 0.0001$). After adjusting for introduction of the guideline, analysis showed that the number of days studied ($p = 0.0001$) and absence of an indication for prophylaxis ($p = 0.0015$) were also positively associated with appropriateness (odds ratios of 2.57 (95% CI 1.44, 4.60) and 1.34 (95% CI 1.19, 1.49) respectively; Figures 2 and 3).

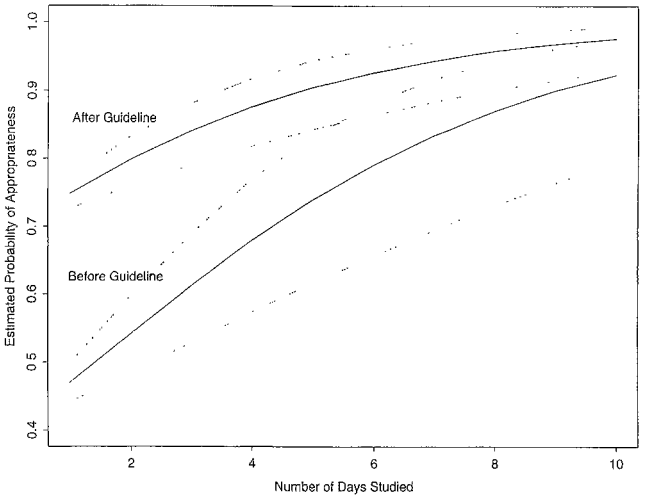

Fig. 2 Relationship between number of days studied and probability of appropriateness of stress ulcer prophylaxis in patients who had a clinical indication for stress ulcer prophylaxis, before and after introduction of the guideline. Probability of appropriateness of prophylaxis increased after introduction of the guideline. After adjusting for introduction of the guideline, probability of appropriateness increased over the duration of ICU stay (*solid line:* point estimates; *dotted lines:* 95% confidence intervals)

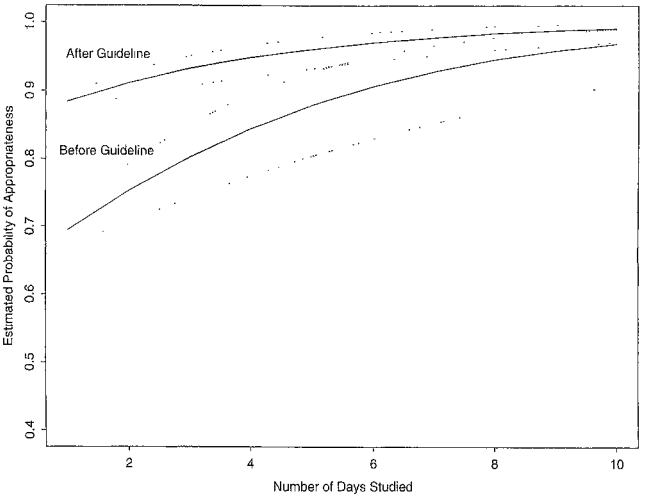

Fig. 3 Relationship between number of days studied and probability of appropriateness of stress ulcer prophylaxis in patients who did *not* have a clinical indication for stress ulcer prophylaxis, before and after introduction of the guideline. Probability of appropriateness of prophylaxis increased after introduction of the guideline. After adjusting for introduction of the guideline, probability of appropriateness increased over the duration of ICU stay (*solid line:* point estimates; *dotted lines:* 95% confidence intervals)

Discussion

Clinical practice guidelines are "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" [30]. Systematic reviews of available evidence support the use of stress ulcer prophylaxis in appropriate circumstances [13, 14, 17, 18]. Based on these systematic reviews, we developed and implemented a practice guideline for this intervention in our ICU. Our evaluation of this guideline shows that introduction of the guideline increases the appropriate use of prophylaxis (based on the criteria in the guideline) and reduces related medication costs without affecting clinical outcomes.

The patients in this study were similar in severity of illness and spectrum of diagnoses to other ICU populations, implying the generalizability of these results. There was no change in length of stay, mortality, incidence of gastrointestinal bleeding or incidence of ventilator-associated pneumonia. Although ICU length of stay has been reduced through the introduction of other guidelines [31], our study was not designed to detect a difference in clinical outcomes related to the use of stress ulcer prophylaxis and, therefore, our sample size is probably inadequate to detect a difference in any one of these outcomes.

Sucralfate was selected as the preferred form of stress ulcer prophylaxis for several reasons. First, sucralfate has no influence on the pH of the stomach [18, 32, 33] and may have antibacterial properties [34, 35]. Its use has been associated with a lower incidence of gastric colonization and a significantly lower incidence of pneumonia than other forms of prophylaxis which increase gastric pH [18, 32, 33]. A recent meta-analysis has also shown a trend toward a lower rate of pneumonia with sucralfate compared with antacids or histamine$_2$-receptor antagonists [13]. However, it is not known whether sucralfate differs from placebo or no therapy in this regard. Second, sucralfate may be associated with reduced mortality compared with histamine$_2$-receptor antagonists and antacids [13]. Thirdly, its use has also been linked to a decrease in the risk of detection of *Clostridium difficile* cytotoxin b in the stools of patients who have diarrhea [36]. Finally, using standard prophylactic doses, sucralfate is less expensive than ranitidine, the most commonly used alternative in our institution.

Both total and average daily mediation costs related to stress ulcer prophylaxis decreased after the introduction of this guideline. The primary reasons for this decrease were an increase in the use of sucralfate, a simultaneous reduction in the use of ranitidine and more appropriate withholding of prophylaxis where it was not indicated. Average daily costs decreased by 48% from C$2.50 to C$1.31 after the introduction of the guideline. While this absolute figure is small, based on a median length of stay in ICU of 5 days and an average of 600 ICU admissions per year, we calculate a savings to our pharmacy of at least C$3570 each year. If this guideline was implemented successfully in the 416 ICU beds throughout the province of British Columbia (population 3 million), based on a median length of ICU stay

of 5 days, potential savings would be at least C$106,000 per year.

Average daily drug costs reflect drug costs on a daily basis distributed throughout the duration of ICU stay and may be more useful for comparative purposes than total costs. However, average daily costs are significantly altered by the denominator figure, the number of days studied. Hence, the reduction in average daily costs is due in part to the greater number of days studied after the introduction of the guideline (271 versus 217 before introduction). Presumably there were more days during the follow-up period than during the baseline period, when patients were being fed by the enteral route and were not receiving any prophylaxis. Therefore, no costs for prophylaxis were incurred during those days. Nevertheless, total medication costs also decreased by 18% over the period of study.

Predictors of the appropriate use of stress ulcer prophylaxis (according to the criteria in the guideline) included introduction of the guideline, lack of an indication for prophylaxis and the number of days studied. These findings mean that patients were more likely to be treated according to the guideline after the guideline was publicized, or if they had no indication for prophylaxis, or if they were further into their ICU stay, at a time when they were more likely to be receiving enteral nutrition. Before and after introduction of the guideline, the proportion of appropriate days was least during the first 48 h after admission to ICU but increased after the first 48 h (Figs. 2 and 3). This time effect is probably due to the general preference in our ICU to begin enteral feeding as soon as possible after admission. Once enteral feeding has begun, either continuing or discontinuing prophylaxis is considered appropriate. This time effect also implies that the greatest opportunity to improve the appropriateness of prophylaxis is early in the course of ICU stay. This finding has led to more intensive interaction with prescribing physicians immediately after admission to ICU.

The strategy we used to facilitate implementation was based on 'academic detailing' [37]. The effectiveness of such an approach in altering physician behavior has been documented [38]; dissemination of information alone is insufficient to improve practice [38]. In settings where such a strategy is not feasible, it is possible that the same results would not occur. Nevertheless, the use of a locally-developed strategy involving interventions such as 'academic detailing', influence of local opinion leaders, audit, feedback and reminders, or a combination of these techniques, has been shown to produce at least a moderate effect on practice [38, 39].

One limitation of this study is the relatively short period of evaluation after introduction of the guideline. It will be important to assess the sustainability of the changes induced and to explore the effect of alterations to the implementation strategy. In addition to decreased application of the recommendations in the guideline due to a return to previous practice habits, any change in the relative cost of different prophylaxis regimens could have a significant impact on implementation. However, our current strategies to facilitate implementation are part of daily operations in our ICU and the difference in medication costs is unlikely to change in the near future. Therefore, we would expect the change in practice that we observed to be sustained over time.

A second limitation of this study is that it was a program evaluation conducted in a time-series design and not a prospective, randomized trial. Therefore some of the changes that we observed could be due to secular trends unrelated to introduction of the guideline. However, we were unaware of any other changes in patient profiles, practice patterns or administrative constraints during the period of this study that might explain our findings.

A third limitation of this study is the limited perspective of the economic evaluation. We have not included the costs of nasogastric tubes (although these tubes are placed not just for the administration of sucralfate), the costs of fixing or replacing blocked nasogastric tubes, the costs of complications of either medication, or the costs of gastrointestinal bleeding or of ventilator-associated pneumonia. However, the incidence of gastrointestinal bleeding or pneumonia was not different between the two groups. Therefore, we would not expect any difference in these unmeasured costs. Nevertheless, a more rigorous approach to cost inferences would require a broader economic perspective than has been used in this study.

In summary, we have demonstrated that the development and implementation of a clinical practice guideline for stress ulcer prophylaxis in an ICU increases the appropriateness of stress ulcer prophylaxis without changing clinical outcomes. At the same time, the costs of stress ulcer prophylaxis decrease as a consequence of more appropriate use (and withholding) of stress ulcer prophylaxis and the increased use of sucralfate as the preferred agent for prophylaxis. Predictors of appropriate use of the guideline include introduction of the guideline, lack of an indication for prophylaxis and the number of days studied.

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