should—be guided by recent guidelines, such as Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis checklist (11) for developing, validating, and justifying new algorithms as decision support tools. We note, however, that common metrics to evaluate continuous predictive models such as area under the receiver (AUC), sensitivity, specificity, predictive accuracies, and so on do not necessarily translate into bottom line effect in clinical practice. For example, heart rate characteristics monitoring for neonatal sepsis has a modest AUC and yet allowed more than 20% relative reduction in mortality in a large randomized controlled trial (12). And, of course, it also may be true that a test with high AUC may result in no useful effect on clinical practice.

The optimism of forward-thinkers like Eric Topol (@EricTopol) is contagious, justifiably so. For sure, clinical decision support from computerized algorithms will more and more be a part of our daily practice. Just as a certain generation of clinical cardiologists looks back in awe at how technology has improved our practice in the past 30 years, future healthcare providers may wonder how one ever made do without modern decision support tools .

But it still comes down to standing next to one patient at a time today, and the sinking feeling that you are missing something. Let's look forward to apps for that, ones that were made the right way.

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Is A Diagnosis of Sepsis Sufficient to Warrant Stress Ulcer Prophylaxis?*

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***See also p. e464.**

Key Words: prophylaxis; sepsis; stress; ulcer

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The use of stress ulcer prophylaxis is common in the ICU. Although it is commonly accepted that a subset of critically ill patients is at risk for stress-related mucosal damage (1), the prevalence of clinically important bleeding in the ICU is quite low (1–4). Well-established indications for stress ulcer prophylaxis in the ICU include mechanical ventilation for at least 2 days and coagulopathy (5). Other risk factors that have been implicated as being potentially associated with clinically important bleeding include sepsis, ICU stay longer than 1 week, occult bleeding lasting longer than 6 days, use of high-dose corticosteroids, and history of gastrointestinal bleeding or ulceration within the previous year (2).

The evidence for routine use of stress ulcer prophylaxis for patients who are not ventilated or coagulopathic is mixed, at best, and is limited by a lack of high-quality studies. The Surviving Sepsis Guidelines recommend the use of stress ulcer prophylaxis for patients with severe sepsis or septic shock who have risk factors for bleeding (defined as "coagulopathy, mechanical ventilation for 48 hours, possibly hypotension") but also suggests that patients without risk factors not receive prophylaxis (6).

In this issue of *Critical Care Medicine*, Sasabuchi et al (7) examined the risks and benefits of stress ulcer prophylaxis in adult patients with sepsis (previously referred to as severe sepsis) from a database of over 1,000 hospitals in Japan. After excluding patients with a history of peptic ulcer disease or death, discharge, gastrointestinal bleeding, or anticoagulant or antiplatelet drugs within 2 days of admission, the authors analyzed over 70,000 patients, of whom 44% received stress ulcer prophylaxis within 2 days of admission. The results demonstrate a low prevalence of gastrointestinal bleeding requiring endoscopic hemostasis of between 0.4% and 0.6%. Because the patients receiving stress ulcer prophylaxis were sicker at baseline, the authors identified a propensity score–matched cohort of 15,651 patients who received stress ulcer prophylaxis and a control group who did not. No significant differences in the prevalence of gastrointestinal bleeding requiring endoscopic hemostasis were identified between the groups. Furthermore, important secondary endpoints of 30-day mortality and *Clostridium difficile* infection were similar regardless of whether patients received stress ulcer prophylaxis. Notably, there was a small but statistically significant increase in the prevalence of hospital-acquired pneumonia in the stress ulcer prophylaxis group.

The study has a number of strengths. The number of patients analyzed is extremely large. The methods were meticulous, and the authors performed numerous subgroup analyses that strengthen their findings. Because the database used is drawn from a population representing half of all discharges from acute care hospitals in Japan, the data represent a wide variety of practice types and are likely representative of a "real-world" mix of patients with sepsis.

There are, however, inherent limitations of drawing conclusions from a retrospective database analysis. Although the authors did their best to match patients, there is no information about severity of disease (Acute Physiology and Chronic Health Evaluation II score, Sequential Organ Failure Assessment score), so that there may be differences in patient acuity despite propensity score matching. In addition, it is worth questioning how representative the patient population is of all patients with sepsis. Patients were generally healthy (more than half had no comorbidities) and had body mass index (BMI) that were lower than are seen in many countries (< 15% of patients had a BMI over 25, compared with over 65% of patients in the United States).

Notably, in the propensity score–matched cohort, less than 15% of patients were admitted to the ICU. There was no difference in gastrointestinal bleeding in patients on stress ulcer prophylaxis in the ICU, nor was there a difference in infections. However, perhaps unexpectedly, there was a significant increase in 30-day mortality in the control group compared with the stress ulcer prophylaxis group. The reason for this increased mortality is unclear, and it is difficult to draw firm conclusions from the subgroup analysis of ICU patients where stress ulcer prophylaxis did not prevent gastrointestinal bleeding yet was associated with decreased mortality.

Criteria for ICU admission vary widely between different countries. In fact, 25% of patients in this study were on mechanical ventilation and 45% were on vasopressor or inotrope therapy. This suggests that patients managed on the floor in Japan may look more like ICU patients in other portions of the world. Nonetheless, unlike the ICU subgroup where mortality was decreased in patients on stress ulcer prophylaxis, the authors found no evidence of benefit of stress ulcer prophylaxis on the hospital wards, and, if anything, there was a question of harm because this was associated with a slight increase in hospital acquired pneumonia. This suggests that in the absence of other risk factors, stress ulcer prophylaxis does not need to be prescribed for the majority of patients with sepsis if they are not sick enough to be in the ICU.

It is notable that the prevalence of bleeding requiring endoscopic hemostasis was quite low in this study, occurring in approximately one out of every 200 patients, a finding that has a significant face validity. However, although sepsis is not necessarily considered an indication for stress ulcer prophylaxis unless other risk factors are present, nearly half of all patients received prophylaxis within 2 days of admission to the hospital. This appeared somewhat related to known risk factors, but perhaps not as closely as might have been predicted. For example, of over 20,000 patients on mechanical ventilation identified, 65% were on stress ulcer prophylaxis whereas 35% were not.

Whenever choosing to prescribe any medication, it is important to assess the risk to benefit ratio. Unfortunately, both benefit and risk are frequently unclear with stress ulcer prophylaxis in acutely ill patients. The data supporting prophylaxis usage outside of a few targeted patient populations are scarce. At the same time, data suggesting potential harm are conflicting and not conclusive although stress ulcer prophylaxis has been linked to infectious complications such as hospital-acquired pneumonia, as seen in this study, and *C. difficile* infection (8).

Given the potential risks and increasing reports of overuse of stress ulcer prophylaxis (9), an important effort has been made to decrease its inappropriate use in hospitalized patients (10, 11). Successful strategies include a pharmacist-managed program and an educational program in addition to a pharmacist-managed program. As demonstrated by Sasabuchi et al (7), the general population of sepsis patients (at least on the hospital floor) likely do not benefit from stress ulcer prophylaxis. This, in turn, yields an opportunity to assure that prophylaxis is given when significant risk factors are present but appropriate stewardship is performed to prevent prescribing unnecessary, costly, and potentially harmful agents without a clear indication.

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Will the GlideScope Soar in the Prehospital Environment?*

The machine does not isolate man from the great problems of nature, but plunges him more deeply into them. –Antoine de Saint-Exupery

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The past decade has inarguably been witness to some of the most rapid and innovative (or "disruptive" in Silicon Valley lingo) technological advances in the history of mankind. The field of medicine has been no exception to this trend, which can be expected to continue to advance at an exponential pace. Although the many benefits of technological adjuncts in medicine are well described, there are also unique concerns and questions that must be anticipated, understood, and addressed. The introduction of new technology or devices for clinical use involves far fewer regulatory hurdles and evidentiary requirements when compared with the introduction of a new pharmaceutical. Although this allows for more rapid development and deployment of potentially beneficial devices, there is also a very real possibility for failure of the technology to produce a benefit, or to actually cause harm. There is also a danger of extrapolating results from early use of a technology by a select group of experts under very controlled conditions, to what will be obtained with mainstream adoption. Similar to the lay public, physicians can be categorized as "early adopters," "mainstreamers," or "late adopters" when it comes to new technologies, and radically different results may be obtained by each group. As critical care providers, we are generally well trained and versed in the use of cutting-edge medical technologies and may be more likely to be among the "early adopter" or "mainstream" categories. Thus, it is incumbent upon us to understand the unique issues and potentially harmful problems associated with adopting new technologies and to proceed with the same evidence-based standards that we require of any therapeutic intervention.

Advanced airway management is one technique-focused area of emergency and critical care that is ideal for technological innovation. It is a high-stakes procedure that involves manual dexterity and a complex set of physical maneuvers, requires specialized equipment and training, and has little margin for error or failure. Despite this, the techniques and equipment for performing direct laryngoscopy (DL) and intubation have remained relatively unchanged for decades. In 2001, the first commercially available video laryngoscopy system, the GlideScope (Verathon Inc., Bothell, WA), was introduced. The touted advantages of the GlideScope included a shape and curvature designed to provide better direct visualization of the glottis, as well as a built-in camera that projects a high-resolution image of the visualized anatomy to an attached monitor. Over the subsequent 15 years of experience, there has been a large volume of high-quality evidence comparing video laryngoscopy with DL in settings including the operating room, emergency department, ICU, and with manikins or other simulators. These series have also included a wide variety of personnel with varying degrees of airway experience, from novices to experts. Although there have been some variation among results, the

***See also p. e470.**

Key Words: airway management; direct laryngoscopy; GlideScope; intubation; technology; video laryngoscopy

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Risks and Benefits of Stress Ulcer Prophylaxis for Patients With Severe Sepsis*

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Objectives: The Surviving Sepsis Campaign Guidelines recommend stress ulcer prophylaxis for patients with severe sepsis who have bleeding risks. Although sepsis has been considered as a risk factor for gastrointestinal bleeding, the effect of stress ulcer prophylaxis has not been studied in patients with severe sepsis. Furthermore, stress ulcer prophylaxis may be associated with an increased risk of hospital-acquired pneumonia or *Clostridium difficile* infection. The aim of this study was to investigate the risks and benefits of stress ulcer prophylaxis for patients with severe sepsis.

Design: Retrospective cohort study.

Setting: Five hundred twenty-six acute care hospitals in Japan.

Patients: A total of 70,862 patients with severe sepsis.

Interventions: None.

Measurements and Main Results: One-to-one propensity score matching created 15,651 pairs of patients who received stress ulcer prophylaxis within 2 days of admission and those who did not. Patient characteristics were well balanced between the two groups. No significant differences were seen between the stress ulcer prophylaxis group and the control group with regard to gastrointestinal bleeding requiring endoscopic hemostasis (0.6% vs 0.5%; $p = 0.208$), 30-day mortality (16.4% vs 16.9%; $p = 0.249$), and *Clostridium difficile* infection (1.4% vs 1.3%; $p = 0.588$). The stress ulcer prophylaxis group had a significantly higher proportion of hospital-acquired pneumonia (3.9% vs 3.3%; $p = 0.012$) compared with the control group.

Conclusions: Since the rate of gastrointestinal bleeding requiring endoscopic hemostasis is not different comparing patients with and without stress ulcer prophylaxis, and the increase in hospital-acquired pneumonia is significant, routine stress ulcer prophylaxis for patients with severe sepsis may be unnecessary. (*Crit Care Med* 2016; 44:e464–e469)

Key Words: *Clostridium difficile* infection; gastrointestinal bleeding; hospital-acquired pneumonia; severe sepsis; stress ulcer prophylaxis

The prevalence of severe sepsis is increasing (1–4) and becoming a major healthcare problem. The mortality associated with severe sepsis has been reported as high as 30% (5–7). Gastrointestinal bleeding is one of the most serious complications in patients with severe sepsis. The reported incidence varies widely from 1.1% to 9.2% (8, 9), because of different definitions used in the studies. Furthermore, clinically significant gastrointestinal bleeding has been reported to be associated with a 1–4 times increased risk of death in critically ill patients (10).

The Surviving Sepsis Campaign Guidelines (11) were introduced in 2004 and have been revised periodically. In the latest version (12), stress ulcer prophylaxis is recommended for patients with a risk of bleeding. Although sepsis itself has been considered as a risk factor for gastrointestinal bleeding (13, 14), few studies have investigated the effects of stress ulcer prophylaxis specifically in patients with severe sepsis and the recommendation is based on evidence from the general population in an ICU (15, 16). Furthermore, stress ulcer prophylaxis may be associated with an increased risk of ventilator-associated pneumonia (17) or *Clostridium difficile* (*C. difficile*) infection (18).

The aim of this study was to investigate the risks and benefits of stress ulcer prophylaxis in patients with severe sepsis, using a national inpatient database in Japan.

*See also p. 1450.

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This study was performed at the University of Tokyo, Tokyo, Japan.

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MATERIALS AND METHODS

The Institutional Review Board of the University of Tokyo approved this study. Informed consent was waived because of the anonymous nature of the data.

Data Source

Data for this study were extracted from the Japanese Diagnosis Procedure Combination database (19, 20). The database has been used extensively for clinical epidemiology research (21, 22). The Diagnosis Procedure Combination is a case-mix inpatient classification system for acute care hospitals linked to healthcare reimbursement in Japan. More than 1,000 hospitals voluntarily participate in the Diagnosis Procedure Combination system. The database includes data from approximately 7 million inpatients per year, which represents approximately 50% of all discharges from acute care hospitals, and includes hospital identification number, patient age, gender, diagnosis (coded with the *International Classification of Diseases*, 10th revision [ICD-10], codes and text in the Japanese language), dates of hospital admission and discharge, and discharge status. Admission-precipitating diagnosis, preexisting comorbidities at admission, and post-admission complications during hospitalization are separately recorded. Dates of procedures performed and medications or blood products prescribed are also included.

Case Definition

We included all patients with a diagnosis of severe sepsis at admission between July 2010 and March 2013. Severe sepsis was defined as sepsis with failure of at least one organ system. Previous studies estimated the epidemiology of severe sepsis based on ICD-9 Clinical Modification and ICD-10 Australian Modification, using administrative databases (7, 23) In this study, the presence of sepsis was defined as patients who have any bacterial or fungal infection in the admission-precipitating diagnosis using ICD-10 codes used in the previous study (7, 23) (listed in **Supplemental Table S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B742). To detect a diagnosis of organ dysfunction, ICD-10 codes (7, 23) and Japanese procedure codes listed in **Supplemental Table S2** (Supplemental Digital Content 2, http://links.lww.com/CCM/B743) were extracted. We excluded patients who 1) were younger than 20 years, 2) had a history of peptic ulcer disease, 3) received sucralfate within 2 days of admission (because a previous study showed that sucralfate decreased the incidence of stress ulcers compared with placebo (24)), 4) died within 2 days of admission (because these patients may have died before they received stress ulcer prophylaxis), 5) had gastrointestinal bleeding within 2 days (because these patients were likely to receive proton pump inhibitors or H2 blockers not for prophylaxis, but for treatment of gastrointestinal bleeding), 6) were discharged within 2 days, or 7) received anticoagulant or antiplatelet drug within 2 days of admission.

Study Variables

The exposure of interest was whether patients received stress ulcer prophylaxis. Patients who received proton pump inhibitors or histamine H2 receptor antagonists within 2 days of admission were defined as the stress ulcer prophylaxis group. Patients who did not receive any of these medications within 2 days of admission were defined as the control group. Other variables included age, gender, body mass index, treatment year, whether patients were transferred to the hospitals by ambulance, academic medical center, and average annual hospital volume of patients with severe sepsis. The hospital volume of patients with severe sepsis was defined as the average number of patients with severe sepsis who were admitted to each hospital annually. We identified the following procedures within 2 days of admission: institution of mechanical ventilation, renal replacement therapy, catecholamine administration, and enteral nutrition. Whether patients received blood products within 2 days and whether patients were admitted to the ICU within 2 days were also extracted. The Charlson comorbidity index was calculated using algorithms developed by Quan et al (25).

Outcome Measures

Assessed outcomes included gastrointestinal bleeding requiring endoscopic hemostasis within 30 days of admission; death within 30 days; and pneumonia and *C. difficile* infection acquired during hospitalization, which were coded as complications during hospitalization.

Subgroup Analyses

We performed subgroup analyses for the subgroups with and without 1) ICU admission within 2 days, 2) mechanical ventilation within 2 days, 3) vasopressor or inotropes within 2 days, 4) renal replacement therapy within 2 days, 5) enteral nutrition, 6) failure of two or more organ systems, 7) failure of three or more organ systems, and 8) diabetes mellitus. In addition, patients who received only H2 blockers within 2 days of admission were compared with those who received only proton pump inhibitors within 2 days of admission.

Sensitivity Analyses

We performed two sensitivity analyses. First, patients who received heparin within 2 days of admission were included in the main analysis. However, IV and subcutaneous heparin cannot be differentiated because of a lack of these data in the database. For sensitivity analysis, we excluded patients who received heparin within 2 days of admission. Second, because the procedure code for endoscopic hemostasis in the database cannot differentiate hemostasis for upper and lower gastrointestinal bleeding, patients who received endoscopic hemostasis might possibly have had lower gastrointestinal bleeding. We therefore performed another sensitivity analysis for patients with a confirmed diagnosis of gastrointestinal bleeding as well as a receipt of endoscopic hemostasis.

Statistical Analyses

Continuous variables are presented as the average with the SD and the median with the interquartile range. Categorical variables are presented as the number with a percentage. To account for differences in baseline characteristics between patients who did and did not receive stress ulcer prophylaxis, propensity score analyses were conducted. To account for the clustering

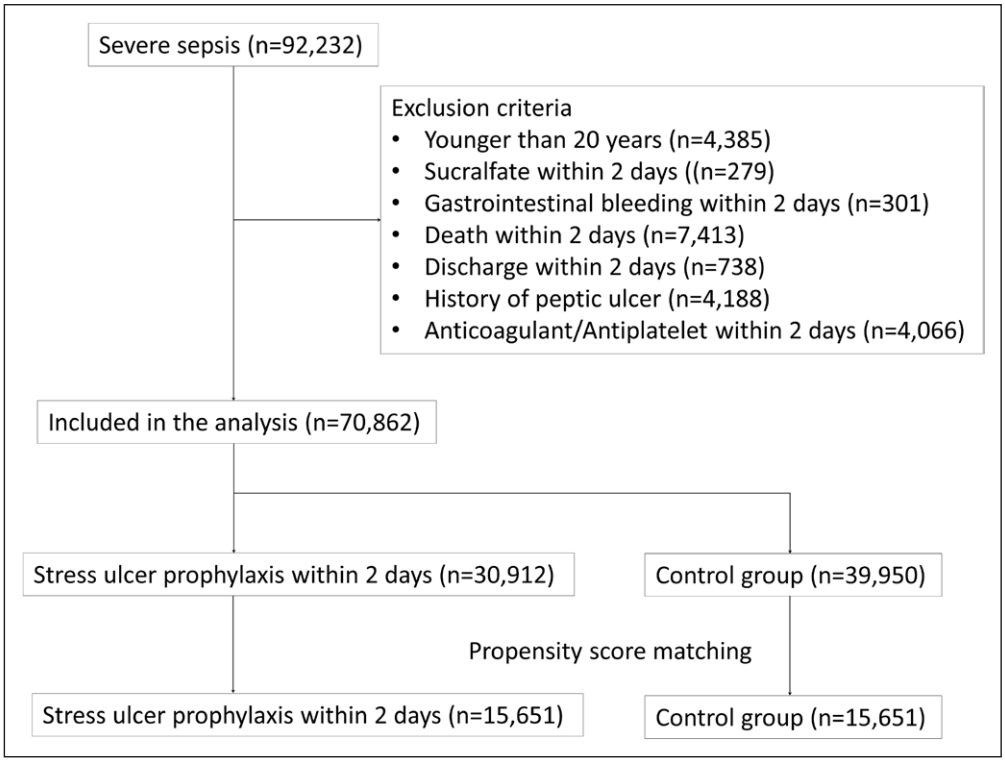

Figure 1. Flowchart of patient selection.

within hospitals, a generalized estimating equation was linked to a logistic regression model. The *c*-statistic for evaluating the goodness of fit was calculated. A one-to-one propensity score matching was then performed by nearest neighbor matching without replacement. A caliper width was set at 20% of SD of the propensity scores. Comparisons for distribution of the propensity score before and after matching are presented in **Supplemental Figure S1** (Supplemental Digital Content 3, http://links.lww.com/CCM/B744) and **Supplemental Figure S2** (Supplemental Digital Content 4, http://links.lww.com/CCM/B745). Differences between the two groups before and after propensity score matching were assessed by standardized differences. Standardized differences of less than 10% are considered negligible imbalances in baseline characteristics between groups (26). Statistical power was estimated to be 97% to detect a 0.3% risk difference in the proportion of gastrointestinal bleeding requiring endoscopic hemostasis in patients with stress ulcer prophylaxis compared with controls (0.3% vs 0.6%), at a significance level of 0.05, with inclusion of 14,682 patients in each group. Our estimation of 50% risk reduction was derived from a previous meta-analysis (27), which showed that relative risk of stress ulcer prophylaxis for gastrointestinal bleeding was 0.44. A p value of less than 0.05 is considered statistically significant. All analyses are performed using SPSS version 22 (SPSS, Chicago, IL).

RESULTS

Study Population

After application of inclusion and exclusion criteria, a total of 70,862 patients from 526 acute care hospitals are included in the analysis (**Fig. 1**). Of these, 30,912 patients received stress ulcer prophylaxis within 2 days of admission. The number of hospitals which treated patients with severe sepsis in 2011 and 2012 was 386 and 485, respectively. The established model for estimating propensity scores had a *c*-statistic of 0.753 (95% CI, 0.749–0.756). **Supplemental Table S3** (Supplemental Digital Content 5, http://links.lww.com/CCM/B746) shows patient characteristics before and after propensity score matching. Before propensity score matching, patients in the stress ulcer prophylaxis group were more likely to be admitted to academic hospitals, transferred by ambulance, or admitted to the ICU. Patients in the prophylaxis group were more likely to receive blood products and to have respiratory, cardiovascular, or neurological organ failure. By propensity score matching, 15,651 patients who received stress ulcer prophylaxis were matched to those who did not. Patient characteristics were well balanced between the two groups. The number of patients in the control group who received stress ulcer prophylaxis 2 days after admission before and after propensity score matching was 14,781 (37.0%) and 6,252 (39.9%), respectively.

Outcomes

Table 1 shows the proportions of gastrointestinal bleeding within 30 days, death within 30 days, hospital-acquired pneumonia, and *C. difficile* infection for the stress ulcer prophylaxis group and the control group. Among the full cohort, patients in the stress ulcer prophylaxis group are less likely to have gastrointestinal bleeding within 30 days, more likely to die within 30 days, and more likely to have hospital-acquired pneumonia. The proportion of *C. difficile* infection is not different between the groups. In the propensity score–matched cohort, the stress ulcer prophylaxis group shows a higher proportion of hospital-acquired pneumonia (3.9% vs 3.3%; $p = 0.012$) compared with the control group. The proportion of gastrointestinal bleeding (0.5% vs 0.6%; $p = 0.208$), 30-day mortality (16.4% vs 16.9%; $p = 0.249$), and the proportion of patients with *C. difficile* infection (1.4% vs 1.3%; $p = 0.588$) are not significantly different between the groups.

Subgroup Analyses

The results of subgroup analyses are presented in **Supplemental Table S4** (Supplemental Digital Content 6, http://links.lww.

TABLE 1. Outcomes Before and After Propensity Score Matching

Outcomes, *n* (%)	Full Cohort			Propensity Score–Matched Cohort		
	Stress Ulcer Prophylaxis (*n* = 30,912)	Control (*n* = 39,950)	*p*	Stress Ulcer Prophylaxis (*n* = 15,651)	Control (*n* = 15,651)	*p*
Gastrointestinal bleeding within 30 d	134 (0.4)	226 (0.6)	0.014	73 (0.5)	89 (0.6)	0.208
30-d mortality	5,492 (17.8)	6,305 (15.8)	< 0.001	2,569 (16.4)	2,645 (16.9)	0.249
Hospital-acquired pneumonia	1,355 (4.4)	1,256 (3.1)	< 0.001	606 (3.9)	523 (3.3)	0.012
Clostridium difficile infection	390 (1.3)	535 (1.3)	0.367	215 (1.4)	204 (1.3)	0.588

Number of patients and percentages are presented.

com/CCM/B747), **Supplemental Table S5** (Supplemental Digital Content 7, http://links.lww.com/CCM/B748), **Supplemental Table S6** (Supplemental Digital Content 8, http://links.lww.com/CCM/B749), **Supplemental Table S7** (Supplemental Digital Content 9, http://links.lww.com/CCM/B750), and **Supplemental Table S8** (Supplemental Digital Content 10, http://links.lww.com/CCM/B751). Interactions are not seen in any of the subgroups for gastrointestinal bleeding, hospital-acquired pneumonia, or *C. difficile* infection. Statistically significant interactions are observed for 30-day mortality in patients who were admitted to the ICU within 2 days of hospital admission, underwent mechanical ventilation, received vasopressors or inotropes, and had failure of two or more organ systems as compared with the control group. In these subgroups, 30-day mortality was lower in the stress ulcer prophylaxis group compared with the control group (Supplemental Table S5, Supplemental Digital Content 7, http://links.lww.com/CCM/B748). More patients who received proton pump inhibitors alone died within 30 days compared with those who received H2 blockers alone (Supplemental Table S8, Supplemental Digital Content 10, http://links.lww.com/CCM/B751).

Sensitivity Analyses

The results of the two sensitivity analyses are similar to those in the main analysis (**Supplemental Table S9**, Supplemental Digital Content 11, http://links.lww.com/CCM/B752; and **Supplemental Table S10**, Supplemental Digital Content 12, http://links.lww.com/CCM/B753).

DISCUSSION

This nationwide study demonstrates that the risk of gastrointestinal bleeding requiring endoscopic hemostasis in patients with severe sepsis is 0.6% and stress ulcer prophylaxis within 2 days of admission is not associated with the risk of gastrointestinal bleeding requiring endoscopic hemostasis within 30 days of admission, 30-day mortality, and *C. difficile* infection during hospitalization. The risk of hospital-acquired pneumonia increases with administration of stress ulcer prophylaxis.

Our results are different from those in previous meta-analyses, which showed that stress ulcer prophylaxis significantly decreases the risk of gastrointestinal bleeding (27, 28) compared with placebo or no prophylaxis. One possible reason for this difference is that none of the studies included in the meta-analyses specifically focused on patients with severe sepsis. Furthermore, most of the studies included in the meta-analyses were published before "epochs of care" (29), that is, prior to the year 2000. Care for critically ill patients in these studies is different from current practice. Another possible reason for this difference is the definition of gastrointestinal bleeding. Since gastrointestinal bleeding was defined in this study as a condition requiring endoscopic hemostasis, patients who received only pharmacotherapy for minor gastrointestinal bleeding were not included. The present study cannot evaluate the potential effect of stress ulcer prophylaxis for decreasing the risk of minor gastrointestinal bleeding.

It has been controversial whether stress ulcer prophylaxis increases the risk of hospital-acquired pneumonia. Previous meta-analyses (27, 28) showed that stress ulcer prophylaxis did not increase the risk of hospital-acquired pneumonia. However, only approximately 1,000 patients were included in the meta-analysis and the authors acknowledged that the sample size was insufficient (27). The sample size of 15,651 patients in the present study is sufficient to detect a difference in the proportion of patients who developed hospital-acquired pneumonia.

It also remains unknown whether stress ulcer prophylaxis increases the risk of *C. difficile* infection (30, 31). In the present analysis, stress ulcer prophylaxis is not associated with *C. difficile* infection. Theoretically, gastric acid suppression may allow more vegetative organisms to reach the colon. However, *C. difficile* spores are acid-resistant and viable at typical gastric pH levels (32).

The present study shows that stress ulcer prophylaxis is not significantly associated with a decrease in patients with gastrointestinal bleeding requiring endoscopic hemostasis. Furthermore, stress ulcer prophylaxis is associated with a significant increase in hospital-acquired pneumonia. These results support the consensus that stress ulcer prophylaxis should not be used in patients without risk factors for gastrointestinal bleeding (12).

Subgroup analyses show that stress ulcer prophylaxis is associated with a significantly decreased risk of 30-day mortality in patients who underwent mechanical ventilation, received renal replacement therapy, received vasopressors or

inotropes, had failure of two or more organ systems, and were admitted to the ICU. However, the interaction was not significant for infectious outcomes in the subgroups. Stress ulcer prophylaxis may have decreased mortality in these subgroups through decreasing minor gastrointestinal bleeding, which is not captured in the present study. However, in other patients, stress ulcer prophylaxis significantly increased the number of patients with hospital-acquired pneumonia without decreasing the 30-day mortality. The results of subgroup analyses suggest that physicians should carefully consider the indications for stress ulcer prophylaxis. Further study to determine which patients actually benefit from stress ulcer prophylaxis is warranted.

The present study has several strengths. The study design was set in a pragmatic context, based on a real-world clinical setting. The study includes a large representative sample of approximately 50% of inpatients admitted to acute care hospitals in Japan.

We acknowledge that the present study has some limitations. First, the proportion of patients with gastrointestinal bleeding may have been underestimated because we only included patients with severe bleeding that required endoscopic hemostasis. Second, the database does not include certain clinical information such as severity scores or sites of infection. However, we assessed the number of organ systems failing and the use of procedures/therapies such as renal replacement therapy or vasopressors, which in part substitute for a specific severity score. Mortality was associated with the number of organ systems failing (**Supplemental Table S11**, Supplemental Digital Content 13, http://links.lww.com/CCM/B754). Third, patients transferred from another hospital to treat nosocomial infections may have an admission diagnosis of severe sepsis. Fourth, because the prevalence of overweight/obesity differs from Western countries, the results regarding body mass index may not be generalizable to other countries. Fifth, because patients undergoing mechanical ventilation are sometimes managed on general wards in Japan (33, 34), our results might not be generalizable to other countries where mechanical ventilation is solely conducted in ICUs and operating rooms. Lastly, although we made an effort to reduce selection bias using propensity score matching, clinical contraindications to the use of stress ulcer prophylaxis cannot be captured in the propensity score matching. We believe that this study is a first step toward a randomized trial of stress ulcer prophylaxis in patients with severe sepsis.

CONCLUSIONS

Gastrointestinal bleeding requiring endoscopic hemostasis is rare in patients with severe sepsis. Stress ulcer prophylaxis is not associated with a reduction in the rate of gastrointestinal bleeding requiring endoscopic hemostasis, 30-day mortality, or *C. difficile* infection in patients with severe sepsis, whereas it is associated with increased hospital-acquired pneumonia. Routine stress ulcer prophylaxis for patients with severe sepsis may be unnecessary.

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