REVIEW ARTICLE

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Prophylaxis against Upper Gastrointestinal Bleeding in Hospitalized Patients

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Beginning approximately four decades ago, a series of randomized trials suggested that, in seriously ill hospitalized patients, primary prevention of clinically important upper gastrointestinal bleeding — stress-ulcer prophylaxis — significantly reduces the risk of bleeding.[1] In response, practice guidelines have consistently supported prophylaxis for patients in the intensive care unit (ICU) who have risk factors for bleeding.[2-5] Clinicians worldwide administer prophylaxis in the form of acid suppression for 80 to 90% of critically ill and injured patients,[6,7] and prescriptions for acid suppressants in less severely ill patients are prevalent.[8-11] Recently, however, the net benefit of acid suppression has been questioned.[6,12] In this review, we define upper gastrointestinal bleeding in hospitalized patients and discuss the pathophysiological features, incidence, risk factors, prognosis, and consequences of prophylaxis, as well as our perspectives on current and future practice.

Definitions

Hemorrhage from the upper gastrointestinal tract (esophagus, stomach, or duodenum) is defined as primary when it is the cause of hospital admission and is defined as secondary when it complicates the hospital course for patients who have been admitted for other reasons. Patients with secondary upper gastrointestinal bleeding are generally older, more seriously ill, and more likely to have coexisting conditions such as cardiopulmonary disease or chronic renal failure, as compared with patients who have primary bleeding.[13,14]

Hospitalized patients with a history of gastrointestinal bleeding who are considered to be at sufficient risk for rebleeding commonly receive, or continue to receive, medication for prevention of secondary bleeding. In most cases, however, prophylaxis is prescribed for hospitalized patients who are at risk for bleeding from new gastroduodenal lesions or from previously asymptomatic disease that has been unmasked by the illness that prompted hospitalization. Primary prevention of secondary bleeding is the focus of this article.

Pathophysiological Features

The human stomach produces a unique acidic milieu in the foregut that is essential for digestion of food and elimination of ingested pathogens. In the healthy state, neurohormonal influences on parietal cells stimulate hydrochloric acid secretion, resulting in a pH of approximately 2. Although this pH level would rapidly disintegrate most tissues, prostaglandins and nitric oxide help to sustain a protective mucous layer that protects the gastric epithelium.[15] Normal blood flow supplies oxygen and bicarbonate and removes hydrogen ions diffusing from the lumen into the gastric mucosa. Multiple acid sensors monitor extracellular pH, potentially triggering diminished gastrin production and reduced acid output. Coordinated lower esophageal and pyloric sphincter function can further balance pH in the esophagus and duodenum relative to the more acid-resistant stomach.

This network of defenses is crucial for protecting the gastric epithelium. In seriously ill patients, proinflammatory states, splanchnic hypoperfusion, and impaired microcirculation due to conditions such as hypovolemia, low cardiac output, or shock can induce ischemia, reperfusion injury, and low gastric intramucosal pH.[16] These factors can converge to impair the integrity of the mucosal lining, causing unchecked gastric acidity (Fig. 1). Gastroduodenal erosions and ulceration may ensue, exacerbated by stress-triggered vagal stimulation. Although gastric acid is thought to predispose hospitalized patients to gastrointestinal bleeding or to precipitate or perpetuate bleeding, disruption of the mucosal barrier is probably more salient in the genesis of gastrointestinal bleeding.

INCIDENCE AND RISK FACTORS

CRITICALLY ILL PATIENTS

The incidence of secondary upper gastrointestinal bleeding varies with the diagnostic definition, the prophylaxis prescribed, and the publication era (Table 1). Approximately 50 years ago, endoscopies showed stress-related gastric mucosal ulceration in 75 to 100% of critically ill, injured, or burned patients.[17,18] Current data from surveillance studies are unavailable, but asymptomatic endoscopic ulceration during critical illness may be inconsequential.[19] Historically, occult bleeding occurred in 15 to 50% of critically ill patients, and overt bleeding occurred in 5 to 25% of critically ill patients not receiving prophylaxis. In an international period-prevalence study reported in 2015, Krag and colleagues documented overt bleeding in 49 of 1034 heterogeneous patients who had been admitted to the ICU (4.7%).[6] Patients with a bleeding diathesis, including those receiving extracorporeal life support, may have higher rates of overt bleeding, as reported in a study involving 132 such patients, 18 of whom had overt bleeding (13.6%).[20]

By contrast, clinically important bleeding has hemodynamic consequences that may warrant red-cell transfusions or invasive interventions.[21,22] The pervasive impression is that clinically important upper gastrointestinal bleeding has declined over time because of advances in critical care practice; however, this postulate is not concordant with all the evidence. In two large studies from the 1990s, the incidence of clinically important bleeding was 1.5%[21] and 3.5%.[22] Recently, in two small feasibility trials involving heterogeneous patients, the rates were 0%[23] and 5.5%[24]; these estimates are outside the confidence limits for the rate of clinically important bleeding in the large 2015 study by Krag et al. (2.8% [29 of 1034 patients]; 95% confidence interval [CI], 1.6 to 3.6).[6]

Many investigations have examined predictors of clinically important upper gastrointestinal bleeding in patients in the ICU. One large, multicenter study showed two independent risk factors: invasive mechanical ventilation for 48 hours or longer (odds ratio for bleeding, 15.6; 95% CI, 3.0 to 80.1) and coagulopathy (odds ratio, 4.5; 95% CI, 1.8 to 10.3).[21] In another large, multicenter study, additional factors independently associated with clinically important bleeding were three or more coexisting diseases (odds ratio, 8.9; 95% CI, 2.7 to 28.8), liver disease (odds ratio, 7.6; 95% CI, 3.3 to 17.6), renal-replacement therapy (odds ratio, 6.9; 95% CI, 2.7 to 17.5), acute coagulopathy (odds ratio, 4.2; 95% CI, 1.7 to 10.2), and a high organ-failure score (odds ratio, 1.4; 95% CI, 1.2 to 1.5), as well as use of acid suppressants (odds ratio, 3.6; 95% CI, 1.3 to 10.2), which may reflect confounding by indication.[6] Neurologic injury combined with severe physiological stress (e.g., traumatic brain injury) that prompts ICU admission may amplify the probability of stress-related bleeding.[25] Population-specific risk profiles are based on the severity of acute and chronic illnesses and on certain drugs and interventions (e.g., mechanical ventilation, renal-replacement therapy, and extracorporeal life support) used in the hospital (Fig. 2). In view of differences in candidate predictors and analytic approaches across studies over time, interpretation of data on risk factors for bleeding must take into account the competing risks of bleeding-prevention strategies themselves.

The chief nonpharmacologic approach to decreasing the risk of bleeding is enteral administration of nutrients that buffer gastric acid, in-

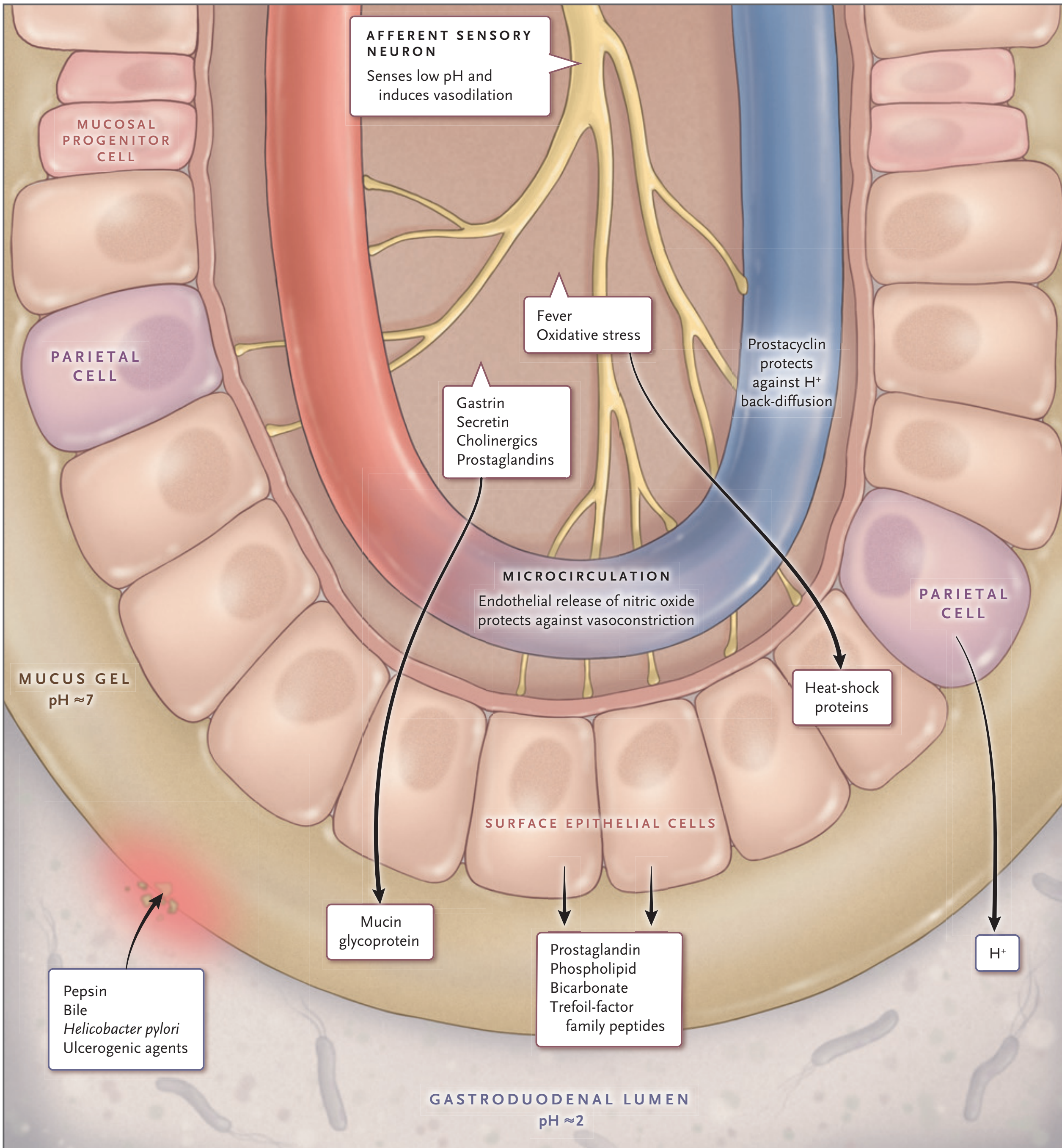

Figure 1. Pathophysiological Features of the Gastroduodenal Mucosa.

A layer of alkaline mucus gel is a key feature of gastroduodenal mucosal defense. Beneath this lining are surface epithelial cells that secrete mucus, bicarbonate, prostaglandins, and other protective factors. These surface epithelial cells are regenerated by mucosal progenitor cells. The underlying capillary microcirculation provides oxygen and produces prostaglandins and nitric oxide. Multiple acid sensors monitor extracellular pH, potentially triggering diminished gastrin production and reduced acid output. In seriously ill patients, proinflammatory states, splanchnic hypoperfusion, and impaired microcirculation due to conditions such as hypovolemia, low cardiac output, or shock can induce ischemia, reperfusion injury, and low gastric intramucosal pH. These factors can converge to impair the integrity of the mucosal lining, causing unchecked gastric acidity. Gastric acid is often considered to precipitate, perpetuate, or be a predisposing factor in gastrointestinal bleeding in hospitalized patients; however, disruption of the mucosal barrier may be the most salient factor in the genesis of such bleeding.

Table 1. Categories, Definitions, and Incidence of Bleeding.*

Category	Definition	Incidence	Considerations
Mucosal or submucosal ulceration	Endoscopically documented gastroduodenal mucosal or submucosal erosions or ulcerations	Historically, approximately 75–100% among selected critically ill patients; no current estimates for bleeding risk	No available contemporary endoscopic surveillance studies; no estimates for patients in medical and surgical units; low clinical relevance
Occult bleeding	Gastric or fecal samples with guaiac-positive testing for blood	Historically, approximately 15–50% among heterogeneous critically ill patients; no current estimates for bleeding risk	No available contemporary surveillance studies of occult bleeding, but most patients receive prophylaxis; no estimates for patients in medical and surgical units; low clinical relevance
Overt bleeding	Hematemesis, frank blood or coffee-grounds findings in nasogastric aspirate, or melena	Approximately 5% among heterogeneous critically ill patients; approximately 0.3% among heterogeneous patients in medical and surgical units	Critically ill patients: data from contemporary, international period-prevalence study in which 70% of patients received prophylaxis[6]; patients in medical and surgical units: data from contemporary, 4-yr hospital database in which 60% of patients received prophylaxis[11]
Clinically important bleeding	Overt bleeding in addition to one or more of the following findings: a spontaneous drop in systolic or diastolic BP of ≥20 mm Hg within 24 hr before or after bleeding; an orthostatic increase in pulse of ≥20 beats/min and decrease in systolic BP of 10 mm Hg; a decrease in hemoglobin of ≥2 g/dl over a 24-hr period or transfusion of ≥2 units of PRBCs within 24 hr after the start of bleeding; or invasive interventions (e.g., therapeutic endoscopy or vasopressor initiation or increase)	Approximately 3% among heterogeneous critically ill patients; approximately 0.2% among heterogeneous patients in medical and surgical units	Critically ill patients: data from contemporary, international period-prevalence study in which 70% of patients received prophylaxis[6]; patients in medical and surgical units: data from contemporary, 4-yr hospital database in which 60% of patients received prophylaxis[11]

* Shown are categories of upper gastrointestinal bleeding in heterogeneous hospitalized patients according to various definitions, presented in order of increasing clinical importance. Mucosal ulceration and occult bleeding rates are from studies published before 2000. With respect to research performed in the past decade, rates of overt and clinically important bleeding are from a study involving critically ill patients that was published in 2015[6] and a study involving non–critically ill patients in medical and surgical units that was published in 2011.[11] Most recent investigations that have provided the data for current bleeding rates enrolled patients who were already receiving prophylaxis against stress ulcer. Bleeding rates in specific subgroups of patients (e.g., those with thermal injury) are not shown. BP denotes blood pressure, and PRBCs packed red cells.

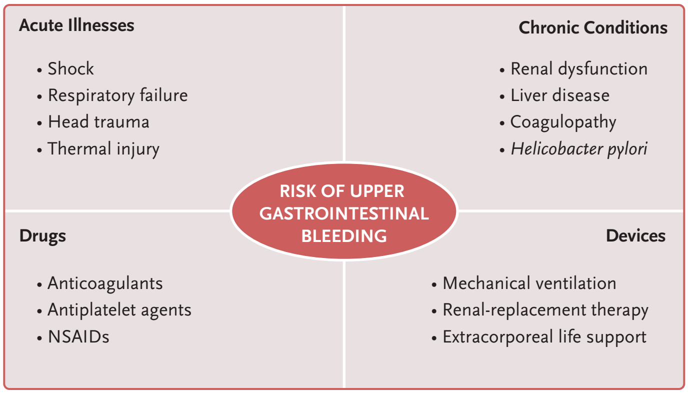

Figure 2. Risks of Clinically Important Gastrointestinal Bleeding.
Data on risk factors for bleeding are derived from large epidemiologic studies and from many smaller studies of mixed populations or specific subgroups of patients cared for in medical and surgical wards and intensive care units. The severity of acute and chronic illnesses, along with certain drugs and devices used in the hospital, form the basis for population-specific risk profiles.

duce prostaglandin production, and enhance regional mucosal perfusion,[26-29] optimizing mucosal energy and intramucosal pH.[30] Enteral nutrition may provide protection against ischemic bleeding[28,31] and increase gastric pH to a greater extent than acid suppression does,[32] as well as theoretically reduce the risk of stress-related bleeding during critical illness.[33] A meta-analysis of trials that explicitly reported standard early enteral feeding showed that acid suppression does not decrease the risk of bleeding and may increase the risk of pneumonia.[34] However, trials have not directly compared bleeding rates for patients receiving enteral nutrition with the rates for those not receiving enteral nutrition. Recommendations for early enteral nutrition during critical illness[35] and timely feeding to ameliorate hospital-acquired malnutrition[36] signal the need for more careful attention to enteral alimentation practices in future trials evaluating acid suppression.

HOSPITALIZED PATIENTS WHO ARE NOT CRITICALLY ILL

Definitions of bleeding vary more among studies of patients admitted to medical and surgical units than among studies of patients in the ICU, generating a wide range in the incidence of bleeding, although it is generally much lower than the incidence among patients in the ICU. A 4-year audit of 17,707 medical patients documented a 0.4% bleeding rate, with bleeding defined by the use of esophagogastroduodenoscopy.[37] Among 13,330 diverse patients, excluding obstetrical and psychiatric patients, the rate of clinically important bleeding was 0.005%; bleeding episodes, primarily due to duodenal ulcer disease, occurred after a mean period of 14 days in the hospital.[38] The incidence of bleeding may differ among subgroups of patients. For example, a study involving 514 patients admitted with acute kidney injury showed that 40 of the patients (7.8%) had clinically important bleeding.[39] In a 4-year analysis of 75,723 hospital admissions, overt gastrointestinal bleeding occurred in 224 patients (0.29%) and clinically important bleeding occurred in 176 patients (0.23%).[11]

In the limited number of studies involving patients admitted to medical and surgical units, predictors of risk vary. A study focused on patients with acute kidney injury showed that bleeding was associated with severe overall illness, severe renal failure, severe thrombocytopenia, and cirrhosis.[39] In another study, involving 13,330 critically ill and non–critically ill patients, only ICU admission during the index hospitalization and mechanical ventilation were risk factors for bleeding.[38] Among 17,707 patients admitted to a general medicine service, the main risk factors for bleeding were anticoagulant therapy and treatment with clopidogrel.[37] Independent risk factors for overt bleeding in a study involving 75,723 inpatients included an age of more than 60 years, male sex, liver disease, acute renal failure, sepsis, care by a medical service, prophylactic anticoagulation, and coagulopathy with or without the administration of antiplatelet agents.[40] This study profiled a high-risk group of patients (13% of the cohort) in whom the number needed to treat with acid suppression to avert one episode of bleeding would be less than 100.

PROGNOSIS

CRITICALLY ILL PATIENTS

In earlier epochs, stress-related gastrointestinal bleeding portended a poor prognosis, including perforation, hemorrhagic shock, and death.[17,18] More recently, in an analysis of data from 1666 heterogeneous patients enrolled in two studies, clinically important bleeding was associated with an additional ICU stay of 4 to 8 days and an increased risk of death, which was significant with the use of two of three adjustment methods.[41] In their large observational study, Krag and colleagues could not rule out an association between the risk of bleeding and 90-day mortality, after adjusting for confounders (odds ratio, 1.7; 95% CI, 0.7 to 4.3).[6] Some populations may be at particular risk for adverse outcomes, such as patients receiving extracorporeal life support, for whom the risk of gastrointestinal bleeding may be independently associated with in-hospital mortality (odds ratio, 5.9; 95% CI, 1.4 to 24.3).[21]

Hospitalized Patients Who Are Not Critically Ill

For patients admitted to medical or surgical units, the prognosis after an episode of bleeding may depend as much on the acute and chronic illnesses and the amount of blood loss as on the endoscopically identified cause of the bleeding.[42] In one large cohort, shock, sepsis, renal failure, and cirrhosis were associated with an increased risk of death among patients who had an episode of bleeding.[37] Data from rigorous analyses of the consequences of hospital-acquired bleeding are lacking; prediction models for patients admitted to medical and surgical units need to be replicated before bedside application is feasible.

Prophylaxis with Acid Suppression for Critically Ill Patients

Possible Benefits

In keeping with global practice, we center our discussion of prophylaxis against stress ulcer on proton-pump inhibitors and histamine H_2–receptor antagonists. Although the latter were the most commonly used drugs years ago, proton-pump inhibitors now predominate.[6,43-45]

Recently, systematic reviews have outnumbered new randomized trials addressing the possible benefits of acid suppression during critical illness. Table 2 summarizes the results of the most recent network meta-analysis, involving 57 trials.[1] Network meta-analyses combine direct evidence (findings from trials that conduct head-to-head comparisons of agent A with agent B) with indirect evidence (inferences about A vs. B that are based on their effects relative to a third agent, C), yielding what are called network estimates, the most credible estimates of effect. Clinically important gastrointestinal bleeding was reported in 31 trials enrolling a total of 5283 patients. Network estimates provide moderate-quality evidence for three comparisons showing a significant reduction in the risk of bleeding: proton-pump inhibitors versus histamine H_2–receptor antagonists (odds ratio for bleeding, 0.4; 95% CI, 0.2 to 0.7), proton-pump inhibitors versus no prophylaxis or placebo (odds ratio, 0.2; 95% CI, 0.1 to 0.6), and proton-pump inhibitors versus sucralfate (odds ratio, 0.3; 95% CI, 0.1 to 0.7). Moderate-quality evidence from 36 trials enrolling a total of 5498 patients suggests that none of the management options differ significantly with respect to the risk of death from all causes.

Possible Harms

There is growing concern that the adverse effects of acid suppression may predispose patients to nosocomial infections, which are more common and are associated with higher morbidity, mortality, and costs than the bleeding that acid suppression is prescribed to prevent. Evidence linking infections and acid suppression is mounting, with the association potentially mediated through modification of the gastrointestinal microbiome,[46] exacerbating the dysbiosis that characterizes critical illness.

Network estimates provide moderate-quality evidence of an increase in pneumonia with proton-pump inhibitors or histamine H_2–receptor antagonists, but confidence intervals for the comparisons with placebo or no treatment are wide.[1] Pharmacoepidemiologic studies provide further support for an increased risk of pneumonia with acid suppression.[47,48] In a cohort of 35,312 mechanically ventilated patients, those receiving proton-pump inhibitors had an increased propensity-adjusted odds of ventilator-associated pneumonia (odds ratio, 1.2; 95% CI, 1.03 to 1.41).[47] Among 21,214 patients admitted for cardiac surgery, the risk of nosocomial pneumonia associated with proton-pump inhibitors versus histamine H_2–receptor antagonists was increased after propensity matching (risk ratio, 1.19; 95% CI, 1.03 to 1.38).[48]

Table 2. **Direct, Indirect, and Network Meta-Analysis (NMA) Estimates of the Risks of Clinically Important Bleeding and Pneumonia among Critically Ill Patients Receiving Prophylaxis against Stress Ulcer.***

Comparison	No. of RCTs	Odds Ratio for Clinically Important Bleeding or Pneumonia					
		Direct Estimate (95% CI)	Quality of the Evidence	Indirect Estimate (95% CI)	Quality of the Evidence†	NMA Estimate (95% CI)	Quality of the Evidence
Clinically important bleeding							
H2RA vs. placebo	7	0.53 (0.23–1.19)	Moderate‡	1.36 (0.29–6.51)	Low§	0.64 (0.32–1.30)	Moderate‡
PPI vs. H2RA	14	0.35 (0.18–0.69)	Moderate¶	0.86 (0.11–7.02)	Low§	0.38 (0.20–0.73)	Moderate‡
H2RA vs. sucralfate	12	0.86 (0.48–1.55)	Moderate‡	0.32 (0.04–2.67)	Low§	0.80 (0.46–1.40)	Moderate‡
PPI vs. placebo	4	0.66 (0.12–3.74)	Low§	0.17 (0.06–0.49)	Moderate‡	0.24 (0.10–0.60)	Moderate‡
Sucralfate vs. placebo	4	1.15 (0.41–3.23)	Low§	0.48 (0.14–1.64)	Moderate‡	0.80 (0.37–1.73)	Low‡‖
PPI vs. sucralfate	1	0.23 (0.02–2.30)	Low§	0.32 (0.13–0.76)	Moderate**	0.30 (0.13–0.69)	Moderate‡
Pneumonia							
H2RA vs. placebo	8	1.09 (0.70–1.71)	Moderate‡	1.94 (0.73–5.20)	Low‡**	1.19 (0.80–1.78)	Moderate‡
PPI vs. H2RA	13	1.15 (0.85–1.57)	Moderate‡	2.10 (1.04–4.21)	Moderate**	1.27 (0.96–1.68)	Moderate‡
H2RA vs. sucralfate	16	1.32 (0.98–1.77)	Moderate¶	1.35 (0.64–2.86)	Low‡**	1.30 (1.08–1.58)	Moderate¶
PPI vs. placebo	3	1.48 (0.55–3.99)	Low‡¶	1.53 (0.90–2.59)	Moderate**	1.52 (0.95–2.42)	Moderate¶
Placebo vs. sucralfate	4	0.67 (0.34–1.32)	Low‡¶	1.54 (0.84–2.80)	Moderate**	1.09 (0.72–1.66)	Low‡‖
PPI vs. sucralfate	4	2.16 (1.24–3.77)	Moderate¶	1.44 (0.97–2.14)	Moderate**	1.65 (1.20–2.27)	Moderate¶

* Odds ratios from the direct, indirect, and NMA results are shown for four preventive strategies: a histamine H_2–receptor antagonist (H2RA), a proton-pump inhibitor (PPI), sucralfate, or placebo. Data are from Alhazzani et al.[1] RCT denotes randomized clinical trial.

† None of the indirect estimates were downgraded for intransitivity (defined as differences in direct comparisons of treatment effect, such as comparisons between A and C and between B and C, from which one infers differences in the indirect comparison [i.e., the comparison between A and B]).

‡ The quality of the evidence was downgraded by one level for serious imprecision.

§ The quality of the evidence was downgraded by two levels for very serious imprecision.

¶ The quality of the evidence was downgraded by one level for serious risk of bias.

‖ The quality of the evidence was downgraded by one level for serious incoherence (defined as differences between direct and indirect estimates of effect).

** The quality of the evidence was downgraded by one level for risk of bias.

Two small, randomized trials, both focused on proton-pump inhibitors,[23,24] have addressed the effect of acid suppression on *Clostridium difficile* infection during critical illness. The small samples and small numbers of events made the results uninformative (relative risk of infection, 2.2; 95% CI, 0.3 to 15.0). In a case–control study involving 408 patients in the ICU, investigators identified two independent predictors of *C. difficile* infection: a long duration of exposure to proton-pump inhibitors (odds ratio, 2.0; 95% CI, 1.2 to 3.4) and use of antimicrobial agents (odds ratio, 2.5; 95% CI, 1.2 to 5.2).[49] Another study, involving 3286 critically ill patients, showed an adjusted risk of *C. difficile* infection that was increased by a factor of 3 among patients receiving proton-pump inhibitors (odds ratio, 3.1; 95% CI, 1.1 to 8.7).[50]

ACID SUPPRESSION IN PATIENTS WHO ARE NOT CRITICALLY ILL

POSSIBLE BENEFITS

Acid suppression may be reasonable for hospitalized patients in whom new indications for prophylaxis against bleeding develop, such as use of dual antiplatelet therapy. Proton-pump inhibitors decreased the risk of gastrointestinal bleeding in a trial involving 3761 outpatients receiving dual antiplatelet therapy[51] and are recommended in patients requiring antiplatelet therapy who have additional risk factors for bleeding.[52]

Few randomized trials evaluating prophylaxis against stress ulcer in patients admitted to medical and surgical units have been performed. One trial randomly assigned 100 medical patients with risk factors for bleeding to receive magaldrate (an antacid containing aluminum and magnesium) or placebo.[53] Clinically important bleeding developed in 6% of the patients in the placebo group but in none of the patients in the antacid group. In a trial involving 139 medical patients randomly assigned to treatment with cimetidine or sucralfate,[54] clinically important bleeding developed in 3% of the patients in the sucralfate group but in none of those in the cimetidine group. More recently, a propensity-matched study involving 37,966 hospitalized patients showed that after adjustment for confounders, proton-pump inhibitors were associated with a reduced risk of clinically important bleeding (odds ratio, 0.58; 95% CI, 0.37 to 0.91).[40]

POSSIBLE HARMS

An observational study involving 63,878 inpatients who were not critically ill showed that acid suppression was associated with hospital-acquired pneumonia; in adjusted analyses, the increase in risk reached conventional levels of significance for proton-pump inhibitors (odds ratio, 1.3; 95% CI, 1.1 to 1.4) but not for histamine H_2–receptor antagonists (odds ratio, 1.2; 95% CI, 0.98 to 1.4).[55] A recent systematic review of 10,307 cases of hospital-acquired *C. difficile* infection showed an association with proton-pump inhibitors among patients in medical and surgical units (odds ratio, 1.8; 95% CI, 1.5 to 2.1).[56] In a multicenter study involving 4143 such patients, proton-pump inhibitors significantly increased the risk of health care–associated *C. difficile* infection (odds ratio, 2.6; 95% CI, 1.7 to 4.0).[57] Recurrent infection — not just the index infection with *C. difficile* — was also associated with acid suppression in a systematic review involving 7703 patients (adjusted odds ratio, 1.5; 95% CI, 1.2 to 1.9).[58]

Given the very low risk of bleeding, the dearth of direct evidence that acid suppression is beneficial, and the possibility of appreciable harm, guidelines published in 1999 recommended that acid suppression not be used for routine primary prevention of gastrointestinal bleeding in patients in medical and surgical units.[2] More recent practice guidelines are lacking.

OVERPRESCRIPTION OF ACID SUPPRESSION ACROSS THE CONTINUUM OF CARE

Primary prophylaxis against bleeding for critically ill patients is often encoded by electronic or preprinted admission order sets, irrespective of risk — so-called indication creep — such as for ICU patients even if they are breathing without assistance or are mechanically ventilated only overnight. Prescription may target presumed risk factors for bleeding; the established risk for patients needing invasive ventilation provides indirect evidence of risk in patients receiving noninvasive ventilation.

Unnecessary acid suppression in the ICU and continued acid suppression after discharge from the ICU may also drive unnecessary prescription. A survey of 119 trauma centers showed that 40% of respondents continued acid suppression for more than 50% of patients transferred out of the ICU.[59] Two studies showed continued prophylaxis without indication for approximately 60%

of patients transferred from the ICU to a medical unit and for approximately 35% of patients discharged home.[60,61]

Despite an often tenuous rationale, initiation of prophylactic acid suppression in patients admitted to medical and surgical units is also common, with studies showing up to 60% of such patients receiving primary prophylaxis against bleeding,[8-11,37] which is often continued after discharge. For instance, among 255 surgical inpatients, 138 (54%) received prophylaxis with a proton-pump inhibitor and 33% had new prescriptions for continued acid suppression at home.[62] A study of stress-ulcer prophylaxis in patients admitted to a general surgery unit showed that, after the exclusion of patients receiving concurrent nonsteroidal antiinflammatory agents or antiplatelet therapy, 53 of 67 patients (79%) had no risk factors for bleeding that warranted the prophylaxis.[10] In a study involving 1769 patients in six medical units for whom clinicians prescribed acid suppression, prescriptions were continued after discharge in 54% of the patients, none of whom met appropriateness criteria.[63] Fear of rebound hypersecretion after cessation of acid suppression may drive continued use. However, a systematic review showed that although discontinuation of proton-pump inhibitors induced refluxlike symptoms in asymptomatic volunteers, it did not increase symptoms in patients with reflux disease.[64] These findings in outpatient series that focused on reflux symptoms may not be relevant to efforts aimed at preventing hospital-acquired bleeding.

Further fueling concerns about indiscriminate acid suppression are complications such as chronic kidney disease[65] and osteoporosis,[66] as well as Food and Drug Administration warnings about infection.[67] Medication reconciliation after sentinel events such as *C. difficile* infection[57] and during transitions in care may result in timely cessation of acid suppression and mitigate overuse. The promising prescriptive authority of a focused, pharmacist-led management program for prophylaxis against stress ulcer safely reduced inappropriate acid suppression in ICU and non-ICU populations by 58% and 84%, respectively.[68]

SUMMARY

Prophylactic acid suppression is routinely used for critically ill patients with risk factors for bleeding, but it is also used for critically ill patients at low risk and for many hospitalized patients who are not critically ill and have a very low risk of bleeding. Even for patients at high risk, the number needed to treat in order to prevent one episode of bleeding may now be larger than previously estimated. Given the possible adverse effects of acid suppression, widespread use — even in high-risk patients — may not achieve a net benefit. For low-risk patients in the ICU, in medical and surgical units, or in the community, use of acid suppression in the absence of a clear indication for it may confer a net harm.[12]

In alignment with the Choosing Wisely campaign,[69] established practices may sometimes be abandoned not because a better replacement is identified but because a previously useful intervention proves to be unhelpful or actually results in worse outcomes.[70,71] As the Declaration of Helsinki reminds us, “Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.”[72] Responding to the challenge by increasing the number of patients enrolled in randomized trials,[73] ICU research consortia are now helping to answer the question of which patients, if any, should receive prophylaxis against stress ulceration. In accordance with the Institute for Healthcare Improvement’s spotlight on the costs of unnecessary medical care, determining which non-ICU inpatient populations are best served by prophylactic acid suppression, as well as which patients need not receive acid suppression, is a pressing health care priority.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Alhazzani W, Alshamsi F, Belley-Cote E, et al. Efficacy and safety of stress ulcer prophylaxis in critically ill patients: a network meta-analysis of randomized trials. Intensive Care Med 2018;44:1-11.
2. ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis: ASHP Commission on Therapeutics and approved by the ASHP board of directors on November 14, 1998. Am J Health Syst Pharm 1999;56:347-79.
3. Guillamondegui OD, Gunter OL Jr, Bonadies JA, et al. Stress ulcer prophylaxis. Chicago: Eastern Association for the Surgery of Trauma, 2008 (http://www.east.org/education/practice-management-guidelines/stress-ulcer-prophylaxis).
4. Madsen KR, Lorentzen K, Clausen N, et al. Guideline for stress ulcer prophylaxis in the intensive care unit. Dan Med J 2014;61:C4811.
5. Rhodes A, Evans LE, Alhazzani W,

et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 2017;43:304-77.
6. Krag M, Perner A, Wetterslev J, et al. Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients. Intensive Care Med 2015;41:833-45.
7. Barletta JF, Kanji S, MacLaren R, Lat I, Erstad BL. Pharmacoepidemiology of stress ulcer prophylaxis in the United States and Canada. J Crit Care 2014;29:955-60.
8. Parente F, Cucino C, Gallus S, et al. Hospital use of acid-suppressive medications and its fall-out on prescribing in general practice: a 1-month survey. Aliment Pharmacol Ther 2003;17:1503-6.
9. Pham CQ, Regal RE, Bostwick TR, Knauf KS. Acid suppressive therapy use on an inpatient internal medicine service. Ann Pharmacother 2006;40:1261-6.
10. Bez C, Perrottet N, Zingg T, Leung Ki EL, Demartines N, Pannatier A. Stress ulcer prophylaxis in non-critically ill patients: a prospective evaluation of current practice in a general surgery department. J Eval Clin Pract 2013;19:374-8.
11. Herzig SJ, Vaughn BP, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for nosocomial gastrointestinal tract bleeding. Arch Intern Med 2011;171:991-7.
12. Pappas M, Jolly S, Vijan S. Defining appropriate use of proton-pump inhibitors among medical inpatients. J Gen Intern Med 2016;31:364-71.
13. Loperfido S, Monica F, Maifreni L, et al. Bleeding peptic ulcer occurring in hospitalized patients: analysis of predictive and risk factors and comparison with out-of-hospital onset of hemorrhage. Dig Dis Sci 1994;39:698-705.
14. Zimmerman J, Meroz Y, Siguencia J, Tsvang E, Arnon R. Upper gastrointestinal hemorrhage: comparison of the causes and prognosis in primary and secondary bleeders. Scand J Gastroenterol 1994;29:795-8.
15. Laine L, Takeuchi K, Tarnawski A. Gastric mucosal defense and cytoprotection: bench to bedside. Gastroenterology 2008;135:41-60.
16. Maynard N, Bihari D, Beale R, et al. Assessment of splanchnic oxygenation by gastric tonometry in patients with acute circulatory failure. JAMA 1993;270:1203-10.
17. Skillman JJ, Bushnell LS, Goldman H, Silen W. Respiratory failure, hypotension, sepsis, and jaundice: a clinical syndrome associated with lethal hemorrhage from acute stress ulceration of the stomach. Am J Surg 1969;117:523-30.
18. Czaja AJ, McAlhany JC, Pruitt BA Jr. Acute gastroduodenal disease after thermal injury: an endoscopic evaluation of incidence and natural history. N Engl J Med 1974;291:925-9.
19. Ovenden C, Plummer MP, Selvanderan S, et al. Occult upper gastrointestinal mucosal abnormalities in critically ill patients. Acta Anaesthesiol Scand 2017;61:216-23.
20. Mazzeffi M, Kiefer J, Greenwood J, et al. Epidemiology of gastrointestinal bleeding in adult patients on extracorporeal life support. Intensive Care Med 2015;41:2015.
21. Cook DJ, Fuller HD, Guyatt GH, et al. Risk factors for gastrointestinal bleeding in critically ill patients. N Engl J Med 1994;330:377-81.
22. Cook D, Guyatt G, Marshall J, et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. N Engl J Med 1998;338:791-7.
23. Selvanderan SP, Summers MJ, Finnis ME, et al. Pantoprazole or placebo for stress ulcer prophylaxis (POP-UP): randomized double-blind exploratory study. Crit Care Med 2016;44:1842-50.
24. Alhazzani W, Guyatt G, Alshahrani M, et al. Withholding pantoprazole for stress ulcer prophylaxis in critically ill patients: a pilot randomized clinical trial and meta-analysis. Crit Care Med 2017;45:1121-9.
25. Liu B, Liu S, Yin A, Siddiqi J. Risks and benefits of stress ulcer prophylaxis in adult neurocritical care patients: a systematic review and meta-analysis of randomized controlled trials. Crit Care 2015;19:409.
26. Kazamias P, Kotzampassi K, Koufogiannis D, Eleftheriadis E. Influence of enteral nutrition-induced splanchnic hyperemia on the septic origin of splanchnic ischemia. World J Surg 1998;22:6-11.
27. Braga M, Gianotti L, Gentilini O, Parisi V, Salis C, Di Carlo V. Early postoperative enteral nutrition improves gut oxygenation and reduces costs compared with total parenteral nutrition. Crit Care Med 2001;29:242-8.
28. Ephgrave KS, Kleiman-Wexler RL, Adair CG. Enteral nutrients prevent stress ulceration and increase intragastric volume. Crit Care Med 1990;18:621-4.
29. Yan H, Peng X, Huang Y, Zhao M, Li F, Wang P. Effects of early enteral arginine supplementation on resuscitation of severe burn patients. Burns 2007;33:179-84.
30. Fiddian-Green RG, McGough E, Pittenger G, Rothman E. Predictive value of intramural pH and other risk factors for massive bleeding from stress ulceration. Gastroenterology 1983;85:613-20.
31. Hurt RT, Frazier TH, McClave SA, et al. Stress prophylaxis in intensive care unit patients and the role of enteral nutrition. JPEN J Parenter Enteral Nutr 2012;36:721-31.
32. Bonten MJ, Gaillard CA, van Tiel FH, van der Geest S, Stobberingh EE. Continuous enteral feeding counteracts preventive measures for gastric colonization in intensive care unit patients. Crit Care Med 1994;22:939-44.
33. Raff T, Germann G, Hartmann B. The value of early enteral nutrition in the prophylaxis of stress ulceration in the severely burned patient. Burns 1997;23:313-8.
34. Huang HB, Jiang W, Wang CY, Qin HY, Du B. Stress ulcer prophylaxis in intensive care unit patients receiving enteral nutrition: a systematic review and meta-analysis. Crit Care 2018;22:20.
35. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr 2016;40:159-211.
36. Barker LA, Gout BS, Crowe TC. Hospital malnutrition: prevalence, identification and impact on patients and the healthcare system. Int J Environ Res Public Health 2011;8:514-27.
37. Qadeer MA, Richter JE, Brotman DJ. Hospital-acquired gastrointestinal bleeding outside the critical care unit: risk factors, role of acid suppression, and endoscopy findings. J Hosp Med 2006;1:13-20.
38. Terdiman JP, Ostroff JW. Gastrointestinal bleeding in the hospitalized patient: a case-control study to assess risk factors, causes, and outcome. Am J Med 1998;104:349-54.
39. Fiaccadori E, Maggiore U, Clima B, Melfa L, Rotelli C, Borghetti A. Incidence, risk factors, and prognosis of gastrointestinal hemorrhage complicating acute renal failure. Kidney Int 2001;59:1510-9.
40. Herzig SJ, Rothberg MB, Feinbloom DB, et al. Risk factors for nosocomial gastrointestinal bleeding and use of acid-suppressive medication in non-critically ill patients. J Gen Intern Med 2013;28:683-90.
41. Cook DJ, Griffith LE, Walter SD, et al. The attributable mortality and length of intensive care unit stay of clinically important gastrointestinal bleeding in critically ill patients. Crit Care 2001;5:368-75.
42. Zimmerman J, Meroz Y, Arnon R, Tsvang E, Siguencia J. Predictors of mortality in hospitalized patients with secondary upper gastrointestinal haemorrhage. J Intern Med 1995;237:331-7.
43. Eastwood GM, Litton E, Bellomo R, et al. Opinions and practice of stress ulcer prophylaxis in Australian and New Zealand intensive care units. Crit Care Resusc 2014;16:170-4.
44. Krag M, Perner A, Wetterslev J, et al. Stress ulcer prophylaxis in the intensive care unit: an international survey of 97 units in 11 countries. Acta Anaesthesiol Scand 2015;59:576-85.
45. Shears M, Alhazzani W, Marshall J, et al. Stress ulcer prophylaxis in critical illness: a Canadian survey. Can J Anesth 2016;63:718-24.

46. Freedberg DE, Lebwohl B, Abrams JA. The impact of proton pump inhibitors on the human gastrointestinal microbiome. Clin Lab Med 2014;34:771-85.
47. MacLaren R, Reynolds PM, Allen RR. Histamine-2 receptor antagonists vs proton pump inhibitors on gastrointestinal tract hemorrhage and infectious complications in the intensive care unit. JAMA Intern Med 2014;174:564-74.
48. Bateman BT, Bykov K, Choudhry NK, et al. Type of stress ulcer prophylaxis and risk of nosocomial pneumonia in cardiac surgical patients: cohort study. BMJ 2013;347:f5416.
49. Barletta JF, Sclar DA. Proton pump inhibitors increase the risk for hospital-acquired *Clostridium difficile* infection in critically ill patients. Crit Care 2014;18:714.
50. Buendgens L, Bruensing J, Matthes M, et al. Administration of proton pump inhibitors in critically ill medical patients is associated with increased risk of developing *Clostridium difficile*-associated diarrhea. J Crit Care 2014;29:696.e11-e15.
51. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. N Engl J Med 2010;363:1909-17.
52. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;68:1082-115.
53. Estruch R, Pedrol E, Castells A, Masanés F, Marrades RM, Urbano-Márquez A. Prophylaxis of gastrointestinal tract bleeding with magaldrate in patients admitted to a general hospital ward. Scand J Gastroenterol 1991;26:819-26.
54. Grau JM, Casademont J, Fernández-Solá J, Cardellach F, Urbano-Márquez A. Prophylaxis of gastrointestinal tract bleeding in patients admitted to a general hospital ward: comparative study of sucralfate and cimetidine. Scand J Gastroenterol 1993;28:244-8.
55. Herzig SJ, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. JAMA 2009;301:2120-8.
56. Arriola V, Tischendorf J, Musuuza J, Barker A, Rozelle JW, Safdar N. Assessing the risk of hospital-acquired *Clostridium difficile* infection with proton pump inhibitor use: a meta-analysis. Infect Control Hosp Epidemiol 2016;37:1408-17.
57. Loo VG, Bourgault AM, Poirier L, et al. Host and pathogen factors for *Clostridium difficile* infection and colonization. N Engl J Med 2011;365:1693-703.
58. Tariq R, Singh S, Gupta A, Pardi DS, Khanna S. Association of gastric acid suppression with recurrent *Clostridium difficile* infection: a systematic review and meta-analysis. JAMA Intern Med 2017;177:784-91.
59. Barletta JF, Erstad BL, Fortune JB. Stress ulcer prophylaxis in trauma patients. Crit Care 2002;6:526-30.
60. Farrell CP, Mercogliano G, Kuntz CL. Overuse of stress ulcer prophylaxis in the critical care setting and beyond. J Crit Care 2010;25:214-20.
61. Farley KJ, Barned KL, Crozier TM. Inappropriate continuation of stress ulcer prophylaxis beyond the intensive care setting. Crit Care Resusc 2013;15:147-51.
62. Zink DA, Pohlman M, Barnes M, Cannon ME. Long-term use of acid suppression started inappropriately during hospitalization. Aliment Pharmacol Ther 2005;21:1203-9.
63. Heidelbaugh JJ, Inadomi JM. Magnitude and economic impact of inappropriate use of stress ulcer prophylaxis in non-ICU hospitalized patients. Am J Gastroenterol 2006;101:2200-5.
64. Fossmark R, Johnsen G, Johanessen E, Waldum HL. Rebound acid hypersecretion after long-term inhibition of gastric acid secretion. Aliment Pharmacol Ther 2005;21:149-54.
65. Lazarus B, Chen Y, Wilson FP, et al. Proton pump inhibitor use and the risk of chronic kidney disease. JAMA Intern Med 2016;176:238-46.
66. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA 2006;296:2947-53.
67. FDA drug safety communication: *Clostridium difficile*-associated diarrhea can be associated with stomach acid drugs known as proton pump inhibitors (PPIs). Silver Spring, MD: Food and Drug Administration, February 8, 2012 (http://www.fda.gov/Drugs/DrugSafety/ucm290510.htm).
68. Buckley MS, Park AS, Anderson CS, et al. Impact of a clinical pharmacist stress ulcer prophylaxis management program on inappropriate use in hospitalized patients. Am J Med 2015;128:905-13.
69. Bulger J, Nickel W, Messler J, et al. Choosing wisely in adult hospital medicine: five opportunities for improved healthcare value. J Hosp Med 2013;8:486-92.
70. Zelmer J. De-prescribing: when less is more in healthcare. Health Policy 2016;11:6-10.
71. Prasad V, Cifu A, Ioannidis JP. Reversals of established medical practices: evidence to abandon ship. JAMA 2012;307:37-8.
72. World Medical Association. Declaration of Helsinki: ethical principles for medical research involving human subjects. Adopted by the 64th WMA General Assembly. Fortaleza, Brazil: WMA General Assembly, October 2013 (https://www.wma.net/wp-content/uploads/2016/11/DoH-Oct2013-JAMA.pdf).
73. Krag M, Perner A, Wetterslev J, et al. Stress ulcer prophylaxis with a proton pump inhibitor versus placebo in critically ill patients (SUP-ICU trial): study protocol for a randomised controlled trial. Trials 2016;17:205.