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CRITICAL CARE

REVIEW

Stress ulceration: prevalence, pathology and association with adverse outcomes

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Introduction

So-called 'stress-related mucosal damage' (SRMD) is the broad term used to describe the spectrum of pathology attributed to the acute, erosive, inflammatory insult to the upper gastrointestinal tract associated with critical illness [1]. SRMD represents a continuum from asymptomatic superficial lesions found incidentally during endoscopy, occult gastrointestinal bleeding causing anemia, overt gastrointestinal bleeding and clinically significant gastrointestinal bleeding.

Prevalence

Stress ulceration was first described in 1969 when focal lesions in the mucosa of the gastric fundus were reported during post-mortem examinations in 7 (out of 150) critically ill patients [2]. Endoscopic studies have since identified that between 74–100 % of critically ill patients have stress-related mucosal erosions and subepithelial hemorrhage within 24 hours of admission (Figure 1a) [3]. These lesions are generally superficial and asymptomatic, but can extend into the submucosa and muscularis propria and erode larger vessels causing overt and clinically significant bleeding (Figure 1b).

The prevalence of overt and clinically significant bleeding depends on how these conditions are defined, with the definitions by Cook and colleagues the most widely accepted [4]. These authors defined overt gastrointestinal bleeding as the presence of hematemesis, bloody gastrointestinal aspirate or melena, while clinically significant bleeding is the association of overt gastrointestinal bleeding and either hemodynamic compromise, or the requirement for blood transfusion, or surgery. It is important to emphasize that SRMD excludes variceal bleeding. However, bleeding *per se* is a clinical endpoint, and some studies may have incorrectly included bleeding attributable to varices, as well as that from the lower gastrointestinal tract, as part of the SRMD spectrum. This distinction is often not clear in the literature, particularly in observational studies of SRMD in which clinically significant bleeding is a primary outcome, which may led to investigators inappropriately including variceal, or non-SRMD bleeding. The importance of this distinction is highlighted in a prospective study by Cook and colleagues, which identified the cause of hemorrhage in 22 (of 33) patients with clinically significant gastrointestinal bleeding by the use of endoscopy or surgery [4]. In this study, stress ulceration was identified as the sole source of bleeding in 14 patients, with evidence of ulceration noted in 4 (of the remaining 8) patients in whom another bleeding site was identified, which included esophageal and gastric varices, vascular anomalies, and an anastomosis bleed [4]. Accordingly, variceal or non-SRMD pathologies, which will not be prevented by stress ulcer prophylactic therapies, are a frequent cause of overt and clinically significant bleeding. This distinction is often not identified in observational studies, whereas randomized controlled studies comparing different therapies for the prevention of SRMD have excluded patients with previous ulcer and variceal disease. For this reason, prevalence data from intervention studies may not be comparable to that from observational studies.

Nevertheless, data from earlier studies suggested that overt gastrointestinal bleeding occurred frequently, and in some studies up to 25 % of critically ill patients developed overt gastrointestinal bleeding [5]. It is now accepted that the condition is far more infrequent, with the prevalence reported as between 0.6 and 4 % of patients [4], [6]. The variation in prevalence is due, at least in part, to the cohort of patients studied and their risk factors for developing SRMD and it has been estimated that episodes of clinically significant stress

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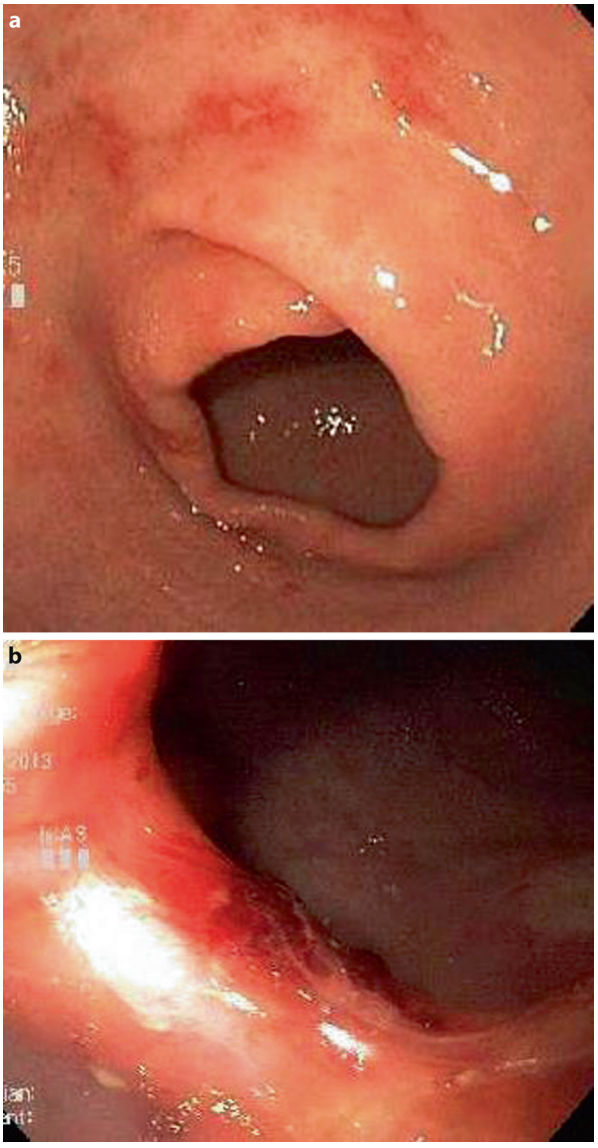

Figure 1. Stress-related mucosal disease. a Gastric antral erosions; **b** Pyloric ulcer with adherent clot.

ulcer bleeding in patients without risk factors is negligible (~ 0.1 %) [4]. The infrequency of the diagnosis in more recent epidemiological studies probably reflects an improvement in the overall management of the critically ill patient, including a focus on early aggressive resuscitation, attenuating mucosal hypoperfusion, and an awareness of the importance of early enteral nutrition [7].

Importance

Clinically significant gastrointestinal bleeding, as the name suggests, indicates that bleeding is substantive and important. It has been estimated that up to half of all patients with clinically significant upper gastrointestinal bleeding die in the intensive care unit (ICU) and, in survivors, the length of ICU stay increases by approximately 8 days [8]. It is, therefore, intuitive that preventing episodes of clinically significant gastrointestinal bleeding will lead to better patient outcomes. However, interventional studies that have reduced the incidence of stress ulceration have had no effect on either mortality or length of stay [6], [9]. Plausible explanations for this lack of effect following intervention are that:

(i) a demonstrable proportion of clinically significant bleeding is not attributable to SRMD and will not respond to acid suppressive therapy;
(ii) previous studies were underpowered;
(iii) the interventions studied have adverse effects that negate any benefit from a reduction in stress ulceration; and
(iv) the association between development of clinically significant bleeding and mortality may not be causal, and that clinically significant bleeding may just be heralding a poor outcome.

Mechanisms

Putative mechanisms underlying SRMD include reduced gastric blood flow, mucosal ischemia and reperfusion injury, all of which occur frequently in the critically ill [9]. In a prospective observational study of 2,200 critically ill patients, mechanical ventilation > 48 hours and coagulopathy were identified as substantial risk factors for clinically significant bleeding (odds ratios 15.6 and 4.3, respectively) [4]. Studies of smaller cohorts, which were performed over 30 years ago, also reported associations between clinically significant bleeding and hypotension, sepsis, hepatic failure, renal failure, burns and major trauma [10].

Prevention of stress ulceration

Although clinically significant bleeding occurs infrequently, the severity of the associated complications has encouraged preventative approaches. For example, the FAST HUG mnemonic reminds clinicians to consider the need for stress ulcer prophylaxis on a daily basis [11]. Moreover, the recent Surviving Sepsis Campaign guidelines recommend the use of stress ulcer prophylaxis in patients with severe sepsis who have a risk factor, one of which is need for mechanical ventilation > 48 hours [12]. Somewhat surprisingly, the recommendation to prescribe a stress ulcer prophylaxis drug was listed as a 1B recommendation – translating into a 'strong' recommendation. This recommendation was endorsed despite the accompanying discussion acknowledging that there are no data to demonstrate a mortality benefit when prescribing these drugs [12].

Several drugs/techniques have been described to reduce the incidence of SRMD, including sucralfate,

histamine-2 receptor blockers (H2RBs) and proton pump inhibitors (PPIs). Sucralfate acts by adhering to epithelial cells forming a physical cytoprotective barrier at the ulcer site, thereby protecting the gastric mucosa from the effects of acid and pepsin. Sucralfate is more effective than placebo in reducing overt bleeding, but has been shown to be inferior to H2RBs to reduce clinically significant bleeding [13]. Furthermore, sucralfate can impair the absorption of enteral feeds and co-administered oral medication [14], and there is a potential risk of bezoar formation (particularly in the setting of impaired gastric motility) when administering sucralfate to patients who are concurrently receiving enteral liquid nutrient [15]. Since intravenous H2RBs and PPIs are now widely available, sucralfate is rarely used as a first-line therapy.

H2RBs competitively inhibit histamine binding to its G-protein coupled receptor on the basolateral membrane of gastric parietal cells, which results in a reduction in acid production and an overall decrease in gastric secretions. H2RBs were used in early studies as first-line stress ulcer prophylaxis therapy, and were shown to significantly reduce the risk of clinically important bleeding when compared to placebo [13]. A limitation of H2RB administration is that tachyphylaxis can occur rapidly. In health, the anti-secretory effect of continuously infused intravenous ranitidine is dramatically reduced within the first day of administration [16]. With intragastric pH monitoring, studies in health have demonstrated that 70 % of patients have an intragastric pH > 4 in the first 24 hours of ranitidine intravenous infusion which falls to 26 % on the third day of continuous infusion [16]. Although similar studies have not been performed in the critically ill, these data raise concerns about the efficacy of H2RBs during longer term use in the critically ill [16].

PPIs inactivate the H^+/K^+ ATPase enzyme at the secretory surface of the parietal cell, inhibiting the secretion of H^+ ions and thereby increasing the pH of the gastric contents. In contrast to H2RBs the use of PPIs is not associated with the development of tolerance, with 100 % of healthy subjects maintaining an intragastric pH > 4 after 72 hours of continuous infusion of omeprazole [16]. In a recent meta-analysis, Alhazzani and colleagues reported that PPIs were more effective than H2RBs at reducing clinically important and overt upper gastrointestinal bleeding, without appearing to increase the risk of nosocomial pneumonia [6]. The Surviving Sepsis Campaign guidelines recommend the use of PPIs rather than H2RBs for stress ulcer prophylaxis citing level 2C evidence [12]. Previous studies of SRMD prophylaxis in the critically ill with PPIs are summarized in Table 1 [17]–[29]. Although these studies have been subject to meta-analyses by various groups [6], [9], with somewhat divergent results, even when these analyses have shown a reduction in clinically significant bleeding with PPI use, there has been no corresponding reduction in mortality.

Potential adverse effects associated with stress ulcer prophylaxis therapy

Controversy surrounds the relationship between the use of stress ulcer prophylaxis and the development of infectious complications, particularly infection-related ventilator-associated complications (IVAC) and *Clostridium difficile* infection. Gastric acid plays an important role in natural host defense, with an intragastric pH < 4 being optimal for bactericidal action [30]. Accordingly, suppressing gastric acid production and raising the intragastric pH above this bactericidal threshold has the capacity to increase colonization of the stomach with pathogenic organisms.

Stress ulcer prophylaxis and infection-related ventilator-associated complications

For the purpose of this review, the updated term 'infection-related ventilator-associated complication' has been used in preference to the previous term ventilator-associated pneumonia (VAP). In 2013, the Centers for Disease Control and Prevention proposed new definitions for patients receiving mechanical ventilation, including IVAC to improve objectivity and facilitate comparability [31]. Although prior studies investigating stress ulcer prophylaxis have exclusively used the term VAP to report data, with the inherent subjectivity associated with this diagnosis, we believe that using the recently proposed definitions for IVAC in future studies will more accurately determine whether stress ulcer prophylaxis increases adverse events during mechanical ventilation. It should be recognized, however, that the previous studies all referred to VAP rather than IVAC.

A mechanism that has been proposed to contribute to IVAC is the contamination of the oropharyngeal area by reflux of gastric fluid, with subsequent aspiration of the oropharyngeal bacteria to the lower airways [32]. Because numerous organisms are unable to live in an acidic environment, the administration of drugs to increase gastric pH could facilitate gastric colonization with pathogenic organisms and predispose to respiratory infections [30]. In ambulant patients, use of PPIs has been associated with an increased risk of community-acquired pneumonia (CAP) [33]. Laheij et al. reported a 1.89 fold increase in the risk of CAP in those taking PPIs versus those who had stopped using PPIs [33], with a correlation between dose of PPI and risk of pneumonia [33].

In the critically ill, however, data relating intragastric pH and pulmonary infections are inconsistent. Some studies have reported a higher occurrence of IVAC in

Table 1. A summary of trials of proton pump inhibitors for stress ulcer prophylaxis

Author (year)	Population	Intervention	UGI bleeding	Pneumonia
Powell et al. (1993) [17]	Post-CABG, surgical ICU. Age: 57; APACHE II: N/R	Omeprazole i.v. 80 mg × 1, then i.v. 40 mg/day (n = 10)	0 (0 %)	N/R
		Omeprazole i.v. 80 mg × 1, then i.v. 40 mg/8 h (n = 10)	0 (0 %)	N/R
		Ranitidine i.v. 50 mg/8 h (n = 11)	0 (0 %)	N/R
Risaliti and Uzzau (1993) [18]	Post-major surgery, surgical ICU. Age: 62; APACHE II: N/R	Omeprazole i.v. 40 mg, then PO 20 mg/day (n = 14)	0 (0 %)	N/R
		Ranitidine i.v. 150 mg, then PO 300 mg/day (n = 14)	0 (0 %)	N/R
Levy et al. (1997) [19]	Medical and surgical ICU. Age: 57; APACHE II: 19	Omeprazole NG 40 mg/day (n = 32)	1 (3 %)*	5 (14 %)
		Ranitidine i.v. 50 mg bolus, then i.v. 50 mg/day (n = 35)	11 (35 %)	6 (18 %)
Lasky et al. (1998) [10]	Post-trauma, mechanically ventilated. Age: N/A; APACHE II: N/R	Omeprazole NG 40 mg × 2, then NG 20 mg/day (n = 60)	0 (0 %)	17 (28 %)
Phillips et al. (1998) [21]	General ICU. Age: N/A; APACHE II: N/R	Omeprazole NG 40 mg × 2, then NG 20 mg/day (n = 33)	1 (3 %)*	6 (18 %)
		Ranitidine i.v. 50 mg × 1, c.i.v. 150–200 mg/24 h (n = 25)	4 (16 %)	4 (16 %)
Azvedo et al. (1999) [22]	General ICU. Age: 57; APACHE II: N/R	Omeprazole i.v. 40 mg/12 h (n = 38)	0 (0 %)	5 (13.1 %)
		Ranitidine c.i.v. 150 mg/24 h (n = 38)	4 (11 %)	4 (11 %)
		Sucralfate NG 1 mg/6 h (n = 32)	3 (9 %)	3 (9 %)
Kantorova et al. (2004) [23]	Surgical ICU. Age: 47; APACHE II: 18	Omeprazole i.v. 40 mg/day (n = 72)	1 (1 %)	8 (11 %)
		Famotidine i.v. 40 mg/12 h (n = 71)	2 (3 %)	7 (10 %)
		Sucralfate NG 1 mg/6 h (n = 69)	3 (4 %)	6 (9 %)
		Placebo (n = 75)	1 (1 %)	5 (7 %)
Pan and Li (2004) [24]	Critically ill patients with severe acute pancreatitis. Age: 48; APACHE II: 12	Rabeprazole PO 20 mg/day (n = 20)	0 (0 %)	N/R
		Famotidine i.v. 40 mg/12 h (n = 10)	1 (10 %)	N/R
Conrad et al. (2005) [25]	General ICU. Age: 55; APACHE II: 23	Omeprazole NG 40 mg × 2, then NG 40 mg/day (n = 178)	7 (4 %)	20 (11 %)
		Cimetidine i.v. 300 mg bolus, then c.i.v. 1200 mg/24 h (n = 181)	10 (6 %)	17 (9 %)
Hata et al. (2005) [26]	Cardiac ICU. Age: 65; APACHE II: N/R	Rabeprazole PO 10 mg/day (n = 70)	0 (0 %)	N/R
		Ranitidine PO 300 mg/day (n = 70)	4 (6 %)	N/R
		Teprenone NG 150 mg/day (n = 70)	4 (6 %)	N/R
Kotlyanskaya et al. (2008) [27]	Medical ICU. Age: 72; APACHE II: 28	Lanzoprazole PO (n = 45), dose not given	0 (0 %)	2 (4 %)
		Ranitidine (n = 21), dose and route not given	3 (14 %)	4 (19 %)
Somberg et al. (2008) [28]	Mixed ICU. Age 42; APACHE II: 15	Pantoprazole i.v. 40 mg/day (n = 32)	0 (0 %)	3 (9 %)
		Pantoprazole i.v. 40 mg/12 h (n = 38)	0 (0 %)	8 (21 %)
		Pantoprazole i.v. 80 mg/day (n = 23)	0 (0 %)	1 (4.3 %)
		Pantoprazole i.v. 80 mg/12 h (n = 39)	0 (0 %)	2 (5.1 %)
		Pantoprazole i.v. 80 mg/8 h (n = 35)	0 (0 %)	2 (5.7 %)
		Cimetidine i.v. 300 mg bolus, then CIV 1200 mg/24 h (n = 35)	0 (0 %)	3 (9.1 %)
Solouki and Kouchak (2009) [29]	General ICU. Age 50; APACHE II: N/R	Omeprazole NG 20 mg/12 h (n = 61)	4 (7 %)	8 (13 %)
		Ranitidine i.v. 50 mg/12 h (n = 68)	18 (26 %)	6 (9 %)

* Study reported clinical significance, age and APACHE data are presented as mean.
APACHE II: Acute Physiological and Chronic Health Evaluation II; CABG: coronary artery bypass graft; c.i.v.: continuous intravenous infusion; i.v.: intravenous; NG: nasogastric; N/R: not recorded, PO: per oral; UGI: upper gastrointestinal.

patients who received drugs to increase gastric pH compared to those who received sucralfate [34], supporting the importance of gastric acidity and the role of the entero-pulmonary route. However, Heyland et al. reported that while the delivery of acidified enteral feeds (pH 3.5) preserved gastric acidity and dramatically reduced gastric bacterial growth and lowered the rate of Gram-negative bacterial growth in tracheal suction, there was no reduction in frequency of VAP [35]. In a meta-analysis of data comparing H2RBs and placebo, which

did not adjust for enteral nutrition, Cook et al. reported a trend towards increased rates of pneumonia with the routine use of H2RBs [13].

Despite PPI prophylaxis being a key recommendation of the Surviving Sepsis Guidelines, there have been no large-scale prospective randomized trials that have compared PPIs and placebo to determine the efficacy and/or adverse events associated with their use [12]. Nevertheless, the rate of IVAC associated with PPI use is likely to be at least similar to that observed with H2RBs [6]. Furthermore, if tolerance to H2RBs occurs, and increasing pH increases the risk of IVAC, it is plausible that VAP rates will be even greater in patients receiving PPIs. Regardless of whether H2RBs or PPIs are more harmful in creating the ideal environment to alter bacterial colonization of the stomach, this issue is likely to be particularly relevant for enterally fed patients, as enteral feeding *per se* may be a risk factor for IVAC [36].

Stress ulcer prophylaxis and *Clostridium difficile* infection

Symptomatic infection with *C. difficile* occurs relatively frequently in mechanically ventilated critically ill patients. Using data from over 65,000 patients in the United States who required prolonged ventilation, *C. difficile*-associated diseases were present in > 5 % of patients [37]. Furthermore *C. difficile* infections are important because infection leads to a substantial increase in hospital length of stay (6.1 days; 95 % confidence interval 4.9–7.4) [37].

There is a plausible biological mechanism that acid-suppression increases the risk of developing *C. difficile* colonization, because host immunity is compromised by a higher pH environment in the stomach [38]. Observational studies have reported an association between iatrogenic acid suppression and *C. difficile*-associated diseases [38]. In a prospective case-control study of 303 patients admitted to a general medical ward, Yearsley et al. reported a two-fold increase in *C. difficile*-associated diseases in patients receiving PPIs [39]. However, to the best of our knowledge, there are no epidemiological data detailing *C. difficile*-associated diseases in critically ill patients receiving stress ulcer prophylaxis.

Complications associated with long-term use of drug therapies

Although complications associated with the acute use of H2RBs and PPIs are of more relevance to critically ill patients, it should be recognized that chronic use of PPIs has been associated with osteoporosis and fractures [40]. Adverse effects associated with chronic use may be important, as a recent observational study reported that around a third of patients given PPIs for stress ulcer prophylaxis went home on the drug despite there being no indication on discharge from hospital for their continued use [41].

Enteral feeds and the role of stress ulcer prophylaxis

The majority of the studies on which current recommendations are based were performed over 20 years ago. Over that time, there have been changes to the perceived importance of enteral nutrition, with intragastric feeds commenced sooner after admission [42]. Liquid nutrient buffers gastric acid, increases mucosal blood flow and induces the secretion of cytoprotective prostaglandins and mucus [43]. It is uncertain what influence the route of enteral feeding has on the effect of liquid nutrient. Although it is intuitive that only liquid nutrient administered into the stomach could have these potentially beneficial effects, delivery directly into the small intestine may have other advantages that lead to favorable outcomes [42]. Furthermore, because of duodenal-gastric reflux of liquid [32] and increase in mesenteric blood flow due to small intestinal delivery [44], postpyloric delivery may still prevent development of stress ulceration. Nevertheless the so-called 'early' administration of enteral nutrition into the stomach has been suggested to have contributed substantially to the diminishing frequency of stress ulcer-related bleeding that has been observed over the last 30 years [7]. In the critically ill, continuous enteral nutrition has been shown to be more effective at increasing intragastric pH than H2RBs and PPIs [45] and, in rats, enteral nutrition provides better protection against stress ulceration than do intravenous H2RBs [46]. Studies in humans to evaluate the effects of enteral nutrition on gastrointestinal bleeding reduction have primarily been performed in patients post-burn injury. Interpretation of these data are problematic because of inconsistencies around the definitions of SRMD, clinically significant upper gastrointestinal bleeding and enteral nutrition [47]. Marik et al. performed a meta-analysis to evaluate the effects of H2RBs and placebo [9]. In the subgroup of patients who received enteral feeds, stress ulcer prophylaxis did not reduce the risk of bleeding but increased VAP rates and mortality [9]. However, as acknowledged by the authors, subgroup analysis within a systematic review should be interpreted with caution. For this reason we consider the Marik review hypothesis-generating and prospective studies to determine the influence of enteral nutrition on SRMD and stress ulcer prophylaxis-associated IVAC are urgently required.

Cost of routine prophylaxis

Models of cost-effectiveness of stress ulcer prophylaxis advocate that prophylactic therapy be limited to patients with established risk factors for clinically significant bleeding [48]. In comparison to routine prophylaxis for all critically ill patients, this strategy has been shown to decrease H2RB drug costs by 80 % without altering the

frequency of gastrointestinal bleeding [49]. To our knowledge, a cost analysis has not been performed with PPIs in the critically ill. Based on historical data, however, stress ulcer prophylaxis would need to be routinely administered to 900 hospitalized patients to prevent one episode of clinically significant bleeding [50]. Since clinically significant stress ulcer bleeding occurs infrequently in patients without risk factors, routine stress ulcer prophylaxis is unlikely to be cost-effective and should probably be avoided in this subgroup, particularly given the potential for harm with PPI and H2RB use. As described [41], almost a third of patients have PPIs continued on hospital discharge, which in itself will lead to increases in costs to individual patients and communities, independent of any long-term health concerns.

Conclusions

Using current resuscitation and feeding practices, clinically significant gastrointestinal bleeding, as a consequence of SRMD, appears to occur infrequently. Nevertheless, should clinically significant bleeding occur, it is associated with significant morbidity and at least a 4-fold increase in ICU mortality. Patients with respiratory failure requiring mechanical ventilation for > 48 hours and those with coagulopathy are at the highest risk of clinically significant bleeding. Based on these observations, current guidelines suggest that this group is most likely to benefit from prophylactic therapy. The superior efficacy of PPIs has shaped recommendations that these agents be used as first-line therapy. However, the routine use of stress ulcer prophylaxis in all critically patients may be harmful and is unlikely to be cost-effective. Controversy surrounds pharmacologically increasing gastric pH, but there is mechanistic plausibility that this may increase the rate of IVAC and *C. difficile* infections – both of which are associated with substantial morbidity and increased costs – particularly in those ventilated for > 48 hours. In contrast to recent recommendations from the Surviving Sepsis Campaign, we contend that the issue of stress ulcer prophylaxis is not settled and further prospective randomized trials are required to guide decision-making.

List of abbreviations used

APACHE II: Acute Physiological and Chronic Health Evaluation II; CABG: coronary artery bypass graft; CAP: community-acquired pneumonia; c.i.v.: continuous intravenous infusion; H2RB: histamine-2 receptor blocker; ICU: intensive care unit; i.v.: intravenous; IVAC: infection-related ventilator-associated complications; NG: nasogastric; PO: per oral; PPI: proton pump inhibitors; SRMD: stress-related mucosal damage; UGI: upper gastrointestinal; VAP: ventilator-associated pneumonia.

Competing interests

The authors declare that they have no competing interests.

Declarations

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