Portuguese Society of Intensive Care Medicine Guideline for Stress Ulcer Prophylaxis in the Intensive Care Unit

Mendes JJ[1,2], Silva MJ[3], Miguel LS[4], Gonçalves MA[1,5], Oliveira MJ[6], Oliveira CL[7], Gouveia J[1,4]
[1] Portuguese Society of Intensive Care Medicine
[2] Intensive Care Department, Hospital Prof. Doutor Fernando da Fonseca E.P.E.
[3] Gastroenterology Department, Centro Hospitalar de Lisboa Central E.P.E.
[4] Centre for Evidence Based Medicine, Faculdade de Medicina da Universidade de Lisboa
[5] Intensive Care Department, Hospital Garcia de Orta E.P.E.
[6] Pharmacy Department, Hospital Prof. Doutor Fernando da Fonseca E.P.E.
[7] Portuguese Association of Hospital Pharmacists
[8] Intensive Care Department, Centro Hospitalar de Lisboa Norte E.P.E.

Abstract (english)
Critically ill patients are at risk of developing stress ulcers in the upper digestive tract. Agents that suppress gastric acid are commonly prescribed to reduce the incidence of clinically important stress ulcer-related gastrointestinal bleeding. However, the indiscriminate use of stress ulcer prophylaxis in all patients admitted to the Intensive Care Unit is not warranted and has potential adverse clinical effects and cost implications. The present guideline from the Portuguese Society of Intensive Care Medicine summarizes current evidence and gives six clinical statements and an algorithm aiming to provide a standardized prescribing policy for the use of stress ulcer prophylaxis in the Intensive Care Unit.

Abstract (portuguese)
O doente crítico encontra-se em risco de desenvolver úlceras de *stress* do trato gastrointestinal. Anti-ácidos e anti-ulcerosos de diferentes classes são frequentemente prescritos para reduzir a incidência da hemorragia gastrointestinal clinicamente significativa associada à úlcera de *stress*. No entanto, o uso indiscriminado deste tipo de profilaxia em todos os doentes admitidos em Unidades de Cuidados Intensivos não só não se justifica como tem potenciais efeitos adversos e implicações de custo. A presente *guideline* da Sociedade Portuguesa de Cuidados Intensivos resume a evidência atual e fornece seis afirmações clínicas e um algoritmo com o objetivo de fornecer uma política padronizada de prescrição da profilaxia da úlcera *stress* em Unidades de Cuidados Intensivos.

Introduction

Stress ulcer-related gastrointestinal bleeding is a potential complication of critical illness, whose pathophysiology is complex. Systemic hemodynamic and local alterations result in gastric mucosal blood flow impairment with subsequent ischemic mucosal injury. However, the crucial factor for the development of ulceration and gastric bleeding is the, fasting potentiated, high gastric intraluminal acidity (1). This provides the rationale for the use of acid-suppressive drugs for pharmacological prophylaxis.

Endoscopically evident upper gastrointestinal lesions may be found in up to 90% of critically ill patients within 3 days of admission (2), of which less than 50% will have occult bleeding (defined as guaiac-positive gastric aspirate or guaiac-positive stool) and approximately 5% (3, 4) will have overt bleeding (defined as hematemesis, bloody gastric aspirate, melena, or hematochezia). However, this does not necessarily translate into clinically significant gastrointestinal bleeding (defined as overt bleeding in the presence of hypotension, tachycardia or orthostasis, drop in hemoglobin of >2 g/dL, or need for surgery (5)), whose incidence seems to have decreased over the years. In studies published before 1999, the incidence of clinically significant gastrointestinal bleeding was between 2% and 6% in patients not receiving prophylaxis (5). However, in studies published since 2001, the incidence has been reported to range between 0.1% and 4% with or without prophylaxis (6) which is related to better overall critical care, including increasing use of early enteral feeding. This alongside with concerns related to reported increased frequency of infectious complications (nosocomial pneumonia and *Clostridium difficile* infections (7, 8)) has challenged the traditional cornerstone of pharmacological prophylaxis with agents that suppress gastric acid for stress ulcer prophylaxis (9).

Materials and methods

A group of physicians (specialists in Gastroenterology and Intensive Care Medicine), nurses, pharmacists and economists with special interest and expertise in stress ulcer prophylaxis and/or evidence-based medicine were identified and invited to participate in this guideline.

Subtopics along with Population, Intervention, Comparison, and Outcomes (PICO) questions (10) were formulated and delegated to individual authors within the group who, after a nonsystematic literature

review conducted in PubMed and Cochrane Library through February 2018, handed in a draft for internal peer review.

Trial data identified by the search strategy was considered to represent the best-quality evidence. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system principles guided assessment of quality of evidence from high to very low and were used to determine the strength of recommendations (11). To reach consensus for the recommendations we used a two-round (self-administered questionnaire with no meetings among the participants) simple Delphi method (12) and strong agreement was considered if greater than 80% agreement threshold between panel members. A strong recommendation was worded as “we recommend” and a weak recommendation as “we suggest”.

The guideline was presented and accepted without revisions at the annual symposium of the Portuguese Society of Intensive Care Medicine in Oporto.

Statements

Statement 1

we recommend maintaining (or initiating) therapy with agents that suppress gastric acid (namely proton-pump inhibitors) in patients with compelling indications for acid suppression

strong recommendation, moderate quality of evidence

rational

Several clinical situations require gastric acid suppression (namely proton-pump inhibitors) and indications should be respected, both in the ambulatory and hospital (including intensive care) settings.

Patient with compelling indications include:

- known peptic ulcer disease in healing phase, and maintenance phase in selected circumstances [>50 years old; multiple comorbidities; persistent symptoms; NSAID-negative and *Helicobacter pylori*-negative ulcers; need to continue NSAID or failure to eradicate *Helicobacter pylori*; ulcers complicated at the outset; and giant (>2cm), refractory or recurrent ulcers) (13)
- treatment of *Helicobacter pylori* infection (14)
- Zollinger-Ellison syndrome and other hypersecretory conditions (15)
- gastroesophageal reflux disease and acid-related complications (ie, erosive esophagitis or peptic stricture) (16) and Barrett's esophagus (17)
- eosinophilic esophagitis (18)
- dual antiplatelet therapy or concomitant anticoagulant therapy (19)

Other approved indications (which should be discussed in a case-by-case basis) include:

- Uninvestigated dyspepsia (20) and epigastric pain syndrome (21)

Approved indications may vary with specific acid suppressants, and therefore labelling indications should be considered.

Statement 2

we recommend prophylaxis with agents that suppress gastric acid rather than no prophylaxis in patients who have one *major* risk factor or two *minor* risk factors for stress ulceration

major risk factor:

- coagulopathy (defined as a platelet count <50,000/m^3, an International Normalized Ratio superior to 1.5, or a partial thromboplastin time superior to 2 times the control value)
- respiratory failure (defined as the need for mechanical ventilation for at least 48h)
- traumatic brain injury (Glasgow Coma Scale score ≤8), traumatic spinal cord injury, or burn injury (>35% of the body surface area)
- sepsis [acute change in total SOFA score ≥2 points consequent to infection]

minor risk factors:

- acute or chronic renal failure (needing intermittent or continuous renal replacement therapy)
- shock (defined as continuous infusion with vasopressors or inotropes, mean arterial blood pressure below 70 mmHg or plasma lactate level equal or superior to 4 mmol/l)
- chronic hepatic failure (defined as cirrhosis proven by biopsy, history of variceal bleeding or hepatic encephalopathy)
- glucocorticoid therapy (≥250 mg hydrocortisone equivalent per day)
- multiple trauma with Injury Severity Score ≥16

strong recommendation, low quality of evidence

rational

Meta-analysis and systematic reviews (5, 22, 23) have consistently shown that agents that suppress gastric acid (namely histamine-2-receptor antagonists and/or proton-pump inhibitor) are superior to placebo in reducing the risk of clinically significant gastrointestinal bleeding. However, a recent meta-analysis (24) suggested that in patients receiving enteral, feeding pharmacologic stress ulcer is not beneficial and combined interventions may even increase the risk of some infectious complications. This metanalysis has been criticized and a number of large phase-III trials comparing pharmacological prophylaxis and placebo are under way. Their results and subsequently updated meta-analyses are expected to provide important more relevant data on the balance between benefits and harms of stress ulcer prophylaxis (25).

Most important is that the incidence of stress ulcer-related gastrointestinal bleeding is not equally shared across the spectrum of patients admitted to intensive care, and certain patients appear more at risk for bleeding.

A large multicenter prospective cohort study (3) identified coagulopathy (defined as a platelet count <50,000/m^3, an International Normalized Ratio superior to 1.5, or a partial thromboplastin time superior to 2 times the control value) and respiratory failure (defined as the need for mechanical ventilation for at least 48h) as *major* risk factors for clinically significant gastrointestinal bleeding. The robustness of these risks factors has been confirmed in at least one other smaller observational study (26).

These older studies have been criticized because clinical practice underwent major changes (9) in the last 20 years, which have reduced the incidence of stress ulcer-related gastrointestinal bleeding. Moreover, in line with what was previously described, a recent exploratory randomized clinical trial (27) comparing pharmacologic prophylaxis (with proton-pump inhibitors) and placebo in mechanically ventilated critically ill patients anticipated to receive enteral nutrition did not show benefit (or harm) of acid suppression. Because this was a feasibility trial, no firm evidence could be inferred, and the final conclusion is that it is possible to administer pharmacologic prophylaxis promptly after commencing mechanical ventilation.

Patients with traumatic brain injury (Glasgow Coma Scale score ≤8), traumatic spinal cord injury, or burn injury (>35% of the body surface area) have been routinely excluded from these studies because of a presumed high-risk of stress ulcer-related gastrointestinal bleeding most likely mediated through neurological pathways (28). Nevertheless, small randomized controlled trials (29-31) with different acid suppression regimens have demonstrated significant protection from stress ulcer-related gastrointestinal bleeding in these high-risk populations.

No study has been performed specifically in sepsis, however stress ulcer prophylaxis has been an integral part of care of septic patients and is recommended by current guidelines (32). This makes special sense attending to the new sepsis definitions (33) in which the infection related dysregulated host response has to be associated to a severe (life-threatening) organ dysfunction (identified as an acute change in total SOFA score ≥2 points), and thus including multiple risk factors.

The evidence supporting other *minor* risk factors for stress ulcer-related gastrointestinal bleeding is weaker, as a result of a high risk of systematic and random errors. However, an increasing number of risk factors is associated with an increased risk of bleeding (34), and international guidelines recommended stress ulcer prophylaxis for patients with two or more risk factors (35). In the original description of stress-ulcer bleeding, hypotension (alongside to sepsis and respiratory failure) was associated to stress-related mucosal damage (36). A recent inception cohort study identified the presence of three or more comorbidities (including glucocorticoid therapy), preexisting liver disease, renal failure (with use of renal replacement therapy), coexisting or acute coagulopathy and higher SOFA-score as significant risk factors for stress-ulcer bleeding after multivariate analysis (37). In another large cohort study (38) acute kidney injury (assessed by maximum serum creatinine level) was independently associated with increased risk of gastrointestinal bleeding in patients mechanically ventilated for more than 48 hours. Also, a small prospective randomized trial (31) demonstrated independent significance for the Injury Severity Score.

Statement 3
we recommend the use of a proton-pump inhibitor when prophylaxis with agents that suppress gastric acid is indicated
strong recommendation, low quality of evidence

rational

The choice of the pharmacological prophylaxis agent should take into account factors related to effectiveness, adverse effects and cost.

Sucralfate, a mucosa-protective agent, alone has traditionally been considered as inferior to histamine-2-receptor antagonists for stress ulcer prophylaxis (5, 39). While this has been challenged in a recent meta-analysis of randomized controlled trials (40) the results have been criticized because of significant heterogeneity between studies, of which only three had clinically significant gastrointestinal bleeding as reported outcome (41).

The efficacy of proton-pump inhibitors and to histamine-2-receptor antagonists in preventing stress-ulcer bleeding in critically ill patients has been compared in several randomized control trials and meta-analyses (23, 42-46). The most recent and complete meta-analyses of randomized controlled trials (23, 42) consistently demonstrated that proton-pump inhibitors were more effective than histamine-2-receptor antagonists at reducing clinically significant gastrointestinal bleeding, although this was not accompanied by a reduction of intensive care unit mortality or length of stay. The robustness of these conclusions are limited by the trial methodologies, differences between lower and higher quality trials, sparse data and possible publication bias. An ongoing Cluster-randomized crossover trial [Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG): study number 1415-01] will compare proton-pump inhibitors and to histamine-2-receptor antagonists and the results are expected to provide more relevant data (25).

There are multiple pharmacoeconomic analysis (47-49) focused on the comparison between histamine-2-receptor antagonists and proton pump inhibitors for the prophylaxis of stress ulcer-related gastrointestinal bleeding. Results are contradictory, mainly due to the use of different clinical inputs, and there is no strong evidence on which is the most effective alternative. Data from the most recent meta-analysis of clinical trials indicate that proton pump inhibitors should be used. However, if one relies on a propensity score-matched observational cohort study, histamine-2-receptor antagonists are the preferred option (49). The only clear conclusion is that, as the cost of prophylaxis is small when compared to the costs of the complications, the most effective alternative will constitute a dominant alternative (49).

Although the quality of evidence is suboptimal proton-pump inhibitors have been the preferred regimen in intensive care units across Europe, United States and Canada (50, 51). Finally, it is acknowledged that the published literature on this issue derives from heterogeneous populations of critically ill patients that may differ from the population at risk identified by the previous recommendation. Also, the expected adverse effects proton-pump inhibitors are a concern and must be taken into account. Nevertheless, the desirable consequences of stress ulcer prophylaxis with proton-pump inhibitor are expected to outweigh the undesirable consequences among the population at risk.

Statement 4
we make no recommendation regarding specific proton-pump inhibitor regimens

rational

The ideal drug regimen should be effective in reducing the risk of ulceration, with a low potential for adverse effects and drug interactions, with pharmacokinetic characteristics that facilitate its use in patients with organ dysfunction and should be cost-effective.

There is no head-to-head comparison between different proton-pump inhibitor-based regimens (including drug, dosing, route of administration and galenic formulation) and heterogeneity across studies (comparing proton-pump inhibitor to other regimens) impairs comparison of effect between the individual proton-pump inhibitor-regimens tested to date. *A priori* defined subgroup analysis of at least one meta-analysis suggests that choice of route of administration (enteral *vs* intravenous) and dosing (once *vs* twice a day) does not affect the results (41, 43).

In relation to route of administration, multiple factors (*e.g.* vasopressor use, altered gastric emptying and motility, feeding tube and nutrient interactions) may influence enteral absorption in critically ill patients and the intravenous route is generally preferred (52). This is disputed by a study showing that, despite a lower bioavailability, enteral lansoprazole suppresses acid in intensive care unit patients to a greater extent than the intravenous formulation (53). However, this is not confirmed by further studies and lansoprazole needs a complex and labor intensive galenic formulation for feeding tube administration.

Due to its safety in (at least moderate) organ dysfunction, lower probability of drug-drug interactions, and available formulations, intravenous pantoprazole (40 mg *qd*) may be a reasonable choice (54). However, the definite choice of the specific proton-pump inhibitor regimen should be based on individual patients' and medical values, experience, product labelling, cost-benefit analyses, and anticipated risks of drug-drug interactions and of adverse effects. Table 1 provides a comparison of the different available intravenous proton-pump inhibitor and to histamine-2-receptor antagonists-based regimens

Table 1 – Comparison of the different available proton-pump inhibitor and to histamine-2-receptor antagonists-based regimens.

drug	pharmaceutical formulation	dosing	dosing and route of administration	reconstitution and administration	dose adjustment	relevant *major* pharmacological interactions (grade 1-2 impact)
pantoprazol	powder for injection solution	40mg *qd*	intravenous	reconstitute 40mg with 10cc of 0.9% NaCl and administer for 2 minutes (if necessary dilute in 100cc of 0.9% NaCl or 5% dextrose in H_2O)	hepatic failure (moderate to severe)	azoles[a] reverse protease inhibitors[b]
	gastroresistant tablet		oral[a]	–		
omeprazol	powder for injection solution	40mg *qd*	intravenous	reconstitute 40mg with 5cc of 0.9% NaCl and administer for 20-30 minutes (if necessary dilute in 100cc of 0.9% NaCl or 5% dextrose in H_2O)	hepatic failure (moderate to severe)	azoles[b] reverse protease inhibitors[b] clopidogrel[c]
	gastroresistant capsule		oral	–		
			endogastric or endojejunal feeding tube	open capsules, disperse the content in 40 mL of non-carbonated water, shake vigorously and allow to stand for 2 minutes (until thick)		
lansoprosol	gastroresistant capsule	30mg *qd*	oral	–	hepatic failure (moderate to severe)	azoles[b] reverse protease inhibitors[b]
			endogastric or endojejunal feeding tube	open capsules and disperse the content in 40 mL of (orange or apple) juice		
	orodispersible tablet		oral	–		
			endogastric or endojejunal feeding tube	disperse in 10 mL of non-carbonated water		
esomeprazol 40mg i.v. qd	powder for injection solution	40mg *qd*	intravenous	reconstitute 40mg with 5cc of 0.9% NaCl and administer for 2 minutes (if necessary dilute in 100cc of 0.9% NaCl or 5% dextrose in H_2O)	hepatic failure (moderate to severe)	azoles[b] reverse protease inhibitors[b] clopidogrel[c]
	gastroresistant capsule		oral	–		
			endogastric or endojejunal feeding tube	open capsules, disperse the granules in 40 mL of non-carbonated water		
	gastroresistant tablet		oral	–		
ranitidine	powder for injection solution	50mg *tid*	intravenous	reconstitute 50 mg with 20cc of 0.9% NaCl and administer for 5 minutes *continuous perfusion*: after a 50mg bolus (see above), dilute 150mg to 250cc of 0.9% NaCl or 5% dextrose in H2O in perfusion at 10.4cc/h	renal failure (clearance <50 mL/min/m^2)	azoles[b]
	coated tablet	150mg *qd*	oral	–		
			endogastric or endojejunal feeding tube	grind tablets and reduce to powder, and disperse the content in in 40 mL of non-carbonated water		

[a] no data on enteral administration; consider alternative drugs
[b] consider alternative drugs
[c] consider substitution for pantoprazol

Statement 5
we suggest to use histamine-2-receptor antagonists in patients with *Clostridium difficile* infection and indications for stress ulcer prophylaxis
weak recommendation, very low quality of evidence

rational

Accumulating evidence suggests that use of agents that suppress gastric acid may increase the frequency of infectious complications (7, 8, 55). The most recent and comprehensive meta-analysis (56) found that therapy with agents that suppress gastric acid was associated with a significant risk of *Clostridium difficile* infections, but that the risk is lower for histamine-2-receptor antagonists than with proton-pump inhibitors.

In the critically ill population, the increased risk for *Clostridium difficile* infections is still controversial because metanalysis are underpowered for detecting a modest increase in these events (57). Nevertheless, the risk of *Clostridium difficile* infections remains higher in patients receiving proton-pump inhibitors compared with patients receiving histamine-2-receptor antagonists (7). Moreover, observational studies (58, 59) show that continued proton-pump inhibitors use during the incident case of *Clostridium difficile* infections increased the risk of recurrence.

Based on available data and given the significant disease burden and mortality associated with *Clostridium difficile* infections, proton-pump inhibitors should be avoided and histamine-2-receptor antagonists should be the preferred when stress ulcer prophylaxis is indicated (57).

Statement 6
we recommend stopping prophylaxis with agents that suppress gastric acid when risk factors are no longer present and the patient is receiving enteral nutrition
strong recommendation, low quality of evidence

rational

Acid suppressants are inappropriately continued in a large proportion of patients after the resolution of risk factors and even after intensive care unit or hospital discharge, thus making the potential risks and costs associated with stress ulcer prophylaxis not confined to the intensive care unit (60). This is line with studies that conclude that 88.5% of stress ulcer prophylaxis in non-intensive care unit patients is inappropriate (61), and that a relatively restrictive stress ulcer prophylaxis program not only reduces inappropriate use without increases in rates of hospital-related gastrointestinal bleeding, but also results in an estimated annualized cost savings of more than US$ 200.000 (62).

As previously described (24) there is some evidence to suggest that in patients receiving enteral feeding pharmacologic stress ulcer prophylaxis is not beneficial and combined interventions may even increase the risk of some infectious complications. While compositely, the evidence is still insufficient to justify withholding stress ulcer prophylaxis from patients who are at high risk for gastrointestinal bleeding it is sufficient compelling to support stopping prophylaxis when risk factors are no longer present and the patient is receiving enteral nutrition.

Patients should thus be daily evaluated, during multidisciplinary care rounds, for the continued need for prophylaxis, and once the patient is receiving enteral nutrition and risk factors are no longer present, stress ulcer prophylaxis should be discontinued. This strategy will reduce the overuse and continuation of agents that suppress gastric acid upon discharge and in the outpatient setting (63). As one of the more common indications for stress ulcer prophylaxis is mechanical ventilation, extubation is crucial moment to identify and possibly discontinue acid suppression therapy (57).

General Algorithm

The general algorithm for the prophylaxis of stress ulcer bleeding in the intensive care unit is presented in Figure 1. Patient with compelling indication for acid suppression should have an acid-suppressive regimen in accordance with indication (Statement 1). Then the risk for bleeding should be considered in each patient and use of stress ulcer prophylaxis is appropriate on those with high risk. Patients at low risk should not start (or discontinue if previously initiated) stress ulcer prophylaxis (Statement 2). When a stress ulcer prophylaxis is recommended the use of a proton-pump inhibitor is indicated (Statement 3), with no specific recommended regimen (Statement 4). The exception is the case of *Clostridium difficile* infection for which a histamine-2-receptor antagonists is preferred (Statement 5). Once the patient is receiving enteral nutrition and risk factors are no longer present stress ulcer prophylaxis should be discontinued (Statement 6).

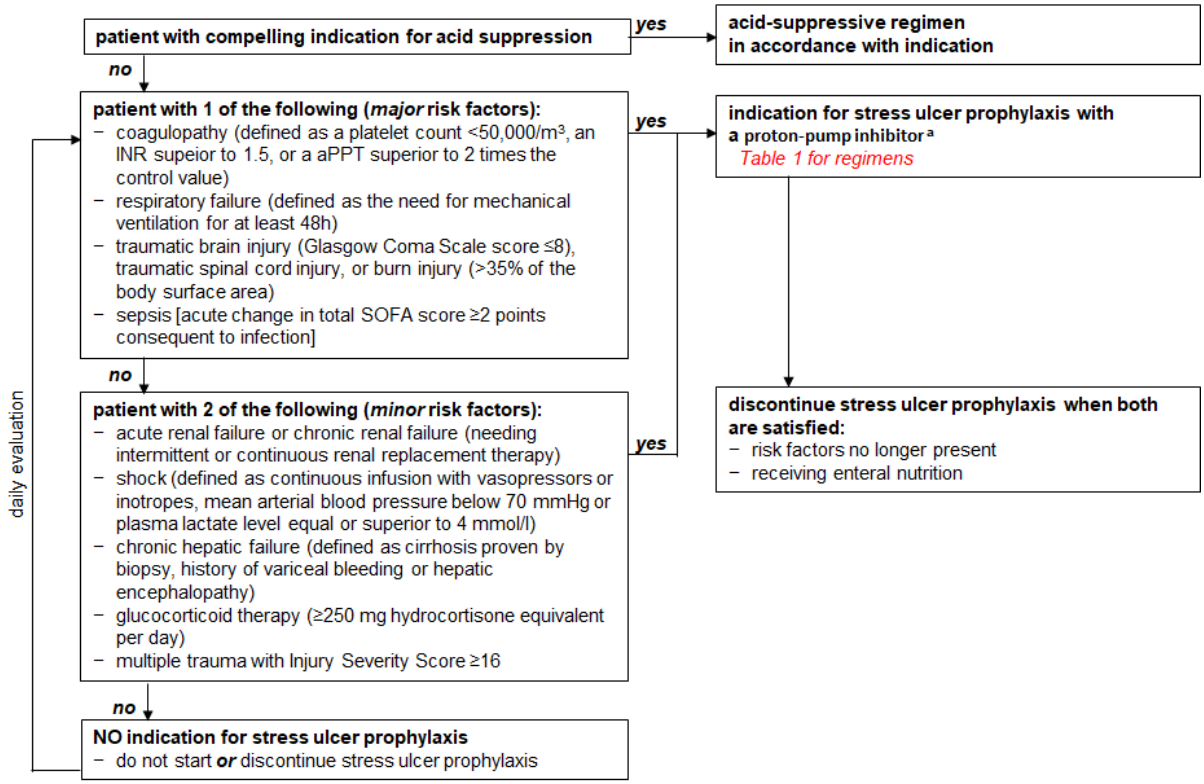

Figure 1 – Algorithm for prophylaxis of stress ulcer bleeding in the intensive care unit.
[a] if *Clostridium difficile* infection and indications for stress ulcer prophylaxis prefer histamine-2-receptor antagonists

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