Guideline for Stress Ulcer Prophylaxis in the Intensive Care Unit

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Limitations: Applies to patients aged > 18 years

List of abbreviations:
H2RA = histamine-2-receptor antagonist
ICU = intensive care unit
GI = gastrointestinal
RCT = randomized controlled trial
PICO = population, intervention, comparator, outcome
PPI = proton pump inhibitor
SUP = stress ulcer prophylaxis

1. INTRODUCTION

SUP is commonly used in the ICU, and is recommended internationally[1]. This guideline from the Danish Society of Intensive Care Medicine (DSIT) and the Danish Society of Anesthesiology and Intensive Care Medicine (DASAIM) aims to summarize current evidence and give clinical recommendations for the use of SUP in the ICU.

Epidemiology

Upper gastrointestinal (GI) mucosal lesions can be found endoscopically in up to 90% of ICU patients[2]. Depending on definitions and case-mix, the reported incidences of overt GI bleeding range from 0.6 to 8.5% in all ICU patients, reaching up to 15% in patients not receiving SUP[3-9]. However, most studies are from the past millennium with a declining incidence in more recent studies, definitions of bleeding and the clinical significance are inconsistent, and European multicenter studies generalizable to Danish conditions are few. Thus the current incidence of stress ulcer bleeding in ICU patients is largely unknown.

Risk factors

In a prospective multicenter cohort study (n=2256) by Cook et al, risk factors for clinically important GI bleeding were mechanical ventilation for more than 48 hours (odds ratio 15.6) and coagulopathy (odds ratio 4.3)[3]. Other commonly cited, but less validated risk factors include severe sepsis and septic shock as stated by the Surviving Sepsis Campaign guidelines; head or spinal trauma, hepatic failure, renal failure, major burns, organ transplantation, high dose glucocorticoid therapy, previous peptic ulcer disease or upper GI bleeding [1,10].

Prognosis

Stress ulcer bleeding is a serious complication. Cook et al. demonstrated a mortality rate of 49%, mostly from decompensation of an underlying condition or multiorgan failure, compared to 9% for patients without GI bleeding[3]. When adjusting for confounding and including an additional multicenter database, the same group confirmed that overt GI bleeding was associated with increased mortality (relative risk ranged from 1.0 to 4.9)[6].

Types of SUP

In modern intensive care, pharmacological options for stress ulcer prevention include proton pump inhibitors (PPIs) and histamine-2-receptor antagonist (H2RAs). Sucralfate and antacids are rarely used in the ICU. Both PPIs and H2RAs raise the intragastric pH and both can be given either orally or intravenously. PPIs may interact with the antitrombotic effect of clopidogrel, thereby potentially triggering cardiovascular events[11]. Prolonged effect of diazepam, carbamezepine, phenytoin, tricyclic antidepressants, escitalopram, disulfiram, metoclopramide and voriconazol may also occur. H2RAs may interact with phenytoin, theophylline, warfarin, beta-blockers, anti-diabetics and some benzodiazepines, thereby prolonging their effect. The clinical significance of these interactions in the ICU is unknown.

2. CONTRIBUTORS, METHODS, SEARCH STRATEGY, AND LEVEL OF EVIDENCE

Contributors

Upon open call for contributors to the guideline by e-mail to the members of DASAIM, a group of physicians with special interest

and expertise in SUP and/or in evidence-based medicine was constituted.

Research question
Should stress ulcer prophylaxis be used in adult critically ill patients in the ICU?

PICO questions
Subtopics and PICO questions [12] were formulated and delegated to individual authors within the group, who in turn handed in a draft for internal peer review.

Population: adult critically ill patients in the ICU
Intervention: stress ulcer prophylaxis
Comparator: any
Outcome: mortality, gastrointestinal bleeding, pneumonia, morbidity, clostridium difficile enteritis and serious adverse events

Search strategy
Using the created PICOs as search terms, PubMed and Cochrane Library were systematically searched for literature. In addition, we hand-searched reference lists of relevant publications. No study designs were per se excluded.

Inclusion criteria
Adult critically ill patients in the ICU.

Exclusion criteria
Age less than 18 years. Studies/trials conducted in a non-ICU setting.

Validation and grading of evidence
We evaluated trial data using the GRADE approach (www.gradeworkinggroup.org). The GRADE system does not grade the quality of single studies but sequentially assesses the quality of evidence from the best available data for the outcomes of interest followed by assessment of the balance between benefits versus risks, burden, and cost [13]. Literature identified by the search strategy was considered to represent the best-quality evidence. The quality of the evidence was quantified (high, moderate, low or very low) and potentially downgraded in the domains 1) risk of bias, 2) inconsistency of results, 3) indirectness of the evidence, 4) imprecision of results, and 5) other considerations including suspicion of publication bias, and was downgraded based on the number of domains with concerns (Table 1).

Recommendations
The recommendations were agreed upon in the group, and if total agreement could not be obtained, the group voted; 2/3 of the votes were needed to issue a strong recommendation. Strong recommendations (marked 1) were given the wording 'we recommend' and weak recommendations (2) 'we suggest'. The level of evidence was graded high (marked A), moderate (B), low (C) or very low (D) based on the number of domains that were downgraded in adherence to GRADE.

Peer-review and approval
The guideline was presented and accepted without revisions at the annual symposium of the DSIT at Hindsgavl,

Denmark, 23 January 2014, and finally accepted for publication by DASAIM on 26 January 2014.tre

Table 1. Rating the quality of evidence. From "GRADE guidelines 3: Rating the quality of evidence" by Balshem et al. [13]

Study design	Quality of Evidence	Lower if	Higher if
Randomized trial ➡	High	Risk of bias -1 Serious -2 Very serious	Large effect +1 Large +2 Very large
	Moderate	Inconcistency -1 Serious -2 Very serious	Dose response +1 Evidence of a gradient
Observational study ➡	Low	Indirectness -1 Serious -2 Very serious Imprecision -1 Serious -2 Very serious	All plausible confounding: +1 Would reduce a demonstrated effect or
	Very low	Publication bias -1 Likely -2 Very likely	+1 Would suggest a spurious effect when results show no effect

3. SUP vs. PLACEBO/NO PROPHYLAXIS
Population: adult critically ill patients in the ICU
Intervention: stress ulcer prophylaxis
Comparator: placebo/no prophylaxis
Outcome: mortality, gastrointestinal bleeding and pneumonia

Recommendation
We recommend not using SUP routinely for adult critically ill patients in the ICU (1C).

Table 2. Summary of findings – SUP vs placebo or no prophylaxis

Out-come	Studies (n)	Event rate *SUP*	Event rate *placebo or no profylaxis*	Relative effect (95%CI)	Quality of evidence (GRADE)
GI-bleed-ing	20	67 / 1001	161 / 970	RR 0.44 (0.28-0.68)	Low
Mor-tality	15	155 / 806	164 / 798	RR 1.00 (0.84-1.20)	Very low
Pneu monia	7	64 / 510	56 / 498	RR 1.23 (0.86-1.78)	Very low

Source: Krag et al[14]. RR= Relative risk CI = Confidence interval

Background
Recently, Krag et al published a systematic review and meta-analysis with trial sequential analysis (TSA) on SUP in adult critically ill patients in the ICU[14]. SUP with PPI or H2RA was not statistically significantly different from placebo or no prophylaxis

in terms of mortality, GI bleeding or pneumonia (summary of findings in table 2). Concerning GI bleeding, a statistically significant difference was found in the conventional meta-analysis, however in the TSA analysis it was shown that only 22% of the required information size had been accrued. In line with this, it has been concluded that previous meta-analyses have been underpowered to reach firm conclusion [15-22].
In conclusion, there is no firm evidence for benefit or harm of SUP as compared to placebo or no prophylaxis. Consequently, we recommend that clinicians who continue to use SUP do so in the context of high quality RCTs.

4. PPI vs. H2RA

Population: adult critically ill patients in the ICU
Intervention: proton pump inhibitors
Comparator: histamine 2 receptor antagonists
Outcome: mortality, gastrointestinal bleeding, pneumonia, morbidity, clostridium difficile enteritis or serious adverse events

Recommendation
We suggest using PPIs when stress ulcer prophylaxis is indicated in adult critically ill patients in the ICU (Grade 2C).

Background
PPIs are generally well tolerated and considered superior in the treatment of acid-related conditions such as peptic ulcer disease. PPIs are more effective at keeping a constant gastric pH > 4.0, which may be sufficient to prevent stress ulceration, compared to H2RAs[23-25] . A recently published meta-analysis in medical and surgical ICU patients concluded that PPIs reduce clinically important bleeding and overt upper GI bleeding, when compared to H2RAs[15]. The findings are in line with another recently published meta-analysis, which concluded that PPIs significantly decreased the incidence of GI bleeding as compared to H2RAs (1.3 versus 6.6 %, OR 0.30, 95% CI 0.17-0.54)[26]. No difference in mortality, duration of ICU stay or in the incidence of nosocomial pneumonia was found in either of the meta-analyses. However, the quality of evidence for a reduction in GI bleeding is low (summary of findings table below). Consequently, more research into possible unwanted effects of acid suppression is warranted; e.g. Clostridium difficile associated colitis, which may be associated to the use of PPIs and H2RAs[27,28].

Table 3. Summary of findings - PPI vs H2RA

Outcome	Studies (n)	Event rate PPI	Event rate H2RA	RR (95% CI)	Quality of evidence (GRADE)
Clinically important GI bleeding	12	12 / 1019	38 / 595	0.36 (0.19-0.68)	Low
Overt GI bleeding	14	41 / 1077	101 / 643	0.35 (0.21-0.59)	Moderate
Mortality	8	127 / 726	100 / 470	1.01 (0.83-1.24)	Moderate
Pneumonia	8	66 / 626	50 / 474	1.06 (0.73-1.52)	Moderate

Source: Alhazzani et al, 2013[15] RR = Relative risk CI = Confidence interval

5. SUP AND NUTRITION

Population: adult critically ill patients in the intensive care unit receiving enteral nutrition
Intervention: SUP
Comparator: any
Outcome: mortality, gastrointestinal bleeding, pneumonia, morbidity, clostridium difficile

Recommendation
There is insufficient evidence to make any recommendation.

Background
Recently, Krag et al published a systematic review and meta-analysis with TSA on SUP in adult critically ill patients in the ICU[14] . SUP with PPI or H2RA was not statistically significantly different from placebo or no prophylaxis, in terms of mortality, GI bleeding or pneumonia. In the predefined subgroup-analyses of patients receiving enteral nutrition vs. patients not receiving enteral nutrition, no statistically significant difference was found. In a 2010 meta-analysis by Marik et al. the incidence of nosocomial pneumonia was increased in the subgroup of patients who received both H2RA and enteral nutrition[19]. However, this finding is limited by the fact that both the quantity and quality of the included trials were low. RCTs are needed to investigate the relation between enteral nutrition and SUP in ICU patients.

6. SUP IN ICU SUBPOPULATIONS: TRAUMA, BURN, SEPTIC AND CARDIOTHORACIC PATIENTS

Population: adult critically ill trauma, burn, sepsis or cardiothoracic patients in the ICU
Intervention: stress ulcer prophylaxis
Comparator: any
Outcome: mortality, gastrointestinal bleeding, pneumonia, morbidity or serious adverse events

Recommendation
There is insufficient evidence to make any recommendation.

Background
A systematic search of RCTs on SUP in trauma, burn, septic and cardiothoracic patients in the ICU was performed. We did not identify any RCTs evaluating patient-centered outcome measures in these specific ICU subgroups. Based on the limited quantity and quality of overall evidence for SUP in the ICU[14,15] we find no basis for making any specific recommendations for ICU subgroups.

SUMMARY:
Stress ulcer prophylaxis (SUP) is commonly used in the intensive care unit (ICU), and is recommended in the Surviving Sepsis Campaign guidelines 2012. The present guideline from the Danish Society of Intensive Care Medicine and the Danish Society of Anesthesiology and Intensive Care Medicine sums up current evidence and gives clinical recommendations for SUP in the ICU. The GRADE approach was used for grading the evidence (www.gradeworkinggroup.org). In conclusion, existing meta-analyses have been underpowered to reach firm conclusions. We recommend not using SUP routinely for adult critically ill patients in the ICU outside the context of randomized controlled trials (GRADE 1C). No robust evidence supports recommendations for subpopulations in the ICU such as septic, burn, trauma, cardiotho-

racic or enterally fed patients. However, if SUP is considered clinically indicated in individual patients, we suggest using proton pump inhibitors over histamine-2-receptor antagonists (GRADE 2C).

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