# Guideline for Stress Ulcer Prophylaxis in the Intensive Care Unit

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Last literature review: Nov 1 2013 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<sup>1</sup>. 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<sup>2</sup>. 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<sup>3-9</sup>. 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)<sup>3</sup>. 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 <sup>1,10</sup>.

#### 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<sup>3</sup>. 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)<sup>6</sup>.

#### 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<sup>11</sup>. 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 <sup>12</sup> 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 <sup>13</sup>. 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. <sup>13</sup>

Study design	Quality of	Lower if	Higher if
	Evidence		
Randomized	High	Risk of bias	Large effect
trial 🔿		-1 Serious	+1 Large
		-2 Very serious	+2 Very large
	Moderate	Inconcistency	Dose
		-1 Serious	response
			+1 Evidence
		-2 Very serious	
		In all an attacks	of a gradient
Observational	Low	Indirectness	
at the state		-1 Serious	All plausible
study 🗪		-2 Very serious	confounding:
			+1 Would
		Imprecision	reduce a
		-1 Serious	demonstrated
		-2 Very serious	effect or
	Very low	Publication bias	+1 Would
	Verylow	-1 Likely	
		,	suggest a
		-2 Very likely	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-	Studies	Event	Event rate	Relative	Quality of
come	(n)	rate	placebo or	effect	evidence
		SUP	no	(95%CI)	(GRADE)
			profylaxis		
GI-	20	67 /	161 / 970	RR 0.44	Low
bleed-		1001		(0.28-	
ing				0.68)	
Mor-	15	155 /	164 / 798	RR 1.00	Very low
tality		806		(0.84-	
				1.20)	
Pneu	7	64 /	56 / 498	RR 1.23	Very low
monia		510		(0.86-	
				1.78)	
Source: Krag et al <sup>14</sup> . RR= Relative risk CI = Confidence interval					

#### Background

Recently, Krag et al published a systematic review and metaanalysis with trial sequential analysis (TSA) on SUP in adult critically ill patients in the ICU<sup>14</sup>. 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 <sup>15-22</sup>. 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<sup>23-25</sup>. 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<sup>15</sup>. 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)<sup>26</sup>. 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<sup>27,28</sup>

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

Source: Alhazzani et al, 2013<sup>15</sup> 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 metaanalysis with TSA on SUP in adult critically ill patients in the ICU<sup>14</sup>. 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<sup>19</sup>. 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

adult critically ill trauma, burn, sepsis or
cardiothoracic patients in the ICU
stress ulcer prophylaxis
any
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<sup>14,15</sup> 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 metaanalyses 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, cardiothoracic 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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