Guideline for Stress Ulcer Prophylaxis in the Intensive Care Unit

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This guideline has been approved by the Danish Society of Anesthesiology and Intensive Care Medicine (DASAIM) and the Danish Society of Intensive Care Medicine (DSIT) 26 January 2014

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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. 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. 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. 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). 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.

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. 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).

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 antithrombotic effect of clopidogrel, thereby potentially triggering cardiovascular events. 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 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. 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.

### Table 1. Rating the quality of evidence. From “GRADE guidelines 3: Rating the quality of evidence” by Balshem et al.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Quality of Evidence</th>
<th>Lower if</th>
<th>Higher if</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized trial</td>
<td>High</td>
<td>Risk of bias</td>
<td>-1 Serious -2 Very serious</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1 Very serious</td>
<td>+1 Large +2 Very large</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>Inconsistency</td>
<td>-1 Serious -2 Very serious</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2 Very serious</td>
<td>Dose response +1 Evidence of a gradient</td>
</tr>
<tr>
<td>Observational study</td>
<td>Low</td>
<td>Indirectness</td>
<td>-1 Serious -2 Very serious</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2 Very serious</td>
<td>All plausible confounding: +1 would reduce a demonstrated effect or</td>
</tr>
<tr>
<td></td>
<td>Very low</td>
<td>Imprecision</td>
<td>-1 Serious -2 Very serious</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2 Very serious</td>
<td>+1 would suggest a spurious effect when results show no effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Publication bias</td>
<td>-1 Likely -2 Very likely</td>
</tr>
</tbody>
</table>

### 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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies (n)</th>
<th>Event rate SUP</th>
<th>Event rate placebo or no prophylaxis</th>
<th>Relative effect (95%CI)</th>
<th>Quality of evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI-bleeding</td>
<td>20</td>
<td>67 / 1001</td>
<td>161 / 970</td>
<td>RR 0.44 (0.28-0.68)</td>
<td>Low</td>
</tr>
<tr>
<td>Mortality</td>
<td>15</td>
<td>155 / 806</td>
<td>164 / 798</td>
<td>RR 1.00 (0.84-1.20)</td>
<td>Very low</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>7</td>
<td>64 / 510</td>
<td>56 / 498</td>
<td>RR 1.23 (0.86-1.78)</td>
<td>Very low</td>
</tr>
</tbody>
</table>

Source: Krag et al. 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. 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

<table>
<thead>
<tr>
<th>Population</th>
<th>adult critically ill patients in the ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>proton pump inhibitors</td>
</tr>
<tr>
<td>Comparator</td>
<td>histamine 2 receptor antagonists</td>
</tr>
<tr>
<td>Outcome</td>
<td>mortality, gastrointestinal bleeding, pneumonia, morbidity, clostridium difficile enteritis or serious adverse events</td>
</tr>
</tbody>
</table>

**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 13-25. A recently published meta-analysis in medical and surgical ICU patients concluded that PPIs reduce clinically important bleeding and upper GI bleeding, when compared to H2RAs 26. 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.

### 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 27. 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-

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**Table 3. Summary of findings - PPI vs H2RA**

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

Source: Alhazzani et al, 2013 13-16 RR = Relative risk CI = Confidence interval
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).

7. REFERENCES