Stress ulcer prophylaxis in critically ill children: A systematic review and meta-analysis

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Background
Critically ill children are at increased risk of gastrointestinal bleeding. Many children are prescribed stress ulcer prophylaxis, most frequently with histamine-2 receptor antagonists (H2RAs) or proton pump inhibitors (PPIs), in attempts to reduce the risk of such bleeding, 60-78% of children receive these drugs during their PICU stay.1,2

Objectives
Our objective was to assess the effect of stress ulcer prophylaxis in critically ill children on the outcomes of gastrointestinal bleeding ( overt and clinically important), ventilator associated pneumonia (VAP) and Clostridium difficile-associated diarrhea.

Methods
Design: Systematic review and meta-analysis.

Searching: To identify trials we used PICUtrials.net (a repository of published randomized controlled trials (RCTs) in pediatric critical care identified by searching MEDLINE, EMBASE, LIILACS, and CENTRAL) using comprehensive search strategies, updated Jan 4, 2016).

Inclusion criteria: RCTs comparing any pharmacological prophylaxis with placebo or no intervention, enrolling children in a PICU.

Exclusion criteria: RCTs enrolling exclusively newborns, those only published as abstracts, and cross-over RCTs.

Study screening and data extraction: Pairs of reviewers screened studies and abstracted data independently.

Outcomes: We used the trial authors’ definitions of clinically important bleeding and VAP.

Analysis: In our primary analysis we combined all prophylactic interventions and we planned a subgroup analysis (sucralfate vs. acid suppression). We used the Cochrane Risk of Bias Tool to classify the trials’ risk of bias. We used RevMan 5.3 to conduct the meta-analysis, using a random-effects model.

Included randomized trials

- **RCTs identified via PICUtrials.net (n=320)**
- **Records identified via other sources (n=0)**

- Full-text RCTs assessed (n=302): Not stress ulcer prophylaxis.
- RCTs Excluded (n=21): Not stress ulcer prophylaxis.
- Full-text RCTs included (n=16)

**Description of included randomized trials**

<table>
<thead>
<tr>
<th>RCT</th>
<th>Participants</th>
<th>Intervention and feeding</th>
<th>Control</th>
<th>Outcomes reported</th>
<th>GRADE Working Group grades of evidence*</th>
<th>High quality</th>
<th>Moderate quality</th>
<th>Low quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulldo2</td>
<td>Randomized: 200</td>
<td>1. sodium citrate 60 mg/kg/day NG</td>
<td>None</td>
<td>GI bleeding: occult or slight</td>
<td>B</td>
<td>Occult bleeding: occult or slight</td>
<td>Occult bleeding: occult or slight</td>
<td></td>
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<tr>
<td>Hecce</td>
<td>Randomized: 136</td>
<td>2. ranitidine 2 mg/kg/day IV</td>
<td>None</td>
<td>GI bleeding: occult or slight</td>
<td>B</td>
<td>Occult bleeding: occult or slight</td>
<td>Occult bleeding: occult or slight</td>
<td></td>
</tr>
<tr>
<td>Hece</td>
<td>Randomized: 140</td>
<td>3. cimetidine 20 mg/kg/day IV</td>
<td>None</td>
<td>GI bleeding: occult or slight</td>
<td>B</td>
<td>Occult bleeding: occult or slight</td>
<td>Occult bleeding: occult or slight</td>
<td></td>
</tr>
<tr>
<td>Ediddo</td>
<td>Randomized: 60</td>
<td>4. sodium citrate 60 mg/kg/day NG</td>
<td>None</td>
<td>GI bleeding: occult or slight</td>
<td>B</td>
<td>Occult bleeding: occult or slight</td>
<td>Occult bleeding: occult or slight</td>
<td></td>
</tr>
<tr>
<td>Lacroix</td>
<td>Randomized: 40</td>
<td>5. ranitidine 2 mg/kg/day IV</td>
<td>None</td>
<td>GI bleeding: occult or slight</td>
<td>B</td>
<td>Occult bleeding: occult or slight</td>
<td>Occult bleeding: occult or slight</td>
<td></td>
</tr>
<tr>
<td>Lacroix</td>
<td>Randomized: 40</td>
<td>5. cimetidine 20 mg/kg/day IV</td>
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</tr>
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</table>

Conclusion:
Few trials of stress ulcer prophylaxis in critically ill children have been published and the overall quality of the evidence is very low. Any estimate of the effect of stress ulcer prophylaxis is very uncertain. There are also important opportunities to improve the conduct and reporting of trials of stress ulcer prophylaxis in critically ill children. The published trials used different definitions of bleeding, only 1 assessed VAP, and none assessed C. difficile-associated diarrhea.

Strengths of this review include rigorous searching strategies to identify relevant RCTs and a transparent approach to grading the quality of the evidence. We did not however, seek unpublished data from trial authors.

In conclusion, the published RCTs are not sufficient to assess the balance of risks and benefits. A large RCT focusing on outcomes important to clinicians and families is needed.

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