Stress ulcer, gastritis, and gastrointestinal bleeding prophylaxis in critically ill pediatric patients: A systematic review

Ludovic Reveiz, MD, MSc; Rafael Guerrero-Lozano, MD; Angela Camacho, MD; Lina Yara, MD; Paola Andrea Mosquera, Psi, MSc

Objective: To identify and evaluate the quality of evidence supporting prophylactic use of treatments for stress ulcers and upper gastrointestinal bleeding. Stress ulcers, erosions of the stomach and duodenum, and upper gastrointestinal bleeding are well-known complications of critical illness in children admitted to the pediatric intensive care unit.

Data Sources: Studies were identified from the Cochrane Central Register of Controlled Trials, PubMed, Lilacs, Scirus. We also scanned bibliographies of relevant studies.

Study Selection: This systematic review of randomized controlled trials assessed the effects of drugs for stress-related ulcers, gastritis, and upper gastrointestinal bleeding in critically ill children admitted to the pediatric intensive care unit.

Data Extraction and Synthesis: Two reviewers independently extracted the relevant data. Most randomized controlled trials were judged as having unclear risk of bias. When pooling two randomized controlled trials, treatment was significantly more effective in preventing upper gastrointestinal bleeding (macroscopic or important bleeding) compared with no treatment (two studies = 300 participants; relative risk, 0.41; 95% confidence interval, 0.19–0.91; I² = 12%). Meta-analysis of two studies found no significant difference in death rates among groups (two randomized controlled trials = 132 participants; relative risk, 1.39; 95% confidence interval, 0.70–2.79; I² = 4%). The rate of pneumonia was not significantly different when comparing treatment and no treatment in one study. When comparing ranitidine with no treatment, significant differences were found in the proportion of mechanically ventilated children with normal gastric mucosal endoscopic findings by histologic specimens (one randomized controlled trial = 48 participants; relative risk, 3.53; 95% confidence interval, 1.34–9.29). No significant differences were found when comparing different drugs (omeprazole, ranitidine, sucralfate, famotidine, amalget), doses, or regimens for main outcomes (deaths, endoscopic findings of erosion or ulcers, upper gastrointestinal bleeding, or pneumonia).

Conclusions: Although pooled data of two studies suggested that critically ill pediatric patients may benefit from receiving prophylactic treatment to prevent upper gastrointestinal bleeding, we found that high-quality evidence to guide clinical practice is still limited. (Pediatr Crit Care Med 2010; 11:124–132)

Key Words: children; stress ulcer; gastrointestinal bleeding; intensive care unit; critical care; prophylaxis; systematic review

Stress ulcers of the stomach and duodenum as well as upper gastrointestinal (UGI) bleeding are well-known complications of critical illness in children admitted to a pediatric intensive care unit (ICU). The prevalence of stress ulceration in critically ill adults and children may vary depending on the severity of the illness and methods used for diagnosis. A cohort of 1006 consecutive admissions enrolled in a pediatric ICU reported that 10.2% of pediatric participants had UGI bleeding and 1.6% had clinically significant UGI bleeding (1). Clinically important UGI bleeding has an important attributable morbidity and mortality in adults, associated with a significant risk of death (relative risk [RR], 4.1; 95% confidence interval [CI], 2.6–6.5) and an excess length of ICU stay of approximately 4 to 8 days (2). Clinically important UGI bleeding is defined as macroscopic bleeding that results in hemodynamic instability and the need for red blood cell transfusion and may lead to complications, such as gastrointestinal perforations and surgery (3, 4).

Prophylaxis against stress ulcers has been recommended for the prevention of UGI bleeding in critically ill adults patients. A systematic review published more than one decade ago found that prophylaxis with histamine2-receptor antagonists decreases the occurrence of overt gastrointestinal bleeding (odds ratio [OR], 0.58; 95% CI, 0.42–0.79) and clinically important bleeding (OR, 0.44; 95% CI, 0.22–0.88) (5). Another study found that, among critically ill adult patients requiring mechanical ventilation, those receiving ranitidine had a significantly lower rate of clinically important gastrointestinal bleeding than those treated with sucralfate and no significant differences were found in the rates of ventilator-associated pneumonia, the duration of the stay in the ICU, or mortality (6). However, a more recent integrative study found that ranitidine was ineffective in the prevention of UGI bleeding in patients in intensive care compared with placebo (OR, 0.72; 95% CI, 0.30–1.70) and might increase the risk of pneumonia when compared with sucralfate (OR, 1.35; 95% CI, 1.07–1.70) and that studies on sucralfate do not provide conclusive positive results (7). A guideline on stress ulcer prophylaxis published in 2006 recommended pharmacologic intervention in adults admitted to the ICU who have coagulopathy, require mechanical ventilation for >48 hrs, have a his-
ory of gastrointestinal ulceration or bleeding within 1 yr before admission, or have at least two of the following risk factors: sepsis, ICU stay of >1 wk, occult bleeding lasting ≥6 days, and use of >250 mg of hydrocortisone or the equivalent (8). Unfortunately, there is still conflicting evidence concerning prophylaxis for stress ulcers in children and we did not find any systematic review on this topic.

The aims of the systematic review presented here are to assess the best evidence on the effects of interventions for stress ulcer in children, to identify gaps in the literature, and to suggest further clinical investigation.

METHODS

Literature Search

Relevant randomized controlled trials (RCTs) were identified from the Cochrane Central Register of Controlled Trials (The Cochrane Library 2008, Issue 3), PubMed (1966 to June 2008), LILACS (1982 to June 2008), and Scirus (June 2008). A search strategy to locate studies on stress ulcer, UGI in children was structured and adapted according to each electronic database (Appendix A). The International Clinical Trials Registry Platform search portal (http://www.who.int/trials/search/Default.aspx), the metaRegister of controlled trials (www.controlled-trials.com) and http://clinicaltrials.gov/ were searched for ongoing trials. Eligible RCTs were included regardless of the language of publication. We also scanned bibliographies of relevant studies for possible references to additional RCTs.

Study Selection

Two authors independently decided which trials fit the inclusion criteria. Any disagreements were resolved by discussion between the reviewers, with referral to a third author if necessary. Only RCTs of interventions for stress ulcer in hospitalized children (studies that included participants aged <18 yrs) were considered in this systematic review. We considered any hospitalized children including critically ill pediatric patients having or not having mechanical ventilation, children admitted to pediatric ICUs or who underwent surgery, preterm and full-term newborns among others. Quasirandomized and nonrandomized controlled studies were not discussed further. We considered all doses and regimen treatments as single or combined therapy used as prophylaxis against stress ulcers. The comparators were placebo, no treatment, or another active compound.

Data Extraction

At least two reviewers (L.R., L.Y., P.A.M.) independently extracted the relevant data, using a prespecified data extraction form; disagreement was resolved by consensus with all authors. We extracted year of publication, patient population, number of patients (by intention to treat), aspects of study quality, sociodemographic, interventions (drug, dose, duration of treatment), clinical, endoscopic, and histologic outcomes and adverse effects.

Risk of Bias Assessment/GRADE System

The Cochrane Collaboration recently proposed a new tool having six domains to assess the risk of bias of RCTs (namely, sequence generation of randomization, allocation concealment to prevent foreknowledge of group assignment in an RCT, blinding, incomplete outcome data, selective outcome reporting and “other issues”). Therefore, a risk of bias evaluation of each RCT was done for the assessment of these features (9). Additional quality information reported included also information of withdrawals, inclusion and exclusion criteria, sample size calculation, and baseline comparability of age, gender, relevant clinical characteristics and diagnoses and duration of complaint.

The tool for assessing risk of bias in each RCT comprises a description and a judgment for each entry in a “risk of bias” table. The judgment for each entry involves answering a question, with answers “Yes” indicating low risk of bias, “No” indicating high risk of bias, and “Unclear” indicating either lack of information or uncertainty over the potential for bias. A study should be considered as having “low risk of bias” if all key domains were judged as “Yes” and with unclear risk if the reviewers judged “Unclear risk of bias” for one or more key domains (9). We also used the GRADE system for grading the quality of evidence and the strength of recommendations by two reviewers. A systematic approach for grading the strength of management recommendations can minimize bias and aid interpretation of clinical practice guidelines. This system takes into account study design, study quality, consistency, and directness in judging the quality of evidence for each important outcome (10).

Definitions and Outcomes

The main outcomes considered were death; presence of ulcers, gastritis, or UGI bleeding; bleeding that requires transfusion; bleeding associated with hemodynamic instability; gastrointestinal perforations; and pneumonia. In addition, endoscopic findings categorized according to the severity of UGI tract lesions were also considered primary outcome. We anticipated that diverse classifications could have been used by trialists. Other outcomes were: delayed gastric emptying; bacteremia during the follow-up; mean patient’s gastric aspirates pH during 24-hr monitoring, pediatric ICU stay; duration of mechanical ventilation hemolologic test; cultures of gastric and tracheal secretion, gastric and tracheal colonization; and complicated postoperative course. We only included data on adverse events from RCTs; no further searches for other types of studies were done (11).

Statistical Analysis

Statistical analyses were done with Review Manager version 5.0 (Cochrane Collaboration) software. The results expressed as RR and 95% CI for dichotomous primary outcomes were calculated by the Mantel-Haenszel fixed-effects model. Weighted mean difference with 95% CI was used for continuous outcomes. For the pooled analysis, we calculated the I² statistic, which describes the percentage of total variation across studies caused by heterogeneity (9). Low, moderate, and high levels of heterogeneity approximately correspond to I² values of 25%, 50%, and 75%, respectively.

RESULTS

Description of Studies

A total of 294 citations were identified from the diverse sources of information. Of the 74 potentially RCTs screened, we excluded 52 references because they were guidelines, observational studies, or case series reports. We identified 22 studies assessing the effects of different therapeutic interventions for stress ulcers in children (Fig. 1). However, we excluded 13 studies because they were nonrandomized or noncontrolled or focused on pharmacokinetics of drugs (12–24). One study in Hungarian is pending for evaluation (25). In total, we included and analyzed eight RCTs evaluating the effects of drugs preventing stress ulcers in children (26–33). The main characteristics of the eight included studies are detailed in Table 1. Table 1: We could not assess publication bias (e.g., funnel plot or Egger regression test) because we found less than nine RCTs and we could not pool outcomes for more than three studies.

Risk of Bias

Seven studies were open and we found no RCT with low risk of bias. Overall six
RCTs were judged as having unclear risk of bias mainly because the description of the method used to generate the sequence of randomization and to conceal the allocation was unclear (Table 2). Some markers of quality in medical research, such as performing a sample size calculation, are unlikely to have direct implications for risk of bias. However, the majority of RCTs did not calculate the sample size, which is a source of potential imprecision. Overall the quality of the reporting and design of the RCTs was poor.

Effects of Interventions

Treatment Versus No Treatment

We found four studies that evaluated a number of medications (cimetidine, almagate, ranitidine, sucralfate, and omeprazole) vs. no treatment or placebo for different outcomes; data were not available in all RCTs for each outcome (26, 28, 30, 33).

When pooling two RCTs (Fig. 2), “treatment” (which included almagate, ranitidine, sucralfate, and omeprazole) was significantly more effective in preventing UGI bleeding (macroscopic or important bleeding) compared with “no treatment” (two studies = 300 participants; RR, 0.41; 95% CI, 0.19–0.91; I² = 12%) (28, 30). However, no significant difference was found when pooling both studies of treatment vs. no treatment with an additional RCT comparing treatment vs. placebo (three studies = 340 participants; RR, 0.69; 95% CI, 0.41–1.17; I² = 63%) (26, 28, 30). In addition, meta-analysis of two studies (30, 33) found no significant difference in death rates among groups (two RCTs = 132 participants; RR, 1.39; 95% CI, 0.70–2.79; I² = 4%). The rate of pneumonia was not significantly different when comparing treatment and no treatment in one study (30). Summary of relevant findings for primary outcomes of RCTs included in the review are detailed in Table 3.

Ranitidine

One RCT (33) in mechanically ventilated preterm and full-term newborns treated in a neonatal ICU showed that rates of normal gastric mucosal endoscopic findings by visual inspection (one RCT = 48 participants; RR, 3.04; 95% CI, 1.30–7.12) and histologic specimens (one RCT = 48 participants; RR, 3.53; 95% CI, 1.34–9.29) were significantly higher in the ranitidine group compared with no treatment groups. However, no significant differences among groups were found in the rates of patients with erosions or ulceration, gastrointestinal problems (bleeding from the gastrointestinal tract and/or vomiting or delayed gastric emptying), positive bacterial cultures from the biopsy specimens, and the risk for later suspected or proven bactereemia during the follow-up. An RCT of children who needed mechanical ventilation on admission (30) showed no significant difference between groups in macroscopic bleeding, pneumonia occurrence, duration of mechanical ventilation (days) and pediatric ICU stay (days). Another RCT of children admitted to a pediatric ICU (28) did not show statistical difference in the rates of patients with important UGI hemorrhage among groups. A significant difference favoring ranitidine was found in the percentage of children with mean pH of >4 during >50% of study time compared with no treatment (one RCT = 70 participants; RR, 8.67; 95% CI, 2.89–26.02).

Amalgate

An RCT (28) showed a significant difference favoring amalgate in the percentage of patients’ gastric aspirates with mean pH of >4 during >50% of study time (one RCT = 70 participants; RR, 11.00; 95% CI, 3.72–32.56). No significant difference was found among groups regarding the rates of patients with important UGI hemorrhage.

Sucralfate

In one RCT (28), a trend favoring sucralfate was found in the percentage of patients’ gastric aspirates with mean pH of >4 during >50% of study time (one RCT = 70 participants; RR, 3.33; 95% CI, 1.00–11.09). However, no significant difference between groups was found for other outcomes, such as rate of patients with important UGI hemorrhage. Another RCT (30) did not report significant difference among groups in rates of macroscopic bleeding, pneumonia, and deaths as well as in the duration of me-

Figure 1. Flow diagram of the process of identifying and including references.
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<th>Study</th>
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<tr>
<td>Aanpreung et al (31)</td>
<td>Open randomized controlled trial</td>
<td>Twenty critically ill pediatric patients aged 2 mos to 12 yrs. Severity of disease was assessed using Zinner index score.</td>
<td>Intravenous ranitidine 1.5 mg/kg every 6 hrs and famotidine 0.4 mg/kg every 8 hrs. The first 36 patients (group 1) were not given treatment to prevent lesions of the UGI tract. Later, 43 patients (group 2) were randomized and treated either with pirenzepine, an anticholinergic (21 patients) or famotidine, a H2 antagonist (22 patients). Both drugs were given intravenously at a dosage of 1 mg/kg/day. In older patients, the drugs were given as two doses; children who weighed &lt;10 kg were given three doses.</td>
<td>Patients’ intragastric pH was measured by continuous pH monitoring digitrapper. Intensity of UGI hemorrhage was classified into three categories: nonhemorrhage; slight; and important. All patients had at least one endoscopic examination performed by the same examiner as the patients still required mechanical ventilation. To assess the severity of lesions of the UGI tract, authors developed a score based on the endoscopic findings: Normal findings 0; MILD-to-moderate inflammation, few petechiae or erosions 1; Pronounced inflammation, multiple petechiae erosions 2; Ulcer(s) 3. Additional outcomes: continuous 24-hr measurement of pH; tracheal and gastric secretions culture; daily routine chest radiographs on the first 3 postoperative days and afterwards chest radiographs were taken if indicated by the clinical findings. The primary outcome variable was mucosal lesions detected endoscopically. The procedure was planned for all patients at the age of 3 to 6 days. The findings were grouped into four categories: a) intact gastric mucosa; b) mucosal friability; c) erythema or (gross) blood; and d) erosions or ulcers. Gastric mucosal biopsy specimens were obtained for histological and bacteriologic evaluation if there were no contraindications. Alcian-blue-periodic-acid-Schiff and modified Giemsa stains were used to demonstrate fungi and bacteria. Biopsy specimens were also obtained for bacterial culture.</td>
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<td>Behrens et al (32)</td>
<td>Open randomized controlled trial</td>
<td>Children who underwent corrective or palliative surgery for congenital heart disease. Age, weight, cardiopulmonary bypass time, aortic cross clamp period, and mean interval between endoscopy and cardiac surgery were not significantly different in the two groups.</td>
<td>Fifty-three mechanically ventilated newborns were randomized into either the treatment group (prophylactic intravenous ranitidine [5 mg/kg body weight/day] divided into three doses throughout 4 days) or the control group (no prophylaxis). Prophylactic treatment commenced immediately parallel to mechanical ventilation. There was no placebo treatment available.</td>
<td>UGI bleeding noted from nasogastric tube. Massive UGI bleeding was defined as brown hemorrhage from nasogastric tube and a decrease in arterial blood pressure of &gt;20 mm Hg or with an acute decrease of hemoglobin of 2 mg/dL. pH measurements.</td>
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<td>Kuusela et al (33)</td>
<td>Open randomized controlled trial</td>
<td>The study group was prospectively collected from mechanically ventilated preterm and full-term newborns treated in a neonatal ICU. The criterion for inclusion in the study was the start of mechanical ventilation during the first 2 hrs of life. Most of the infants were preterm; the mean gestational age was 32 wks (range = 24–41 wks) and the mean birth weight was 1832 g (range = 620–4550 g). Twenty-nine of the neonates were male and 24 were female. Altogether, 37 preterm infants of gestational age of &lt;33 wks and 16 infants of gestational age of ≥33 wks were enrolled in the study.</td>
<td>Patients were randomized to cimetidine 0.13 mL/kg/day (ampoule 150/mg/mL) or placebo every 6 hrs as long as 10 days.</td>
<td>Patients’ intragastric pH was measured by continuous pH monitoring digitrapper. Intensity of UGI hemorrhage was classified into three categories: nonhemorrhage; slight; and important. All patients had at least one endoscopic examination performed by the same examiner as the patients still required mechanical ventilation. To assess the severity of lesions of the UGI tract, authors developed a score based on the endoscopic findings: Normal findings 0; MILD-to-moderate inflammation, few petechiae or erosions 1; Pronounced inflammation, multiple petechiae erosions 2; Ulcer(s) 3. Additional outcomes: continuous 24-hr measurement of pH; tracheal and gastric secretions culture; daily routine chest radiographs on the first 3 postoperative days and afterwards chest radiographs were taken if indicated by the clinical findings. The primary outcome variable was mucosal lesions detected endoscopically. The procedure was planned for all patients at the age of 3 to 6 days. The findings were grouped into four categories: a) intact gastric mucosa; b) mucosal friability; c) erythema or (gross) blood; and d) erosions or ulcers. Gastric mucosal biopsy specimens were obtained for histological and bacteriologic evaluation if there were no contraindications. Alcian-blue-periodic-acid-Schiff and modified Giemsa stains were used to demonstrate fungi and bacteria. Biopsy specimens were also obtained for bacterial culture.</td>
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<td>Lacroix et al (26)</td>
<td>Double-blind randomized controlled trial</td>
<td>Forty children from birth to 18 yrs old admitted to PICU. Inclusion criteria were that illness was severe enough to preclude any oral or enteral nutrition for at least 2 days. Exclusion criteria: UGI bleeding, burns, or surgical problems; need of oral or enteral feeding; renal failure or cerebral death; treatment requiring cimeridine or antiacids. Mean ± so age was 1.85 ± 3.25 yrs.</td>
<td>Patients were randomized to ranitidine 1.0 mg/kg iv every 6 hrs and famotidine 0.4 mg/kg iv every 6 hrs. Patients were randomized into four groups. All of them received ranitidine at different dosages: a) 2 mg/kg by nasogastric tube every 12 hrs; b) 4 mg/kg by nasogastric tube every 12 hrs; c) 0.75 mg/kg iv every 6 hrs; d) 1.5 mg/kg iv every 6 hrs.</td>
<td>Treatment was considered successful when gastric pH was ≥4 during &gt;80% of the study time on each patient.</td>
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<td>Lopez-Herce et al (27)</td>
<td>Open randomized controlled trial</td>
<td>Forty patients admitted to PICU ranging from neonate to 17 yrs old were included.</td>
<td>Patients were randomized into four groups: no treatment; almagate 0.25 mL/kg every 2 hrs; ranitidine 1.5 mg/kg iv every 6 hrs; and sucralfate 0.5 gr if weighing &lt;10 kg and 1 gr if weighing &gt;10 kg every 6 hrs.</td>
<td>Gastric pH evolution, UGI hemorrhage occurrence rate, microscopic upper gastrointestinal hemorrhage, mortality, adverse events.</td>
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<td>Lopez-Herce et al (28)</td>
<td>Open randomized controlled trial</td>
<td>165 children admitted to PICU presenting at least one of the following criteria: shock, acute renal, cardiac respiratory or liver failure, sepsis or serious focal infection, coagulopathy, acute neurologic dysfunction, multiple trauma, severe metabolic acidosis post major surgery. All patients had nasogastric tube inserted. Severity of illness was evaluated with three scores.</td>
<td>Patients were randomized to sucralfate 2 mL/kg every 2 hrs; ranitidine 0.75 mg/kg iv every 6 hrs; famotidine 0.4 mg/kg iv every 6 hrs; and placebo every 6 hrs.</td>
<td>Gastric pH evolution, UGI hemorrhage occurrence rate, microscopic upper gastrointestinal hemorrhage, mortality, adverse events.</td>
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Table 1. —Continued

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<td>Yildizdas et al (30)</td>
<td>Open randomized controlled trial</td>
<td>160 patients who needed mechanical ventilation on admission were enrolled in the study. Patients were excluded if any of the following circumstances occurred in the first 48 hrs after inclusion: extubation, death, pneumonia, or new information that the patient had received one of the study drugs in the last 48 hrs before admission.</td>
<td>Group S received sucralfate suspension 60 mg/kg/day in four doses via the nasogastric tube that was flushed with 10 mL of sterile water; group R received ranitidine 2 mg/kg/day intravenously in four doses; group O received omeprazole 1 mg/kg/day intravenously in two doses; and group P did not receive any medication for stress ulcer prophylaxis.</td>
<td>Ventilator-associated pneumonia was defined as the occurrence of a new or persistent radiographic infiltrate in conjunction with one of the following: positive pleural/blood culture with the same organism recovered in the tracheal aspirate or sputum, radiographic cavitation, histopathologic evidence of pneumonia; or at least two of the following: fever; leukocytosis; and purulent tracheal aspirate or sputum. Pneumonia was considered to be ventilator associated if it occurred after a minimum of 48 hrs after the initiation of mechanical ventilation. Respiratory tract culture specimens were obtained from tracheal aspirates. Hospital mortality was defined as patient death occurring in the PICU and hospital stay was defined as the days in the PICU.</td>
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<td>Osteyee et al (29)</td>
<td>Open randomized cross over trial</td>
<td>Sixteen critically ill children.</td>
<td>Children in group 1 received bolus dosing on day 1 and continuous infusion of ranitidine on day 2. Group 2 received the continuous infusion on day 1 and bolus dosing on day 2. Continuous infusion regimen: ranitidine bolus of 0.15 mg/kg followed by continuous infusion at 0.15 mg/kg per hour for 12 hrs. Bolus regimen: 1 mg/kg, two doses 6 hrs apart.</td>
<td>Gastric pH.</td>
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Other Comparisons

Other significant differences were found between groups in one RCT (30) of critically ill pediatric patients in the rate of patients’ gastric aspirates with mean pH of >4 during >80% of study time.

Drug Vs. Any Other Active Compound

We found seven studies comparing diverse drugs, doses, and regimen (27–32). Most studies did not report outcomes, such as mortality, rates of UGI bleeding, and pneumonia.

Pirenzepine Vs. Famotidine

No significant differences were found between groups in one RCT of children who underwent corrective or palliative surgery for congenital heart disease concerning rates of pneumonia and organism cultured from the stomach and from tracheal secretion (32).

Ranitidine Vs. Sucralfate

One RCT (28) showed that ranitidine was significantly superior to sucralfate in rates of macroscopic bleeding, pneumonia, deaths, and in the duration of mechanical ventilation and pediatric ICU stay.

Cimetidine

In one RCT (26), cimetidine was not superior to placebo in rates of UGI bleeding.

Omeprazole

In one RCT (28), omeprazole was not superior to no treatment in groups in rates of macroscopic bleeding, pneumonia, deaths, and in the duration of mechanical ventilation and pediatric ICU stay.

Ranitidine Vs. Amalgate

Ranitidine was significantly superior to amalgate in the rate of patients’ gastric aspirates with mean pH of >4 during ≥50% of study time (one RCT = 70 participants; RR, 0.79; 95% CI, 0.64—0.97). No significant differences were found between groups in the rates of patients with important UGI hemorrhage and gastrointestinal symptoms, such as nausea, vomiting, or diarrhea (28).

Amalgate Vs. Sucralfate

One RCT (28) showed that amalgate had a significant effect in the rate of patients’ gastric aspirates with mean pH of >4 during >50% compared with sucralfate (one RCT = 70 participants; RR, 3.50; 95% CI, 1.94—5.61). No significant differences were found between groups in the rates of patients with important UGI hemorrhage and gastrointestinal symptoms, such as nausea, vomiting, or diarrhea (28).

Ranitidine Vs. Famotidine

No significant differences were found between groups in one RCT (31) of critically ill pediatric patients in the rate of patients’ gastric aspirates with mean pH of >4 during >80% of study time.

Important UGI hemorrhage and gastrointestinal symptoms, such as nausea, vomiting, or diarrhea (28).

Gastric pH.

Ventilator-associated pneumonia was defined as the occurrence of a new or persistent radiographic infiltrate in conjunction with one of the following: positive pleural/blood culture with the same organism recovered in the tracheal aspirate or sputum, radiographic cavitation, histopathologic evidence of pneumonia; or at least two of the following: fever; leukocytosis; and purulent tracheal aspirate or sputum. Pneumonia was considered to be ventilator associated if it occurred after a minimum of 48 hrs after the initiation of mechanical ventilation. Respiratory tract culture specimens were obtained from tracheal aspirates. Hospital mortality was defined as patient death occurring in the PICU and hospital stay was defined as the days in the PICU.
patients who needed mechanical ventilation on admission concerning rates of macroscopic bleeding, deaths, pneumonia, and the duration of mechanical ventilation and pediatric ICU stay when comparing omeprazole vs. ranitidine and omeprazole vs. sucralfate.

**Ranitidine Versus Ranitidine at Different Doses and Regimen**

One RCT (27) showed that intravenous ranitidine at 2 mg/kg and 4 mg/kg had a significant effect in the rate of patients’ gastric aspirates with mean pH of \( \geq 4 \) during \( \geq 80\% \) of study time compared with ranitidine by nasogastric tube (one RCT = 20 participants; RR, 0.25; 95% CI, 0.07–0.90). Another RCT did not find significant difference in patients’ gastric aspirates pH when comparing bolus dosing and continuous infusion dosing of 4 mg/kg per day of intravenous ranitidine (29).

**DISCUSSION**

The RCTs included in this review have assessed a broad range of treatments that resulted in limited opportunities to describe and pool useful data. Studies available for analysis are a highly heterogeneous group, with different drugs being used and different methods for assessing their efficacy (e.g., some used endoscopy on all patients, others simply monitored nasogastric output for bleeding). Furthermore, because the majority of RCTs had an unclear risk of bias, small sample size, and did not reported relevant outcomes, it was difficult to conclude whether one treatment was more beneficial than the comparator most of the time. Most RCTs focused on secondary outcomes, such as gastric pH control. In addition, methods used for diagnosis of UGI bleeding greatly varied across studies and we could not integrate data for most comparisons.

Pooled data of two studies suggested that pediatric patients may benefit from receiving prophylactic treatment for preventing UGI bleeding. There was reasonable evidence that ranitidine is better than “no treatment” in mechanically ven-
A meta-analysis evaluating the effect of stress ulcer prophylaxis on gastrointestinal bleeding in severely ill pediatric patients. Authors also reported no significant differences in the rates of ventilator-associated pneumonia, the duration of the stay in the ICU, or mortality (6).

A number of risk factors associated with stress ulcers, gastritis, and gastrointestinal bleeding in severely ill pediatric patients have been described in observational studies (Table 4) (1, 34–40). A cohort study found that respiratory failure, mechanical ventilation, authors also reported no significant differences in the rates of ventilator-associated pneumonia, the duration of the stay in the ICU, or mortality (6).
coagulopathy, and a Pediatric Risk of Mortality Score of ≥10 were independent risk factors for clinically significant upper GI bleeding, using multivariable analysis. Based on those findings, authors recommended that prophylaxis to prevent UGI bleeding may be limited to patients who present with at least two risk factors (1). We have produced an updated coverage of RCTs of prophylactic treatments for stress ulcers in children by summarizing the best available data. Although pooled data of two studies suggested that critically ill pediatric patients may benefit from receiving prophylactic treatment for preventing UGI bleeding, the overall quality of the evidence is low, leading to a weak recommendation (using GRADE approach) (10). Although limited evidence is available, some of the drugs studied (histamine2 receptor antagonists, sucralfate, amalgate) have been replaced in clinical use by proton pump inhibitors. However, only one study including patients treated with omeprazole was found (30). We need more evidence demonstrating the effectiveness and safety of different prophylactic drugs and improved design and reporting of RCTs. We should also investigate the use of proton pump inhibitors in children.

ACKNOWLEDGMENT

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APPENDIX A

Search Strategy for PubMed