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ORIGINAL ARTICLE

Indications of gastric ulcer prophylaxis in hospitalized pediatric patients: an integrative review

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Anti-Ulcer Agents,
Intensive Care Units,
Pediatrics,
Peptic Ulcer.

Abstract

Objectives: To determine the main indications for gastric ulcer prophylaxis in hospitalized pediatric patients and, through the analysis of scientific evidence, to point out the main complications of the indiscriminate use of this prophylaxis and to mention alternatives to the use of drugs in the prevention of stress ulcers. **Methods:** We selected articles written in English and Portuguese, published between 2009 and 2019, which show the indications of stress ulcer prophylaxis in critically ill pediatric patients, as well as studies demonstrating the complications of gastric acid suppression therapy. The search was performed in the PubMed, LILACS and SciELO databases. **Results:** In this integrative review, sixteen studies that met the previously established inclusion criteria were analyzed. Of the articles included in this study, four are prospective observational studies, eight are systematic reviews, seven with meta-analysis, two retrospective cohort studies, one case-control study, one expert-opinion guideline, and one case report. **Conclusion:** The indiscriminate use of stress ulcer prophylaxis is not recommended and should only be used when there is an accurate indication. However, even where therapy is recommended, the risk-benefit assessment should be assessed and caution should be exercised with acid-suppressing drugs, as this prophylaxis increases the risk of *Clostridium difficile* infection and pneumonia. It is also suggested the introduction of early enteral nutrition as an alternative to the use of gastric ulcer drug prophylaxis, as the evidence points to its efficacy in reducing adverse effects and maintaining gastric homeostasis.

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INTRODUCTION

Gastrointestinal bleeding related to stress ulcers is a potential complication of critical illness, whose pathophysiology is complex¹. The gastric mucosa is sensitive to hemodynamic changes and inflammatory signs², which results in impaired local blood flow, with subsequent ischemic mucosal injury¹.

Related mucosal disease mucosal disease – SRMD) was introduced to describe damage to the gastric mucosa, ranging from single lesions to multiple ulcers, which may predispose to bleeding complications³. High gastric intraluminal acidity is also an important factor for the development of ulcers and gastric bleeding¹, making it a target in the treatment and prophylaxis of lesions. To reduce gastrointestinal damage and its complications, acid-suppressing drugs are often prescribed⁴.

Proton pump inhibitors (e.g. omeprazole, pantoprazole), histamine 2 receptor antagonists (H2RAs) (e.g. ranitidine), antacids (e.g. calcium/sodium carbonate, magnesium hydroxide/ aluminum) and mucosal protective agents (eg, sucralfate and bismuth salts)⁵, are among the main pharmacological classes available for the prophylaxis of gastric ulcers².

In pediatric patients, the prevalence of stress ulcer-related bleeding ranges from 6% to 43%, and clinically important bleedings range from 1.6% to 5.3%⁶. Antacids and antiulcers of different classes are frequently prescribed⁷ in hospitalized pediatric patients, in an attempt to reduce the incidence of gastric lesions.

In a sporadic visit to a local pediatric intensive care unit, it was observed that 40% of the hospitalized patients were using gastric ulcer prophylaxis, a fact that motivates this study and raises questions regarding the criteria used to indicate the therapy, because there is no established protocol in the sector. Furthermore, when performed without indication, pharmacological prophylaxis can predispose to adverse effects and increase the costs of hospitalization and treatment of these patients⁸.

The objective of this review is to determine the main indications for the use of gastric ulcer prophylaxis in hospitalized pediatric patients and, through the analysis of scientific evidence, to indicate the main complications of the indiscriminate use of this prophylaxis and alternatives to the use of drugs in the prevention of stress ulcers.

METHODS

Kind of study

It is an integrative literature review, a method that provides the synthesis of knowledge and the incorporation of the applicability of results of significant studies in practice⁹.

Search strategy

The research question was defined from the PICO strategy. This strategy assumes the definition of the participant

(P), intervention (I), comparison (C) and outcome/ outcomes (O) (10). To guide the integrative review, we intend to answer the following question: is there consolidated evidence (O) on the prophylaxis of gastric ulcers (I) in hospitalized pediatric patients (P), its indications and adverse effects?

Therefore, two strategies were built : one in English, with MeSH (Medical Subject Headings), and another in Portuguese, with DeCS terms (Health Science Descriptors). (1) Descriptors and strategies in English: Anti-Ulcer Agents AND Pediatrics AND disease prevention (2). Descriptors and strategies in Portuguese: Antiulcerosos AND Úlceras AND Pediatria (Figure 1).

Eligibility Criteria

The inclusion criteria of articles for this integrative review were: studies carried out with children hospitalized in pediatric intensive care units and wards, published between 2009 and 2019, in English and Portuguese, with abstracts available in selected databases. Patients who chronically use acid-suppressing drugs were excluded; patients using gastric ulcer prophylaxis treated on an outpatient basis; and articles published prior to 2009.

Selection of articles

The following steps were taken: establishment of the hypothesis and objectives of the integrative review; definition of inclusion and exclusion criteria for articles; definition of descriptors and search strategies; search in databases; selection of articles; data collection and storage; data analysis; discussion and presentation of results. The searches were carried out in the MEDLINE databases, accessed via PubMed, LILACS and SciELO. The selection of studies consisted of three stages: title phase; abstracts phase; and reading phase of complete articles. This screening was performed after searching the databases (Figure 1A).

RESULTS

Selection of articles

The search in the databases identified 2,493 articles. Of these, 2,314 were excluded by title, 125 by reading the abstract and 24 by reading the article, which resulted in 30 articles. After reading all the articles, 16 were included in the study. A synthesis of this process was demonstrated in Figure 1B.

16 works were analyzed in full. Among these articles, four are prospective observational studies, eight are systematic reviews, seven with meta-analysis, two retrospective cohort studies, a case-control study, a guideline based on expert opinion and a case report.

A brief summary of all works was structured in a table composed of the following topics: main author, year, type of study, level of evidence and results (Table 1). The articles included in this review were categorized according to the levels

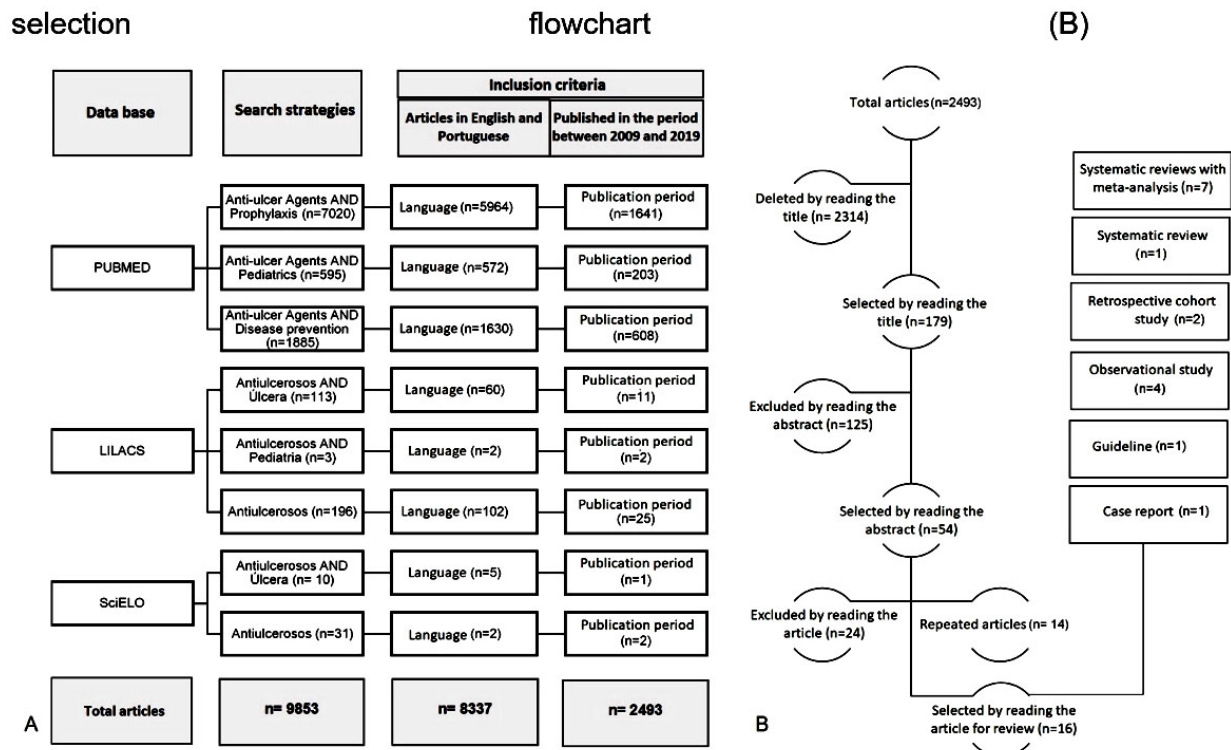


Figure 1. Demonstrates the article search strategies (A) and the article.

of evidence of scientific publications, using the classification of the Oxford Center for Evidence - based Medicine¹¹.

DISCUSSION

Upper gastrointestinal bleeding is typically a mild, self-limiting condition that can affect term and preterm infants and infants, and can be worsened in the face of other comorbidities⁵. The main risk factors for gastrointestinal bleeding described in the literature, according to the Chaibou study *et al.*¹², 4 are: respiratory failure and use of mechanical ventilation, coagulation disorders, *pediatric risk of mortality* > 10 (score used to predict mortality in pediatric intensive care units that assesses clinical and laboratory parameters)^{6,13}.

According to the publications evaluated, it was observed that prophylaxis is empirically performed with proton pump inhibitors (PPIs), H2 receptor inhibitors and sucralfate, without precise indications^{7,13}, contemplating most of hospitalized pediatric patients, regardless of their underlying pathology. A prospective observational study with 398 children from five Pediatric Intensive Care Units (ICUs) in Brazil showed that 78% of the children received stress ulcer prophylaxis and, in 22% of the cases, the physician did not know the reason for performing it⁶.

Some observational studies bring into their discussion possible indications for prophylaxis of gastric ulcers, they are:

documented gastroesophageal reflux disease, coagulopathy, gastroduodenal changes related to stress, hemorrhage or abdominal congenital disorders (for example, diaphragmatic hernia, gastroschisis and omphalocele)¹⁴. The aforementioned etiologies would benefit from prophylaxis due to the increased risk of gastrointestinal bleeding and complications related to hospitalization, especially when added to the underlying disease.

There is available evidence to suggest that the use of Proton Pump Inhibitors is associated with an increased risk of Gram-negative upper airway colonization, pneumonia¹⁵, acute and chronic kidney disease, hypomagnesemia, *Clostridium difficile* infection, and osteoporosis¹⁶.

According to Araújo *et al.*⁶, the incidence of clinically important gastrointestinal bleeding is so low in patients with no risk factors or with only one risk factor, that prophylaxis would not be necessary in the routine way in them^{6,8,17}.

Additional factors are also taken into account, such as the use of antimicrobials, present in the prescriptions of most critically ill and hospitalized patients. Antibiotic exposure and PPI use may be risk factors for *Clostridium difficile* infection in hospitalized pediatric patients.

The presence of infection in critically ill patients increases the incidence of unfavorable outcomes, such as an increase in length of hospital stay, and in the short and long term, the risk of high colectomy, in addition to increasing mortality

Table 1. General characteristics of the included studies.

Main Author	Year	Kind of study	Level of evidence	Results
Anjewierden, S ²⁰	2019	Systematic Review and Meta-analysis	1A	Exposure to antibiotics and use of proton pump inhibitors (PPIs) have been found to be risk factors for <i>Clostridium infection difficile</i> in hospitalized pediatric patients. Clinicians should continue to use antibiotics judiciously in hospitalized patients to minimize the risk of <i>Clostridium infection. difficile</i> , and similar considerations may be beneficial prior to PPI administration. Studies are needed to better define and explore risk factors and validate these results.
Green, DS ⁵	2019	Systematic Review with Meta-analysis	1A	Two-receptor antagonists (H2RA) reduce the risk of gastrointestinal infection and bleeding in high-risk neonates. There is poor-quality evidence that the use of proton pump inhibitors reduces the duration of gastrointestinal bleeding in neonates. However, there is no evidence that the use of a gastric acid inhibitor in newborns affects mortality or the need for blood transfusions. No studies reported the incidence of enterocolitis necrotizing disease, pneumonia, sepsis or prolonged illness associated with mechanical ventilation. There is no evidence that there is any additional benefit from using a higher dose of an H2RA or a proton pump inhibitor in the prevention or treatment of gastrointestinal bleeding in neonates.
Wang, CH ¹⁴	2019	Systematic review and meta-analysis	1A	The primary meta-analysis demonstrates that PPI use may be associated with an increased risk of pneumonia. However, the presence of significant heterogeneity between studies and publication bias raised concerns about the validity of the primary meta-analytic outcome. Protopathic bias, or reverse causality, can cause an overestimated association. Studies that adopted a design to explain protopathic bias did not show a significant association between PPI use and risk of pneumonia. Therefore, concern about pneumonia should not preclude clinicians from initiating indicated PPI therapy.
Buendgens ²	2016	Systematic review with Meta-analysis	1A	This systematic review demonstrates that stress ulcer prophylaxis does not improve ICU patient mortality. In addition, nosocomial pneumonia and <i>Clostridium -associated diarrhea difficile</i> are potentially serious complications of prophylaxis. Among the alternatives, there is enteral nutrition or restriction of gastric ulcer prophylaxis during the initial phase of treatment in the ICU.
Eom, CS ²²	2011	Systematic Review with and Meta-analysis	1A	Use of a proton pump inhibitor or histamine 2 receptor antagonist may be associated with an increased risk of hospital-acquired and community-acquired pneumonia. Given the potential adverse effects, clinicians should exercise caution when prescribing acid-suppressing medications to patients at risk.
Barletta, JF ⁸	2013	Systematic review with meta-analysis	1A	Proton pump inhibitors are increasingly being used as primary agents to provide gastric ulcer prophylaxis in critically ill patients. In addition, these agents are usually started (or continued) in patients who are not admitted to the ICU, where the risk of major bleeding is small and there is no benefit from applying this therapy. Clinical data evaluating PPIs for stress ulcer prophylaxis are of poor quality and most studies were conducted at a time when practices differed from today's approach. The value of meta-analyses in this setting is limited; randomized, multicenter clinical trials are needed.
Marik, PE ²⁸	2010	Systematic Review and Meta-Analysis	1A	The results of this meta-analysis suggest that, in those patients receiving enteral nutrition, stress ulcer prophylaxis may not be necessary and, in fact, such therapy may increase the risk of pneumonia and death. However, as no clinical studies have prospectively tested the influence of enteral nutrition on stress ulcer prophylaxis risk, our findings should be considered exploratory and interpreted with some caution.
Santana, RNS ¹⁸	2017	Retrospective cohort study	2B	According to the study, neonates who received ranitidine were more likely to have nosocomial infection, sepsis, and pneumonia. The mortality rate and length of hospital stay were higher in neonates who received ranitidine. In addition, ranitidine use was not significantly associated with enterocolitis. necrotizing.
Jouret-Descout, P ²⁵	2017	Prospective observational	2C	The study defines that Proton Pump Inhibitor therapy is appropriate in pediatric patients with documented Gastroesophageal Reflux Disease, coagulopathy, stress-related gastroduodenal changes, hemorrhage, or congenital abdominal disorders (eg, diaphragmatic hernia, gastroschisis, and omphalocele). After defining the indications, the proportion of patients with PPI prescriptions dropped from 51% during the first period to 30% after the guidelines were introduced.

Continuation Table 1.

Araújo, TE ⁶	2010	Prospective, cross-sectional and observational study	2C	In this study, the most used drug was ranitidine. An increase in the use of prophylaxis was observed according to the number of systems and dysfunction. There was a direct association between the use of prophylaxis for stress ulcers and the increase in the number of organ failures; There was a high prevalence in all Pediatric Intensive Care Units evaluated. In the researched literature, only two studies provided information on the prevalence of the use of gastric ulcer prophylaxis in children, showing a prevalence of 11 and 14.5%, with indication only for high-risk patients.
Marquito, AB ⁷	2011	Prospective observational	2C	A study showed that the percentage of stress ulcer prophylaxis prescribed without indication was 11% in the analyzed period. The data obtained demonstrate the use of drug prophylaxis without criteria.
Terrin, G ²⁴	2014	Prospective observational	2C	Ranitidine should be administered with care for premature infants because of risk of serious infectious disease, necrotizing enterocolitis, and fatal outcome. Additional studies are needed to investigate the pathogenesis of these effects and the possible prophylactic measures that could be taken to avoid them.
Newberry, C ⁴	2018	Systematic review	3A	Enteral nutrition may reduce the risk of Stress-Related Mucosal Disease (SRMD) and subsequent complications. This issue continues to be explored in the literature with increasing evidence supporting enteral nutrition as an alternative to the use of acid suppression therapy for gastric ulcer prevention. Although large randomized clinical trials should continue to be conducted in this patient population, the literature supporting enteral nutrition for the prevention of SRMD is increasing.
Brown, KE ¹⁹	2015	Retrospective case-control	3B	Use of acid-suppressing agents prior to hospitalization significantly increased the risk of developing <i>Clostridium difficile</i> infection. The use of ranitidine compared to the proton pump inhibitor increased the risk of <i>Clostridium difficile</i> infection by 4.5 times. The use of H2-receptor antagonists in the pediatric population should be monitored and prospectively evaluated to determine possible cause and effect.
Castro, REV ²³	2019	Case report	4	Ranitidine is a histamine -2 receptor antagonist commonly prescribed in the pediatric ICU for the prophylaxis of gastrointestinal bleeding and stress ulcers. However, it may be associated with central nervous system side effects such as delirium in adults. This is the first case of a child who experienced delirium possibly secondary to ranitidine use, resolving after discontinuation of the drug. With this case report, we reinforce that a wide variety of clinical conditions can trigger delirium and that the best therapeutic approach is to minimize risk factors.
Mendes, JJ ¹	2018	Expert opinion	5	Experts recommend initiating gastric ulcer prophylaxis in patients with compelling indications, as well as recommending the use of proton pump inhibitors when gastric suppression is indicated; In addition, Histamine (H2) receptor antagonists should be used in patients with <i>C. difficile</i> infection and indication for stress ulcer prophylaxis; it is also recommended to stop prophylaxis with agents that suppress acidity when the risk factors are no longer present and the patient is on enteral nutrition.

rates¹⁸. A systematic review with meta-analysis performed in 2016 concluded that stress ulcer prophylaxis does not reduce ICU patient mortality². On the other hand, a prospective cohort study showed that the mortality rate and length of hospital stay were higher in neonates who received ranitidine¹⁹. In addition, nosocomial pneumonia and *Clostridium difficile*-associated diarrhea are potentially serious complications related to prophylactic therapy^{2,16,20,21}.

Gastric juice is formed by hydrochloric acid (HCL) and pepsin, presenting an antibacterial action when the pH is lower than three³. Hypochlorhydria caused by gastric acid inhibitor drugs favors an overgrowth of bacteria and infections. It is

inferred that there are changes in the intestinal microbiota, which could contribute to increased susceptibility to infections and abnormal immune activation, such as that observed in necrotizing enterocolitis, supposedly induced by the selection of pathogens during acidity inhibition, especially when associated with ranitidine, because in addition to hypochloridia, it has a direct effect on the immune system of neonates²².

In the same context, it should be noted that the use of ranitidine is associated with a worse outcome, increasing the rate of *Clostridium difficile* infections by 4.5 times, requiring intensive monitoring, as well as more detailed studies on this possible cause-and-effect relationship. effect²³. A prospective

cohort study conducted in 2017 concluded that neonates who received ranitidine were more susceptible to nosocomial infections, sepsis and pneumonia, increasing the length of hospital stay, but there was no relevant association with necrotizing enterocolitis^{14,24}.

Of the various publications on the subject, some demonstrate an increased risk of pneumonia associated with the use of PPIs. There is, however, significant heterogeneity between studies, and publication bias has raised concerns about the validity of the primary meta-analytic outcome.

The project to explain protopathic bias or reverse causality showed no significant association between PPI use and the risk of pneumonia, inferring that pneumonia concern should not preclude clinicians from initiating indicated PPI therapy^{25,26}.

Even lacking larger and well-controlled studies²⁷, the evidence indicates that new strategies to prevent gastric injury should be inserted and thought during the care of critically ill patients². Enteral nutrition is an alternative to the use of gastric acid suppressant drugs; its use is associated with reduced risk of stress-related mucosal disease (SRMD) and subsequent complications^{4,27}.

Enteral nutrition provides maintenance of gastric and intestinal homeostasis, as well as increased cellular immunity, intestinal barrier integrity, intragastric pH change, and increased intraluminal motility²⁸. These mechanisms may be beneficial for critically ill patients and represent a non-pharmacological option for prophylaxis⁴.

CONCLUSION

The indiscriminate use of prophylaxis of stress ulcers is not recommended, its use only when there is a precise indication. However, even in cases where therapy is recommended, the risk-benefit should be evaluated and acid-suppressing drugs should be used with caution, as this prophylaxis increases the risk of *Clostridium difficile* infection and pneumonia. The introduction of early enteral nutrition is suggested as an alternative to the use of drug prophylaxis for gastric ulcers, as evidence points to its effectiveness in reducing adverse effects and maintaining gastric homeostasis.

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