International Journal of Contemporary Pediatrics
Pai UA et al. Int J Contemp Pediatr. 2022 Oct;9(10):987-997
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20222434

Review Article

Ranitidine use in pediatrics: current evidence-based review and recommendations

Uday A. Pai[1], Dhanasekhar Kesavelu[2]*, Abhay K. Shah[3], Arun K. Manglik[4], Arun Wadhwa[5], Bhaswati Acharya[6], Deepak Goyal[7], Lalit Bharadia[8], Lalit Verma[9], Nithya Franklyn[10], Raju C. Shah[11], Somashekara H. R.[12], Subhashish Bhattacharyya[13]

[1]Aangan, Sai Kutir Clinic, Chembur, Mumbai, Maharashtra, India
[2]Apollo Children's Hospitals, Chennai, Tamil Nadu, India
[3]Children's Hospital and Pediatric Infectious Diseases Center, Ahmedabad, Gujarat, India
[4]Ankur Clinic, Kankurgachi, Kolkata, West Bengal, India
[5]Greater Kailash Part 2, Delhi, India
[6]AMRI Hospital, Kolkata, West Bengal, India
[7]Fortis Hospitals, Fortis Gurgaon and Noida, Uttar Pradesh, India
[8]Santokba Durlabhji Memorial Hospital, Jaipur, Rajasthan, India
[9]Wockhardt Group of Hospitals, Mumbai, Maharashtra, India
[10]Vijaya Group of Hospitals, Vihaa Hospitals, Chennai, Tamil Nadu, India
[11]Ankur Institute of Child Health, Ahmedabad, Gujarat, India
[12]Gleneagles Global Health City, Perumbakkam, Chennai, Tamil Nadu, India
[13]CSS College of Obstetrics, Gynaecology and Child Health, Kolkata, West Bengal, India

Received: 29 July 2022
Revised: 26 August 2022
Accepted: 30 August 2022

***Correspondence:**
Dr. Dhanasekhar Kesavelu,
E-mail: drdskgastro@gmail.com

ABSTRACT

Ranitidine plays a pivotal role in routine pediatric practice. The multi-dimensional use and safety of ranitidine are not supported by any practical guidelines, which led to recommendations convened by a group of experts based on evidence and the clinical experience of experts. A group of general pediatricians and pediatric gastroenterologists from India were part of this panel. This group of experts reviewed the literature on topics that were unanimously agreed upon, for which no recommendations were available. The Delphi method was implemented to reach unified decisions, which led to the development of evidence-based recommendations. Gastritis and gastroesophageal reflux disease (GERD) are common conditions seen in pediatric practice. Ranitidine has a rapid onset of action compared to proton pump inhibitors (PPIs). It is a preferred drug for on-demand use for gastritis and managing stress-induced gastric lesions in critically ill pediatric patients. Ranitidine has an established role in the management of GERD, and it also prevents nocturnal acid reflux effectively. It helps in reducing gastric fluid volume when used as preoperative prophylaxis. Also, ranitidine has a better safety profile in comparison to PPIs. Recommendations on the use and safety of ranitidine in pediatrics were developed which will be a guiding tool for all practicing clinicians, highlighting the strength and benefits of ranitidine as a better and safe alternative to PPIs in short-term acid suppression for multiple indications.

Keywords: Ranitidine, GERD, Gastritis, Nocturnal acid reflux, PPI, H2RA

INTRODUCTION

Gastroesophageal reflux (GER) is one of the most common physiologic conditions diagnosed in children. GER has a peak incidence of 60-70% in infants of 3-4 months, which reduces to 5% by one year.[1] In contrast to GER, the prevalence of gastroesophageal reflux disease (GERD) increases with age, reaching 20% by adolescence which is similar to the prevalence in adults.[2] In the post-COVID era, children have had a substantial increase in gastrointestinal (GI) complaints such as acid reflux, bloating, abdominal pain, burping, vomiting, etc., due to home-bound restricted activities and increased idling. The changes in eating habits have also played a key role in worsening these complaints.

Currently, acid suppression therapy in pediatrics, in the form of histamine H2-receptor antagonists (H2RAs) and proton pump inhibitors (PPIs), has mainly focused on symptomatic relief of GERD. However, there are multiple other conditions apart from GERD where acid suppression plays a crucial role in the treatment and prophylaxis, such as drug-induced gastritis, stress ulcers in hospitalized children, nocturnal acid reflux, and preoperative medication.

The first in the class of acid suppression medication, H2RAs, were introduced in the mid-1970s, which played a key role in the pharmacotherapy of GI conditions in adults and children. Cimetidine was the first approved H2RA, followed by ranitidine, famotidine, and nizatidine.[3] Of these drugs in the H2RA series, ranitidine gained popularity owing to its efficacy and better safety profile. Ranitidine shows a better application in pediatric practice, despite the introduction of PPIs. Ranitidine is a short-acting acid suppressant that maintains higher pH for 6 hours. After administration, the maximum concentration is reached within 2.5 hours with a plasma half-life of 2 hours. The onset of action starts within 30 minutes of administration and can be used for on-demand therapy.[2,4] Also, ranitidine interacts less with commonly used drugs in pediatric practice than PPIs. At recommended doses, ranitidine effectively inhibits gastric acid secretion, raising intragastric pH and decreasing the volume of gastric contents available for reflux into the esophagus.[4] The safety of ranitidine is well established in adult and pediatric practice.

NASPGHAN/ESPGHAN guidelines recommend ranitidine in GERD for short-term acid suppression due to its rapid onset and short duration of action. Ranitidine also has indications for treating reflux-related erosive esophagitis in infants and children.[5]

There are multiple formulations of ranitidine available in the market intended for use in children. The available formulations of ranitidine have superior palatability over PPIs and are comparatively easy to administer in children. Liquid formulations of ranitidine are now also available for use in younger children. These formulations also have a sustainable shelf- life in tropical countries like India. In addition, ranitidine is more cost-effective when compared to PPIs in short-term acid suppression and maintenance therapy.[6] General considerations for ranitidine use in pediatric practice are summarized in Table 1.

Table 1: General considerations for the use of ranitidine in pediatric practice.

S. no.	General considerations
1	Ranitidine is considered in GERD for short-term acid suppression due to its rapid onset and short duration of action
2	The recommended oral dose of ranitidine is 5-10 mg/kg in 2 divided doses, and the IV dose is 2-4 mg/kg to be divided and administered every 6 to 8 hours
3	The continuous recommended use of ranitidine is for eight weeks
4	Ranitidine is compatible with most of the common drugs in the pediatric formulary
5	Ranitidine has shown a good safety profile in neonates via enteral and parenteral routes
6	Ranitidine has superior palatability and ease of administration when compared to PPIs
7	The cost of ranitidine therapy is less when compared to PPIs in short-term acid suppression

GERD: Gastroesophageal reflux disease

There are multiple indications of ranitidine in pediatric practice that can be discussed. However, several aspects of ranitidine in pediatrics have no current practice guideline recommendations.

Need for the development of consensus on the use of ranitidine in pediatrics

The sparse literature and lack of published guidelines on the use of ranitidine in pediatric conditions necessitated these recommendations. Being a multi-decade-old molecule with proven efficacy and safety in the real world, this document encompasses an updated overview of ranitidine in routine pediatric practice from experts across India. This document aimed to provide evidence and experience-based recommendations to guide clinicians on the best pediatric care practice.

Target audience and contents

The recommendations in this document are targeted at the general pediatricians, pediatric gastroenterologists,

emergency physicians, primary care physicians, and all health care professionals involved in managing pediatric patients. This document focuses on the uses of ranitidine in pediatric patients. It consists of recommendations across the following sections: role of ranitidine in drug-induced gastritis, prophylactic use of ranitidine in pathological conditions other than gastritis, and comparative safety of ranitidine versus PPIs in pediatric patients.

Objectives

The primary objective was to develop recommendations that would serve as a guide to clinicians for the use of ranitidine in routine pediatric practice in light of evidence on its efficacy and safety.

METHODS

The consensus process employed the three-step modified Delphi method, which is a reliable means of determining consensus for a defined clinical problem considering the insights of an expert panel.[7] Two expert panel meetings were conducted to vote and establish the process.The first meeting was conducted on 07 May 2022, in Panoli, Gujarat, India, and the second on 11 June 2022, in Bangalore, Karnataka, India.

Assembly of the expert panel

Thirteen experts representing general pediatricians and pediatric gastroenterologists across different regions of India were involved in the expert panel. The panel members were divided into three groups; each group consisted of two general pediatricians and two pediatric gastroenterologists. A senior pediatrician chaired the expert panel and moderated the consensus development process.

All panel members equally contributed to the discussions and actively participated in every phase of the consensus development process. All the experts were independent in making decisions and were not influenced or had any conflicts of interest.

Scope of recommendations

The expert panel members developed recommendations about the use of ranitidine in pediatric patients.

Search strategy and criteria

Three groups of the expert panel were assigned with the following topics: role of ranitidine in drug-induced gastritis in the pediatric setting, prophylactic use of ranitidine in pathological conditions other than gastritis in the pediatric setting, and comparative safety of ranitidine versus PPIs in pediatric patients. The groups were asked to conduct a thorough literature search on the given topic, form the initial consensus statements, and augment and consolidate the relevant evidence supporting these consensus statements. MEDLINE, Embase, and Google scholar databases were explored for the literature search. The recommendations in this document were developed following a review of the literature published before 30 April 2022, in English.

Table 2: Modified grade system including grades, and each statement was graded as per the strengths.

Grade of evidence	Criterion
Level 1 evidence	Evidence from ≥1 good quality and well-conducted randomized control trial(s) or meta-analysis of RCTs
Level 2 evidence	Evidence from at least 1 RCT of moderate quality, or well-designed clinical trial without randomization; or from cohort or case-controlled studies
Level 3 evidence	Evidence from descriptive studies
Good practice point (GPP)	Not backed by sufficient evidence; however, a consensus reached by the working group, based on clinical experience and expertise
Additionally, the evidence is given strengths depending on risk and benefits	
Strength A	A strong recommendation to do (or not to do) where the benefits outweigh the risk (or vice versa) for most, if not all, patients, e.g., 1A, 2A
Strength B	Weak recommendation, where benefits and risk are more closely balanced or uncertain, e.g., 1B, 2B, 3B

RCT: Randomized clinical trial

Quality of evidence scoring and strength of recommendation assessment

The expert group members selected the literature and graded it for quality.[8] A modified GRADE approach was used to grade the evidence (Table 2)

Development of recommendations based on current evidence

The expert groups presented the consolidated scientific literature, which formed the basis of the consensus statements. The presentations were followed by a discussion where all the expert panel members reviewed

the recommendation statements and quality of evidence. The opinion shared by experts and agreed by the majority of the panel members based on their vast clinical experience was considered where strong evidence was lacking supporting the recommendation. During the first round of Delphi polling, all the expert panel members voted for the proposed consensus statements on a 5-point Likert scale (strongly agree, agree, neither agree nor disagree, disagree or strongly disagree) using the electronic voting platform (polleverywhere.com). Categorical responses, where at least 80% voted combinedly for strongly agree and agree, were considered to have reached a consensus. These statements were deemed to be final and were not deliberated further. Disagreements were discussed and resolved. Consensus statements were reworded or rephrased with the incorporation of suggestions from the experts. The second round of Delphi polling was carried out, where the voting for the reframed consensus statements was done. All the reframed statements reached the consensus with more than 80% of votes combinedly for strongly agree and agree, so the third round of Delphi polling was not required. The accepted statements were finalized as the expert panel recommendations. The results of the Delphi polling are summarized in Appendix. The consensus document was prepared by the writing committee and reviewed by all the experts

RESULTS

Each recommendation is presented with a relevant evidence summary which follows the structure as a summary of the evidence, table/s to present the data from the evidence, and specific comments or expert opinion relevant to the recommendation. The summary of the recommendations is shown in Table 3.

Table 3: Recommendations on the use of ranitidine in pediatric office practice.

S. no.	Recommendations
A	**Section 1: Role of ranitidine in drug-induced gastritis in pediatric setting**
1	Commonly used drugs in pediatric practice (antibiotics, NSAIDs, steroids, iron, and zinc preparations) cause gastritis
2	Ranitidine has a rapid onset of action compared to PPIs and can be helpful for immediate relief of symptoms of gastritis
3	Ranitidine is preferred for on-demand use for the symptoms of gastritis
B	**Section 2: Prophylactic use of ranitidine in pathological conditions other than gastritis in the pediatric setting**
1	Ranitidine is effective in managing stress-induced gastric lesions in critically ill pediatric patients in ICU
2	Ranitidine reduces the gastric fluid volume when used as preoperative prophylaxis
3	Ranitidine effectively prevents acid reflux at night
C	**Section 3: Comparative safety of ranitidine versus PPIs in pediatric patients**
1	The incidence of GI and non-GI side effects with long-term use of PPI is higher than ranitidine
2	The long-term use of ranitidine therapy for acid suppression has a reduced risk of facture in comparison to PPI use
3	The risk of dysbiosis, *Clostridium difficile* and respiratory infections is higher with PPIs as compared to ranitidine
4	The risk of acute kidney injury is higher with the use of PPI when compared to ranitidine

GI: Gastrointestinal; NSAIDs: non-steroidal anti-inflammatory drugs; PPI: proton pump inhibitor

Section 1: Role of ranitidine in drug-induced gastritis in the pediatric setting

Recommendation 1: Commonly used drugs in pediatric practice (antibiotics, NSAIDs, steroids, iron, and zinc preparations) cause gastritis

Quality of evidence: 3A; and strength of recommendation: strong.

Evidence summary

Drugs-induced gastritis is a considerably evident condition in pediatric practice. Non-steroidal anti-inflammatory drugs (NSAIDs) are among the common causes of gastritis in children. NSAIDs are widely used for treating fever, mild-to-moderate pain, and inflammation in pediatrics. It is reported that high doses or repeated, prolonged treatment with NSAIDs may lead to gastrointestinal tract bleeding, peptic ulcer, and erosive gastritis.[9] A case series evaluating spontaneously reported cases of serious upper GI complications associated with non-salicylate NSAIDs used in children to treat fever or moderate pain reported a strong association between NSAIDs used in children and the risk of serious upper GI complications.

It was also found that the complications increased with the length and dose of the drug, and there was an increased risk when NSAID was combined with salicylate.[10]

While there is well-established evidence relating NSAIDs use to gastritis, the evidence is sparse for other commonly prescribed drugs, such as antibiotics, steroids, iron, and zinc which can potentially cause gastritis (Table 4).

It is important to sensitize clinicians regarding the dose and duration of therapy that can cause gastritis.

Table 4: Commonly used drugs in pediatric practice and level of evidence for causing gastritis.

Commonly used drugs in pediatric practice (e.g.)	Level of evidence for causing gastritis in pediatric patients
NSAIDs	2A
Antibiotics	3A
Steroids	3A
Iron supplements	3A
Zinc supplements	3A

Recommendation 2: Ranitidine has a rapid onset of action compared to PPIs and can be helpful for immediate relief of symptoms of gastritis

Quality of evidence: 1A; and strength of recommendation: strong

Evidence summary

Rapid onset of action is one of the benefits of H2RAs, which makes them useful for immediate relief of symptoms.[2,11] A randomized, single-dose, double-blind, placebo-controlled study evaluating oral ranitidine 75 mg in 29 children (4-11 years of age) with symptoms of GERD showed that intragastric pH begins to rise approximately 30 min after dosing with ranitidine.[4]

On the contrary, PPIs generally require three days to achieve maximum impact; since it does not inhibit all the proton pumps immediately and is slow to achieve steady-state concentration.[12] Although there is no head-to-head comparison between ranitidine and PPIs for the onset of action, the current literature supports that ranitidine has a rapid onset of action compared to PPIs.

Recommendation 3: Ranitidine is preferred for on-demand use for the symptoms of gastritis

Quality of evidence: 1A; and strength of recommendation: strong.

Evidence summary

For an on-demand treatment and in cases of severe symptoms, the onset of drug action should be rapid. This favors H2 receptor antagonists, which rapidly increase the pH of the gastric contents. Ranitidine provides immediate relief of gastritis-associated symptoms due to its rapid onset of action. The high bioavailability of ranitidine from day one also contributes to early symptom relief. This makes ranitidine a suitable choice for on-demand use in gastritis.[13] This rationale has also been echoed in clinical outcomes.[4]

In contrast to ranitidine, PPIs must be administered 30 to 60 minutes before meals for optimal efficacy. Also, PPIs have a slow onset of action, making them less efficacious for on-demand use.[11]

Experts agreed that ranitidine is preferred for on-demand use in pediatric patients, and it should be considered when an immediate effect is expected in pediatric patients with gastritis.

Section 2: Prophylactic use of ranitidine in pathological conditions other than gastritis in the pediatric setting

Recommendation 4: Ranitidine is effective in managing stress-induced gastric lesions in critically ill pediatric patients in ICU

Quality of evidence: 1A; and strength of recommendation: strong.

Evidence summary

Stress-related mucosal damage and upper gastrointestinal bleeding may complicate critical illness in up to 25% of critically ill infants and children. The incidence of upper gastrointestinal bleeding is approximately 10% in critically ill children, which increases to about 51% with mechanical ventilation. The pathophysiology of stress ulcers is not fully understood; however, it is thought to be different from that of peptic ulcers. High concentrations of intragastric hydrogen ions and pepsin may develop stress ulceration. Acid-suppressive therapy is beneficial in preventing stress ulcers. An intragastric pH of >4 is stress ulcer preventive. Pediatric intensive care units with mechanical ventilation are the most frequent indications for stress ulcer prophylaxis (SUP). Prophylactic ranitidine is commonly administered to these high-risk infants and children to reduce the chances of stress ulcers and significant upper GI bleeding.[14,15]

A prospective, randomized, controlled study by Kuusela and colleagues showed that short-term prophylactic ranitidine treatment prevents gastric mucosal lesions in mechanically ventilated newborns in the neonatal intensive care unit (NICU). The dose of ranitidine in this study was 5 mg/kg body weight/day intravenously divided into three doses throughout four days of treatment. The gastric mucosa was visually classified as normal in 61% of neonates compared with 20% of controls ($p<0.004$).[16]

Another prospective, randomized, controlled trial by Lopez-Herce and colleagues evaluated the efficacy of prophylaxis of upper gastrointestinal bleeding in 140 critically ill children. Patients received IV ranitidine 1.5 mg/kg every 6 hours (n=35), almagate 0.25 to 0.5 ml/kg

every 2 hours (n=35) and sucralfate 0.5 to 1 gm every 6 hours (n=35) by nasogastric tube or were randomized to control group (n=35). The rate of significant upper gastrointestinal bleeding was higher in the control group than in the other groups ($p<0.01$).[17]

In the background of a lack of recent literature and a randomized clinical trial, the consensus was reached by the expert group on the prophylactic role of ranitidine in stress ulcer prevention in critically ill pediatric patients based on clinical experience and expertise.

The benefits of stress ulcer prophylaxis should be weighed carefully against adverse outcomes. No untoward side effects are observed with ranitidine when used for prophylaxis against stress ulcers. Hence, ranitidine is appropriate for stress ulcer prophylaxis in critically ill children and can be considered a choice of therapy in mechanically ventilated patients. In addition, evidence also exists for the use of various PPIs in critically ill children.

Recommendation 5: Ranitidine reduces the gastric fluid volume when used as preoperative prophylaxis

Quality of evidence: 2B; and strength of recommendation: good practice point.

Evidence summary

The risk of regurgitation or aspiration is associated with any sedation/general anesthesia procedure, and this risk increases in emergency cases and any child with GI obstruction. Other significant factors for the regurgitation or aspiration at the time of induction of anesthesia are inadequate anesthesia depth or airway disorders.[18] Ranitidine is a potent inhibitor of gastric acid secretion and volume. Previous studies in children have shown that ranitidine effectively increases gastric pH and reduces gastric volume following oral administration before the induction of anesthesia.

A randomized trial conducted by Gombar and co-workers evaluated the effect of pre-operative intake of oral water and ranitidine on gastric fluid volume and pH in 75 children undergoing elective surgery. The trial showed that administration of 5 ml/kg of plain water and 2 mg/kg of ranitidine orally for 3 hours before surgery modifies gastric fluid volume and pH and minimizes the risk of aspiration pneumonitis.[19] Another study by Sandhar and colleagues evaluated the effect of oral liquids and ranitidine on gastric fluid volume and pH in children undergoing outpatient surgery (N=80; age 1 to 14 years). In this study, ranitidine 2 mg/kg with or without fluids decreased both the volume and acidity of gastric contents.[20]

Although, there is a lack of recent literature supporting the role of ranitidine as preoperative prophylaxis to reduce gastric fluid volume. Further research is needed to demonstrate the effect of ranitidine on gastric fluid volume as preoperative prophylaxis. However, based on current clinical evidence, experts agreed that pre-anesthetic use of ranitidine might be considered for preoperative prophylaxis to reduce the risk of aspiration in pediatric patients undergoing operative procedures under anesthesia.

Recommendation 6: Ranitidine effectively prevents acid reflux at night

Quality of evidence: 2A; and strength of recommendation: strong.

Evidence summary

The term "nocturnal acid breakthrough" was first introduced by Peghini and colleagues and defined as the presence of intragastric pH <4 during the overnight period (10:00 PM to 6:00 AM) for at least 60 continuous minutes.[21] A high frequency of nocturnal acid reflux is reported among children with PPIs. A prospective, double-blind study by Pfefferkorn et al, including 18 children with esophagitis (1 to 13 years of age) and treated with 1.4 mg/kg of PPI divided twice daily, demonstrated that 89% of the patients had nocturnal acid reflux when on the PPI.[22]

Nocturnal use of ranitidine is proven more effective than bedtime PPI in preventing acid reflux at night. Although there are trials demonstrating ranitidine in preventing nocturnal acid reflux in adults, there is a lack of literature and trials in pediatric settings. Based on long clinical experience, experts suggest that bedtime administration of ranitidine should be considered as prophylaxis in pediatric patients with nocturnal acid reflux. However, patients should be monitored for improvement in the symptoms.

Section 3: Comparative safety of ranitidine versus PPIs in pediatric patients

Recommendation 7: The incidence of GI and non-GI side effects with long-term use of PPI is higher than ranitidine

Quality of evidence: 1A; and strength of recommendation: strong.

Evidence summary

It was assumed that PPIs are safe in children; however, this belief is being challenged with upcoming evidence of potential GI and non-GI side effects associated with PPIs. Multiple pathogenetic pathways have been proposed for PPIs-associated adverse effects in children, primarily connected to long-term gastric acid suppression-induced hypochlorhydria.[23]

A systemic review including the literature over ten years on GER treatments in children reported fewer adverse effects in 23% of patients treated with H2RAs than 34% of those receiving PPIs.[24]

Key side effects associated with proton pump inhibitors use in children are summarized in Table 5.

Table 5: Side effects associated with proton pump inhibitors use in children and the level of evidence supporting the association.

Proposed side effects of PPI in children	Level of evidence
Risk of fractures	2A
Dysbiosis	1A
***Clostridium difficile* infection associated with GI infections**	1A
Respiratory tract infections	1A
Acute kidney injury	2A

The current literature suggests that PPI is associated with a higher risk of side effects in pediatric patients than ranitidine. Attention should be given to the substantial epidemiological evidence of increased risk of side effects with long-term use of PPIs. Alternative use of H2RA, preferably ranitidine, should be considered appropriate in pediatric indications.

Recommendation 8: The long-term use of ranitidine therapy for acid suppression has a reduced risk of fracture in comparison to PPI use

Quality of evidence: 1A; and strength of recommendation: strong.

Evidence summary

PPIs administration has been linked with an increased risk of osteoporosis and bone fractures.PPIs may compromise bone health by different mechanisms. PPIs may reduce calcium absorption and inhibit the function of osteoclasts, decreasing bone resorption and influencing bone remodeling.[23,25] Data on the risk for fractures associated with PPI were mainly reported in adults; however, there is increasing evidence in children, as summarized in Table 6. Although there is a lack of randomized clinical trials comparing PPI and H2RA for fracture risk, current literature demonstrates the increased likelihood of fractures with PPI use in children. In contrast, no increased risk was observed with H2RA use, including ranitidine. The risk should be considered while prescribing an acid-suppressive drug for different pathological conditions in pediatric patients.

Recommendation 9: The risk of dysbiosis, clostridium difficile, and respiratory infections is higher with PPIs as compared to ranitidine

Quality of evidence: 1A; and strength of recommendation: strong.

Evidence summary

Recent evidence suggests that PPIs modify the microbiome of the mouth, gut, and lungs through inhibition of gastric acid secretion. Following four weeks of therapy with PPIs, substantial disruption of gut microbial composition and diversity can occur.[29] Thus, PPI-associated dysbiosis is further linked with an increased risk of GI and respiratory tract infections (RTIs).[30]

Clostridium difficile infection is the most common GI infection linked to PPI use. The proposed pathogenetic pathway for increased risk of PPI-associated dysbiosis and *C. difficile* infection include alterations in the gut microbiome, reduction of gastric mucus viscosity, and leucocyte activity followed by enhanced bacterial invasion.[23]

RTIs are another common type of infection associated with PPI use in children. Dysbiosis-related invasion of microorganisms from the GI tract into the upper and lower respiratory tract is the proposed pathogenic pathway for this association.[23] PPI-associated dysbiosis and disturbance of the human microbiome are also key factors in provoking asthma flares.[29] Evidence of the association of PPI use with a high risk of *C. difficile* infection and respiratory infections is summarized in Table 7.

Table 6: Evidence for association of PPI and high risk of fractures.

Study	Study design	Study population and interventions	Key outcomes
Li et al, 2021[26]	Meta-analysis of six observational studies	N=2,432,308 children and young adults with the use of acid-suppressive drugs	PPIs use alone increased the risk of fracture in children and young adults (p<0.001), but H2RAs use alone (p<0.038) or PPIs combined with H2RAs didn't increase the risk of fracture
Yang et al, 2022[27]	Meta-analysis of six observational studies	N=9,00,000 children and young adults with acid-suppressive drugs	Pooled relative risk for fracture was significantly higher in children (p<0.001) using PPIs versus non-use. In contrast, H2RA treatment was not significantly associated with the risk of fracture in children (0.083) as well as young adults (p=0.589)
Wang et al, 2020[28]	Register-based cohort study	N= 3,621,940 children (<18 years age), N=117,234	PPI use before the age of one and therapy for a more extended period was linked to a higher risk of

Continued.

Study	Study design	Study population and interventions	Key outcomes
		initiated PPI before age of one year, N=2,373,292 did not receive PPI	fracture and was correlated to an earlier median age at first fracture compared to control (3.8 versus 4.5 years)

Table 7: Evidence of association of PPI use with a high risk of *C. difficile* infection and respiratory infections.

Study	Study design	Study population and interventions	Key outcomes
Anjewierden et al, 2019[31]	Meta-analysis and systematic review of 14 trials	N=10,531,669 children and young adults (age 0 to 18 years), n=22,320 with *C. difficile* infection	Use of PPI was associated with a significantly increased risk of *C. difficile* infection in children (OR, 1.33; 95% CI, 1.07-1.64). While, H2RA did not play a significant role as a risk factor for developing *C. difficile* infection in children (OR, 1.36; 95% CI, 0.31–5.98)
Chang et al, 2020[32]	Retrospective analysis	N=124 children (1-18 years old) with diarrhea and positive for *C. difficile* infection	PPI use was the significant (p<0.01) variable for serious illnesses among patients with *C. difficile* infection. While the use of H2RA before one month was not associated with an increased risk of *C. difficile*
Holbrook et al, 2012[33]	Multicenter, randomized, placebo-controlled trial	N=306 children (6-17 years old) with poor asthma control, n=149 received lansoprazole, n=157 received placebo	In 63% of patients, PPI use was associated with upper respiratory tract infection compared to 49% in the control group (p=0.02)
McCrory et al, 2018[34]	Retrospective study	N=175 children and young adults with cystic fibrosis, n=126 patients in PPI (1 mg/kg/day) group, n=49 patients in control group	Chronic PPI therapy resulted in at least one pulmonary exacerbation in 59.6% of patients compared with 24.5% in the control group (p<0.001)

Cautious and appropriate use of PPIs is required to reduce the risk of dysbiosis and associated risk of GI and RTIs in this vulnerable population. Ranitidine presents a better alternative, which is not found to cause significant dysbiosis in pediatric patients.

Recommendation 10: The risk of acute kidney injury is higher with the use of PPI as compared to ranitidine

Quality of evidence: 2A; and strength of recommendation: strong.

Evidence summary

In adults, PPI use is an established risk factor for incidental chronic kidney disease (CKD), CKD progression, and end-stage renal disease (ESRD).[35] However, this association is not yet well established in the pediatric population.

A multicenter cohort study by Xu and colleagues assessed the epidemiology and clinical correlates of acute kidney injury (AKI) among 101,836 pediatric inpatients (1 month to 18 years of age). The study revealed that PPI use was associated with 52% higher odds for hospital-acquired AKI and was responsible for 9% of hospital-acquired AKI. This was the first study demonstrating an association between PPI use and the high risk of pediatric AKI.[36]

Another recent multicenter retrospective cohort study by Li and colleagues in 2020 evaluated the association between the use of PPI and the risk of hospital-acquired AKI in 42,232 hospitalized children aged one month to 18 years, of which 3,514 patients were reported with hospital-acquired AKI. In this study, 27.2% of patients were prescribed PPIs, while 4.2% received H2RA. The use of PPI was associated with a significantly increased risk of AKI compared with both non-users (p<0.001) and H2RA users (p=0.04). Children with chronic kidney disease and those needing intensive care were at comparatively higher risk.[37]

The risk of acute kidney injury with PPI use increases even within the recommended dosage. This risk should be considered while prescribing PPI to children. Currently, there are only cohort studies demonstrating the association of PPI and AKI; a well-designed meta-analysis may also help to determine the association in pediatrics. Current data suggest that ranitidine has a better renal safety profile than PPIs.

DISCUSSION

Proton pump inhibitors and H2 receptor antagonists are routinely prescribed in children for a wide range of indications. Each class of drug has its place in therapy for

pediatric use. H2RAs like ranitidine have been available for several decades to treat GERD and treatment or maintenance therapy of duodenal and benign gastric ulcers.[38] However, its multi-dimensional use and safety are not supported by any clinical guidelines. Interestingly, the onset of gastric acid relief provided by H2RAs like ranitidine is approximately 60 minutes, with a duration of action that ranges from 4 to 10 hours.[39] Hence, rapid onset and short duration of action make ranitidine a choice of drug for on-demand and short-term acid suppression in pediatric patients, where immediate relief is intended. The recommendation is in line with ISPGHAN and NASPGHAN/ESPGHAN guidelines, which also recommend the use of ranitidine for short-term acid suppression in GERD.[5,11]

Drug-induced gastritis is considerably prevalent in pediatrics. NSAIDs are the well-identified cause of gastritis in children.[10] Although there is a low level of evidence for drug-induced gastritis caused by other commonly prescribed drugs, including antibiotics, steroids, iron, and zinc, there are frequent cases of gastritis reported with these drugs. Ranitidine might play a vital role in the management of drug-induced gastritis when an immediate effect is required in pediatric patients with symptoms of gastritis such as abdominal pain, nausea, vomiting, or bloating.[40] It should be preferred for relieving on-demand symptoms of gastritis due to its rapid onset of action.[4,39] In contrast to ranitidine, PPIs must be administered 30 to 60 minutes before meals for optimal efficacy, and it has a slow onset of action, making them less efficacious for on-demand use.[11]

Nearly one-fourth of critically ill infants and children show complications associated with stress-induced mucosal damage and upper gastrointestinal bleeding. Prophylactic use of ranitidine is suggested in such indications in children. Ranitidine has demonstrated significant prevention of gastric mucosal lesions and reduced upper gastrointestinal bleeding in critically ill children.[16,17] It should be commonly used for stress ulcer prophylaxis in pediatric intensive care units for children requiring mechanical ventilation.[14,15] Also, there is a well-known risk of aspiration in pediatric patients undergoing operative procedures under anesthesia.[18] Hence, ranitidine might prove to be a useful aid in preoperative prophylaxis to reduce this phenomenon, as it significantly inhibits gastric acid secretion and volume of the refluxate. Ranitidine might also be useful in preventing nocturnal acid reflux in pediatric patients. Since clinical data have revealed that PPIs, even though significantly decrease gastric acid secretion, it does not eliminate intragastric acidity completely due to a short plasma half-life of 2–4 hours. In addition, not all proton pumps are active at the same time, and the generation of new proton pumps is a continuous process. Studies have postulated that histamine plays a major role in nocturnal acid secretion. Thus, increased intragastric acidity, primarily during night-time, is an expected phenomenon that can be managed well with bedtime H2RA in patients with persistent nocturnal symptoms.[41,42]

Clinical evidence suggests that the use of PPIs in children has been associated with an increased risk of gastrointestinal and lower respiratory tract infections, bone fractures, and allergies, questioning their safety for pediatric use.[43] Ranitidine has a better safety profile than PPIs with respect to both GI and non-GI side - effects.[26,27,31,32] With this known background, the role of ranitidine is highlighted as a better alternative to PPIs in short-term acid suppression for multiple indications in pediatric use.

The recommendations in this article are based on current real-world evidence and expertise, which provides guidance on issues in which there is a lack of evidence. The safety profile of ranitidine has been backed by multiple decades of scientific evidence, which has helped it stand the test of time despite the increasing usage of PPIs in recent times. Unknown benefits of ranitidine are yet to be explored; with increasing medical evidence, we expect to open avenues in due course of time.

CONCLUSION

The panel of pediatricians and pediatric gastroenterologists have developed ten recommendations on the use of ranitidine in pediatric practice based on the review of the best available scientific evidence. These recommendations would be a guiding tool for all the clinicians looking for the most recent, collated, and practical evidence on Ranitidine. These recommendations consolidate the current evidence on the therapeutic benefits and safety of ranitidine in multiple indications in pediatric practice.

ACKNOWLEDGEMENTS

Authors would like to acknowledge Dr. Mayuresh Garud, Scientific Director, SciPrez, Pune, for providing medical writing support.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Leung AKC, Hon KL. Gastroesophageal reflux in children: an updated review. Drugs in Context. 2019;8:212591.
2. Poddar U. Diagnosis and management of gastroesophageal reflux disease (GERD): An Indian perspective. Indian Pediatr. 2013;50(1):119-26.
3. Zaterka S, Marion SB, Roveda F, Perrotti MA, Chinzon D. Historical perspective of gastroesophageal reflux disease clinical treatment. Arq Gastroenterol. 2019;56(2):202-8.

4. Orenstein SR, Blumer JL, Faessel HM, McGuire JA, Fung K, Li BUK, et al. Ranitidine, 75 mg, over-the-counter dose: pharmacokinetic and pharmacodynamic effects in children with symptoms of gastro-oesophageal reflux: Ranitidine, 75 mg, in children. Aliment Pharmacol Ther. 2002;16(5):899-907.
5. Rosen R, Vandenplas Y, Singendonk M, Cabana M, DiLorenzo C, Gottrand F, et al. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2018;66(3):516-54.
6. Kothari S, Nelson SP, Wu EQ, Beaulieu N, McHale JM, Dabbous OH. Healthcare costs of GERD and acid-related conditions in pediatric patients, with comparison between histamine-2 receptor antagonists and proton pump inhibitors. Curr Med Res Opin. 2009;25(11):27039.
7. Dalkey NC. Delphi. RAND Corporation. 1967. Available at: https://www.rand.org/pubs/papers/P3704.html. Accessed on 02 May 2022.
8. Singh S, Sharma B, Bairwa M, Gothi D, Desai U, Joshi J, et al. Management of interstitial lung diseases: A consensus statement of the Indian Chest Society (ICS) and National College of Chest Physicians (NCCP). Lung India. 2020;37(4):359-78.
9. de Martino M, Chiarugi A, Boner A, Montini G, de' Angelis GL. Working Towards an Appropriate Use of Ibuprofen in Children: An Evidence-Based Appraisal. Drugs. 2017;77(12):1295-311.
10. Autret-Leca É, Bensouda-Grimaldi L, Maurage C, Jonville-Bera AP. Upper Gastrointestinal Complications associated with NSAIDs in Children. Therapies. 2007;62(2):173-6.
11. Mohan N, Matthai J, Bolia R, Agarwal J, Shrivastava R, Borkar VV, et al. Diagnosis and Management of Gastroesophageal Reflux Disease in Children: Recommendations of Pediatric Gastroenterology Chapter of Indian Academy of Pediatrics, Indian Society of Pediatric Gastroenterology, Hepatology and Nutrition (ISPGHAN). Indian Pediatr. 2021;58(12):1163-70.
12. Sachs G, Shin JM, Howden CW. Review article: the clinical pharmacology of proton pump inhibitors. Aliment Pharmacol Ther. 2006;23(2):2-8.
13. Hatlebakk JG, Berstad A. Pharmacokinetic Optimisation in the Treatment of Gastro-Oesophageal Reflux Disease: Clin Pharmacokinet 1996;31(5):386-406.
14. Abu El-Ella SS, Said El-Mekkawy M, Mohamed Selim A. Stress ulcer prophylaxis for critically ill children: Routine use needs to be re-examined. Anales de Pediatría. 2022;96(5):402-9.
15. Lugo RA, Harrison AM, Cash J, Sweeley J, Vernon DD. Pharmacokinetics and pharmacodynamics of ranitidine in critically ill children: Crit Care Med. 2001;29(4):759-64.
16. Kuusela AL, Ruuska T, Karikoski R, Laippala P, Ikonen RS, Janas M, et al. A randomized, controlled study of prophylactic ranitidine in preventing stress-induced gastric mucosal lesions in neonatal intensive care unit patients: Crit Care Med. 1997;25(2):346-51.
17. López-Herce J, Dorao P, Elola P, Delgado MA, Ruza F, S RM. Frequency and prophylaxis of upper gastrointestinal hemorrhage in critically ill children: A prospective study comparing the efficacy of almagate, ranitidine, and sucralfate. Crit Care Med. 1992;20(8):1082-9.
18. Frykholm P, Disma N, Andersson H, Beck C, Bouvet L, Cercueil E, et al. Pre-operative fasting in children: A guideline from the European Society of Anaesthesiology and Intensive Care. Eur J Anaesthesiol. 2022;39(1):4-25.
19. Gombar S, Dureja J, Kiran S, Gombar K, Chhabra B. The effect of pre-operative intake of oral water and ranitidine on gastric fluid volume and pH in children undergoing elective surgery. J Indian Med Assoc. 1997;95(6):166-8.
20. Sandhar BK, Goresky GV, Maltby JR, Shaffer EA. Effect of Oral Liquids and Ranitidine on Gastric Fluid Volume and pH in Children Undergoing Outpatient Surgery. Anesthesiology. 1989;71(3):327-30.
21. Peghini PL, Katz PO, Bracy NA, Castell DO. Nocturnal Recovery of Gastric Acid Secretion With Twice-Daily Dosing of Proton Pump Inhibitors. Am J Gastroenterol. 1998;93(5):763-7.
22. Pfefferkorn MD, Croffie JM, Gupta SK, Molleston JP, Eckert GJ, Corkins MR, et al. Nocturnal Acid Breakthrough in Children with Reflux Esophagitis Taking Proton Pump Inhibitors. J Pediatr Gastroenterol Nutr. 2006;42(2):160-5.
23. Dipasquale V, Cicala G, Spina E, Romano C. A Narrative Review on Efficacy and Safety of Proton Pump Inhibitors in Children. Front Pharmacol. 2022;13:839972.
24. Cohen S, Bueno de Mesquita M, Mimouni FB. Adverse effects reported in the use of gastroesophageal reflux disease treatments in children: a 10 years literature review. Br J Clin Pharmacol. 2015;80(2):200-8.
25. De Bruyne P, Ito S. Toxicity of long-term use of proton pump inhibitors in children. Arch Dis Child. 2018;103(1):78-82.
26. Li J, Xie X, Liu W, Gu F, Zhang K, Su Z, et al. Acid-Suppressive Drugs and Risk of Fracture in Children and Young Adults: A Meta-Analysis of Observational Studies. Front Pharmacol. 2021;12:712939.
27. Yang J, Zhou TJ, Yang J, Bao DN. Use of acid-suppressive drugs and risk of fracture in children and young adults: a meta-analysis of observational studies. Eur J Clin Pharmacol. 2022;78(3):365-373.
28. Wang YH, Wintzell V, Ludvigsson JF, Svanström H, Pasternak B. Association Between Proton Pump

Inhibitor Use and Risk of Fracture in Children. JAMA Pediatr. 2020;174(6):543-51.
29. Wang YH, Wintzell V, Ludvigsson JF, Svanström H, Pasternak B. Association Between Proton Pump Inhibitor Use and Risk of Asthma in Children. JAMA Pediatr. 2021;175(4):394-403.
30. Levy EI, Hoang DM, Vandenplas Y. The effects of proton pump inhibitors on the microbiome in young children. Acta Paediatr. 2020;109(8):1531-8.
31. Anjewierden S, Han Z, Foster CB, Pant C, Deshpande A. Risk factors for Clostridium difficile infection in pediatric inpatients: A meta-analysis and systematic review. Infect Control Hosp Epidemiol. 2019;40(4):420-6.
32. Chang TH, Hsu WY, Yang TI, Lu CY, Hsueh PR, Chen JM, et al. Increased age and proton pump inhibitors are associated with severe Clostridium difficile infections in children. J Microbiol Immunol Infect. 2020;53(4):578-84.
33. Holbrook JT, Wise RA, Gold BD, Blake K, Brown ED, Castro M, et al. Lansoprazole for children with poorly controlled asthma: A randomized controlled trial. JAMA. 2012;307(4):373-80.
34. McCrory BE, Harper HN, McPhail GL. Use and incidence of adverse effects of proton pump inhibitors in patients with cystic fibrosis. Pharmacotherapy. 2018;38(7):725-9.
35. Xie Y, Bowe B, Li T, Xian H, Balasubramanian S, Al-Aly Z. Proton Pump Inhibitors and Risk of Incident CKD and Progression to ESRD. JASN. 2016;27(10):3153-63.
36. Xu X, Nie S, Zhang A, Mao J, Liu HP, Xia H, et al. Acute Kidney Injury among Hospitalized Children in China. Clin J Am Soc Nephrol. 2018;13(12):1791-800.
37. Li Y, Xiong M, Yang M, Wang L, Nie S, Liu D, et al. Proton pump inhibitors and the risk of hospital-acquired acute kidney injury in children. Ann Transl Med. 2020;8(21):1438.
38. Pappa KA, Williams BO, Payne JE, Buaron KS, et al. A double blind, placebo-controlled study of the efficacy and safety of non-prescription ranitidine 75 mg in the prevention of meal-induced heartburn. Aliment Pharmacol Ther. 1999;13:467-73.
39. Nugent CC, Falkson SR, Terrell JM. H2 Blockers. Treasure Island (FL): StatPearls Publishing. 2022.
40. Sasaran MO, Melit LE, Mocan S, Ghiga DV, et al. Pediatric gastritis and its impact on hematologic parameters. Medicine (Baltimore). 2020;99(35):21985.
41. Tutuian R, Castell DO. Nocturnal Acid Breakthrough - Approach to Management. Med Gen Med. 2004;6(4):11.
42. Shim YK, Kim N. The Effect of H2 Receptor Antagonist in Acid Inhibition and Its Clinical Efficacy. Korean J Gastroenterol. 2017;70(1):4-12.
43. Dipasquale V, Cicala G, Spina E, Romano C. A narrative review on efficacy and safety of proton pump inhibitors in children. Front Pharmacol. 2022;13:8399725.

Cite this article as: Pai UA, Kesavelu D, Shah AK, Manglik AK, Wadhwa A, Acharya B, et al. Ranitidine use in pediatrics: current evidence-based review and recommendations. Int J Contemp Pediatr 2022;9:987-97.