Review Article

Clinical use of gastric antisecretory drugs in pediatric patients with gastroesophageal reflux disease: a narrative review

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Background and Objective: Gastroesophageal reflux (GER) is a common condition in infants. Usually, it resolves spontaneously in 95% of cases within 12–14 months of age, but gastroesophageal reflux disease (GERD) may develop in some children. Most authors do not recommend pharmacological treatment of GER, while the management of GERD is debated. The aim of this narrative review is to analyze and summarize the available literature on the clinical use of gastric antisecretory drugs in pediatric patients with GERD.

Methods: References were identified through MEDLINE, PubMed, and EMBASE search engines. Only articles in English were considered. The following keywords were used: "gastric antisecretory drugs", "H2RA", "PPI", "ranitidine", "GERD", "infant", "child".

Key Content and Findings: Increasing evidence of poor efficacy and potential risks of proton pump inhibitors (PPIs) is emerging in neonates and infants. Histamine-2 receptor antagonists (H2RAs), including ranitidine, have been used successfully in older children, although less effective than PPIs at relieving symptoms and healing GERD. However, in April 2020, both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) requested manufacturers of ranitidine to remove all ranitidine products from the market due to the risk of carcinogenicity. Pediatric studies comparing effectiveness and safety of different acid-suppressing treatments for GERD are generally inconclusive.

Conclusions: A proper differential diagnosis between GER and GERD is crucial to avoid the overuse of acid-suppressing medications in children. Further research should be directed towards the development of novel antisecretory drugs, with proven efficacy and good safety profile, for treating pediatric GERD, particularly in newborns and infants.

Keywords: Gastric antisecretory drugs; histamine-2 receptor antagonist (H2RA); proton pump inhibitor (PPI); gastroesophageal reflux disease (GERD); infant; child

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Introduction

Gastroesophageal reflux (GER) is widespread in the pediatric population, especially in infants under 3 months of life where daily episodes of regurgitation are common (1). Usually, GER resolves spontaneously in 95% of infants within 12–14 months of age (2) and causes few or no symptoms (functional GER), but some children may develop symptomatic gastroesophageal reflux disease (GERD) (3). The disease manifestations are different in children compared to adults and vary considerably by age group,

rendering the diagnosis and the management rather difficult. The most common symptoms in the first year of life include regurgitation, vomiting, food refusal, cough and irritability. Young children (1–6 years of age) present with regurgitation, abdominal pain and food refusal, while children aged >6 years have regurgitation or vomiting, cough, epigastric pain, and heartburn (4).

Pharmacological treatment should not be used in infants with functional GER. Therefore, a proper differential diagnosis between GER and GERD, based on an excessive frequency or duration of reflux events, is crucial to avoid the overuse of acid-suppressing medications.

During the last twenty years, the recommendations for the management of GER and GERD in infants changed. In 2001, acid-suppressing medications were proposed as treatment options for symptom relief and mucosal healing in the presence of GERD (5). In 2009, North American and European Societies of Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN and ESPGHAN, respectively) jointly published a clinical practice guideline for the diagnosis and management of reflux in children, confirming this approach (6). More recently, an update of these guidelines, based on an integration of a systematic review of the medical literature with expert opinion, has been published after a 3-day consensus meeting. The approach to be applied in daily practice differs from the 2009 guidelines in some points: (I) it focuses on reducing the use of acid-suppressing medications, whenever possible, with short empirical trials of 4–8 weeks of proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs); (II) it adds two algorithms for typical symptoms, one for infants <1 year of life and one for older infants and children; (III) it adds a recommendation for a 2–4 week trial with hydrolyzed protein formula before acid suppression in infants (7).

In addition, from 2010 onwards, evidence of poor efficacy and potential risks of PPIs began to accumulate (8-10). Therefore, different clinical guidelines and recommendations for recognition, diagnosis, and management of these conditions have been published: most of them do not recommend medications in the treatment of GER, while recommendations for managing GERD are not always clear, and often conflicting. Some guidelines suggest treatment with H2RA or PPI (11), others recommend these medications as a trial (12), and still others do not recommend their use in infants due to their limited efficacy and potential risks (13).

Available treatment options have been limited since April 2020, when the European Medicines Agency (EMA) has recommended an EU-wide suspension of all ranitidine medicines, due to the risk of carcinogenicity (14).

The current limited availability of effective and safe antisecretory drugs makes it difficult to develop evidence-based and consolidated guidelines for the treatment of pediatric GERD. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-401/rc).

Methods

Literature search strategy

References were identified through MEDLINE, PubMed, and EMBASE search engines. Only articles in English were considered. The following keywords were used: "gastric antisecretory drugs", "H2RA", "PPI", "ranitidine", "GERD", "infant", "child". Retrieved studies were evaluated on the basis of their titles and abstracts, and those considered relevant for the review were analyzed. Finally, 33 original studies, 25 review articles and few other relevant publications were included (*Table 1*).

Pharmacological options in pediatric GERD

The treatment of GERD is aimed at relieving symptoms and preventing complications.

A conservative approach including positioning and diet may be adopted for managing mild symptoms. In the presence of troublesome problems, treatment with acid-suppressing drugs is often required (7,12), while surgical intervention is needed for unresponsive cases.

Different approaches are available for the pharmacological treatment of GERD in children (*Table 2*). H2RAs suppress acid secretion by blocking H2 receptors on gastric parietal cells, and have been used in older children and adolescents, although less effective than PPIs at relieving symptoms and healing esophagitis (15,16).

The occurrence of tachyphylaxis is a major drawback of H2RAs that seriously restricts their long-term use (17). In some infants, they cause headache, irritability, and somnolence in the case of inappropriately high dosages (18). Moreover, these agents (particularly cimetidine) have been associated with an increased risk of liver disease (19) and gynecomastia (20).

Among H2RAs, cimetidine, ranitidine, famotidine and

Table 1 Search strategy and selection criteria used in this narrative review

Items	Specification
Date of search	June 2022
Databases and other sources searched	MEDLINE, PubMed, and EMBASE
Search terms used	"gastric antisecretory drugs", "H2RA", "PPI", "ranitidine", "GERD", "infant", "child"
Timeframe	From June 1989 to June 2022
Inclusion and exclusion criteria (study type, language restrictions etc.)	Only articles in English
Selection process	Data were extracted by two independent investigators, and consensus for inclusion was reached after assessment by all investigators. 33 original studies, 25 review articles and few other relevant publications were included

H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor; GERD, gastroesophageal reflux disease.

Table 2 Different pharmacological approaches available for the treatment of GERD in children

Drug	Authorization in children	Recommendation	Dosage
H2 receptor antagonists			
Cimetidine	YES (US)	Neonates and infants	20–40 mg/kg/day
Ranitidine	YES (EU, US)	Suspended (2020)	5–10 mg/kg/day
Famotidine	YES (US)	Neonates and infants (lack of evidence)	1 mg/kg/day
Nizatidine	YES (US)	>6 months	6–10 mg/kg/day
Proton pump inhibitors			
Omeprazole	YES (EU, US)	>1 year	0.5–3.5 mg/kg/day
Esomeprazole	YES (EU), YES (US)	>1 year	1–11 years: 10–20 mg QD; ≥12 years: 20–40 mg QD
Lansoprazole	YES (US)	>3 months (lack of evidence)	Infant: 1–2 mg/kg QD; Child: 0.7–3 mg/kg QD
Pantoprazole	YES (EU), YES (US)	>12 years (EU); >5 years (US)	≥5 yr: 20 mg QD
Antacids			
Magnesium alginate	YES (US) YES (EU)	0–12 years	Variable based on the product and body weight
Sodium Alginate	YES (US) YES (EU)	>12 years	Variable based on the product and body weight
Sucralphate	YES (US)	>14 years	40–80 mg/kg/day
Prokinetics			
Baclofen	NA	NA	<2 years: 10–20 mg/day
			2–7 years: 20–30 mg/day
			≥8 years: 30–40 mg/day
Cisapride	NA	Withdrawal (2000)	0.2–0.3 mg/kg/dose
Metoclopramide	YES (EU)	>16 years	0.1–0.2 mg/kg dose
Domperidone	YES (EU)	>12 years	0.3 mg/kg dose

GERD, gastroesophageal reflux disease; NA, data not available; QD, every day.

nizatidine have been traditionally used in most countries; the last two medications have been licensed for use in children in the USA but not in Europe. Since 2019, the US Food and Drug Administration (FDA) found N-nitrosodimethylamine (NDMA) levels exceeding the acceptable intake limit in many batches of medications including ranitidine. This led to widespread recalls of several products and to concerns among patients and clinicians, given that NDMA was classified as probably carcinogenic to humans. NDMA may form as a result of the degradation of ranitidine itself, especially after the expiration date, although it could also be formed from ranitidine inside the body. As a precaution, in April 2020, both the FDA and the EMA requested manufacturers to remove all prescription and over-the-counter ranitidine products from the market (21,22) because NDMA concentrations can increase over time if the medication is stored above room temperature, therefore reaching dangerous levels (14).

PPIs block Na^+, K^+-ATPase enzyme activity, the final step in parietal cell acid secretion, and their use in the pediatric population has increased considerably during the last decade (23). In particular, PPIs have shown to be the most effective drugs in children older than 1 year, while their efficacy for treatment of GER has not been clearly demonstrated in neonates and infants, being the most of available studies open-label and uncontrolled (24).

Therefore, in this age group, PPIs should be reserved for cases with evidence of pathological exposure to repeated acid reflux episodes and/or esophagitis (25). PPIs do not seem to induce tachyphylaxis and could be more appropriate for long-term therapy (26). In North America, PPIs approved for use in children aged >1 year are omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole. In Europe, the only drug approved in children aged >1 year is omeprazole, while esomeprazole and pantoprazole are licensed for use in children >12 years of age. Together with the raise in the PPI prescriptions for infants and children, there have been increasing safety concerns about their use (24). A review by Cohen *et al.* (27) underlined that 34% of children treated with PPIs developed adverse effects, including headache, nausea, diarrhea and constipation. In addition, a prolonged use of PPIs was found to be associated with gastrointestinal and respiratory infections, food allergy, vitamin B deficiency, hypomagnesemia, and an increased risk of chronic kidney disease (28).

Antacids are a category of drugs that may be used to neutralize gastric acidity in the esophagus or stomach, to reduce heartburn and allow healing of esophagitis (17). Little evidence is available on the use of these medications in the pediatric population (29). The safety and efficacy of antacids such as alginates and sucralfate, an aluminum compound, have not been investigated enough in pediatrics (17). The use of this class of drugs may lead to side effects including increased serum concentrations of magnesium, calcium and aluminum (30).

In children, alginates have been found to significantly reduce reflux episodes and improve symptomatic scores (31,32). In 2018, the Pediatric Gastroesophageal Reflux Clinical Practice Guidelines of NASPGHAN and ESPGHAN stated that the administration of alginates may slightly improve regurgitation and vomiting as signs and symptoms of GER, although it is unclear whether their use in infants with GER leads to side-effects (7).

In pediatrics, prokinetic agents have been used for many years as a first-choice treatment for reflux symptoms. Recent studies have documented that baclofen reduces reflux risk and improves gastric emptying in adults, but there are no pediatric studies in this regard. Furthermore, many adverse effects have been reported in association with baclofen use, which is why it is generally not recommended. Cisapride is effective in increasing peristalsis and promoting gastric emptying (7), but, in 2000, it was removed from the market in most countries due to its cardiac toxicity. Other prokinetic agents such as domperidone and metoclopramide, associated with few adverse events, are now less frequently employed, and should not be used as the first step of treatment. In 2014, the EMA stated that metoclopramide is contraindicated <1 year of age, and should be used as a second choice only for nausea and vomiting post-intervention, or related to chemotherapy; therefore, the use for GERD is off-label. As regards domperidone, rectal formulations are contraindicated in children with body weight <35 kg, and the only approved indication is nausea and vomiting.

Finally, no scientific evidence supports the use of erythromycin and bethanechol in GER and GERD treatment (7). Literature data on the pediatric population are not enough, and no robust evidence supports the use of prokinetics in children with GERD (6,7,33).

Prescribing patterns of antisecretory medications

Different studies report information on the prescribing patterns of acid-suppressing drugs used for GER and GERD in children, throughout the last few years.

A retrospective study investigated a sample of neonatal intensive care unit (NICU) infants admitted to 43 children's hospitals in U.S. by extracting information from the Pediatric Health Information System (PHIS) database related to the period January 2006–March 2013. Among the 122,002 infants evaluated, 28,989 (23.8%) received an H2RA or a PPI. Extremely preterm and term infants affected by GERD or congenital heart disease were the most likely to receive antisecretory drugs: the median postnatal age for the first treatment was 10 days, with a mean treatment duration of 15 days. Treated infants mostly were born at term (≥37 weeks' gestation) or late preterm (35–36 weeks gestation). During the study period, a trend was observed in H2RA/PPI utilization: H2RA use decreased annually from 23.1% in 2006 to 12.9% in 2013, while PPI use increased from 2006 to 2010 (with a peak of 12.2%), and then declined to 7.9% in 2013 (34).

Another retrospective study analyzed PPI and H2RA prescription patterns in newborns and infants in the USA from 2003 to 2008, based on information extracted from the Premier Perspective Inpatient Hospital Database (containing clinical and charge data of approximately 500 hospitals) and from PharMetrics Patient-Centric Database (outpatients). Although during the study period no PPI was approved by FDA for patients <1 year of age, PPIs were found to be commonly prescribed in an off-label manner in newborns and infants in the hospital setting and, to a lesser extent, in the outpatient setting. During the 5-year period, the number of inpatients receiving a PPI prescription increased, while the percentage of patients treated with a H2RA decreased. As regards outpatients, among newborns and infants where a diagnosis of GERD was made, 8.2% received PPIs. The most common PPI used both in the inpatient and outpatient setting was lansoprazole (23).

A national, population-based study was conducted in New Zealand to describe PPI prescription patterns during the first year of life among all infants born between 2005 and 2012. In total, 22,643 children were treated with a PPI (mostly omeprazole, but also lansoprazole and pantoprazole) before their first birthday. Comparing infants born in 2005 to those born in 2012, a doubling in the number of patients treated with a PPI (from 2.4% to 5.2%) was reported. This increase mostly regarded the cohort who began treatment within the first 3 months of age, where the percentage increased from 56.4% for infants born in 2005 to 74.6% for those born in 2012. Only a small proportion of the study population had a hospital-based diagnosis of GERD, before PPI initiation (35).

In an Australian prospective cross-sectional survey of general practice (GP) activity (BEACH Study) carried out between 2006 and 2016, all infants with GER or GERD were identified and acid suppressant prescriptions were analyzed. Of 18,920 visits to GPs regarding infants aged <1 year, 512 visits (2.7%) resulted in a diagnosis of GER or GERD. During the study period, the rates of diagnosis of reflux and GERD resulted steady until 2012, then diagnostic rates declined for reflux and increased for GERD. There was little difference in the acid-suppressing medication prescription between infants with reflux and those with GERD (43.6% *vs.* 48.5%; P=0.405). The only difference in the prescription of antisecretory drugs was the higher PPI use in the presence of GERD (39.4% *vs.* 23%; P=0.001), and the higher prescribing rate of H2RA in infants with reflux (20.8% *vs.* 11.1%; P=0.026). During the study period, no change was observed in the proportion of infants with reflux or GERD, but there were changes in the prescription of specific medicines. In infants with reflux, PPI prescriptions doubled from 2006–2008 to the following two years (12.2% *vs.* 22–28%) while, in the presence of GERD, PPI prescriptions were around 33% in earlier years and 50% in 2014–2016. In the same years, the proportion of infants treated with H2RAs declined and was found to be lowest in 2014–2016, both in the presence of reflux (15.1%) and in the case of GERD (6.5%). The authors underlined an overprescribing of acid-suppressing medications in infants in nearly 50% of visits (36).

A recent Chinese retrospective study investigated H2RA/PPI use in children aged <2 years hospitalized during a 4-year period (2015–2018) in a tertiary children's hospital. The authors reported that H2RAs/PPIs were commonly prescribed (prevalence: 4.4%), PPI use being over two times more frequent than H2RA use (71.9% *vs.* 28.1%). Unexpectedly, the study's findings showed that H2RAs/PPIs were commonly used (57.5%) in the treatment of infants without digestive system diseases, mostly suffering from respiratory diseases including asthma and acute upper respiratory tract infections (37).

In Europe, the approach to GERD management in children was investigated by analyzing the structured questionnaires completed by 567 European general pediatricians from 11 different countries (Portugal, Spain, Belgium, Netherlands, Germany, Italy, Slovenia, Serbia, Macedonia, Greece, Lithuania). Only 1.8% of pediatricians managed patients in full compliance with guideline recommendations, while 45.8% of them diagnosed GERD based on clinical symptoms, without specific tests and

irrespective of the age of the child. Furthermore, 67% of pediatricians considered PPIs the mainstay for the treatment of GERD, 36.2% of them treated uncomplicated recurrent regurgitation with these medications in infants younger than 1 year, while 16.6% considered H2RAs superior to PPIs. No significant difference in the adherence to guidelines was observed among pediatricians of involved countries (38).

The same authors (39) investigated the Italian general pediatricians' approach to the management of children with symptoms of GER. A sample of 100 pediatricians, distributed throughout the country, was invited to complete a structured questionnaire (from September 2012 to March 2013) concerning clinical management, diagnostic tools use, and treatment options in children with symptoms of GERD. From data analysis, emerged an overuse of PPIs, with only 2% of pediatricians completely following international guidelines as regards diagnostic tools and therapeutic prescriptions. Approximately 39% of pediatricians used to diagnose GERD without specific tests, irrespective of the child's age. As regards therapeutic options, 79% of pediatricians were found to prescribe drugs improperly: 56% of them prescribed PPIs in the presence of unexplained crying and/or distress, and 38% in infants presenting with uncomplicated regurgitation and vomiting. Moreover, 72% of pediatricians considered PPIs the first-choice treatment of GERD, while 16% considered H2RAs superior to PPIs. Regarding infants younger than 1 year of age, 38% of pediatricians affirmed to prescribe PPIs despite the lack of evidence.

A prospective cohort study was carried out through the use of The Health Improvement Network (THIN) database containing information entered by primary care physicians on the UK population. Sixteen thousand and seventy-seven pediatric patients, who were prescribed an acid-suppressing drug from October 2009 to September 2012, were divided in three cohorts according to their pharmacological treatment: esomeprazole, another PPI (omeprazole, lansoprazole), or a H2RA (mostly ranitidine). Over half of the patients in each cohort received only one prescription, indicating the effectiveness of the drug used. Surprisingly, esomeprazole was prescribed with a frequency lower than that of other medications, despite its effectiveness and tolerability in children with GERD (40). H2RAs were preferred in infants (about 50% of cases) while PPIs were mostly prescribed in children (>60%) (41).

Efficacy and safety data of antisecretory medications

Little is known about the drug efficacy and safety of acid-suppressing treatments in children. In fact, pediatric studies comparing the efficacy and safety of different medications for GERD treatment are generally characterized by small sample size, absence of controls and unreliable endpoints.

As regards efficacy, neonatal trials did not demonstrate an improvement in GERD clinical symptoms following acid-suppressing drug treatment (42-44), as these symptoms tend to resolve with time (45). Therefore, guidelines have cautioned against using acid-suppressing drugs in neonates (6,46), and the American Academy of Pediatrics (AAP) identified these medications among unnecessary treatments in the neonatal population (47).

A systematic review including 23 randomized-controlled studies (1,598 patients divided into 3 groups comprising children >1 year of age, infants <1 year of age, and children of all ages) evaluated the most important drug classes used for the treatment of pediatric GERD. The study results showed that PPIs seem to be effective against typical manifestations of GERD and that H2RAs (mostly ranitidine) may be a suitable alternative, but there was no evidence that, in infants, both classes improve unspecific symptoms such as crying, vomiting, irritability, and regurgitation, in the absence of documented reflux esophagitis or complications (48).

This weak evidence of efficacy in subjects under 1 year of age was also underlined by other authors (8,49,50).

Regarding the safety of anti-GERD drugs, it is not always clear which adverse event is really related to the drug treatment and which to the disease itself. In fact, in a patient suffering from GERD it is difficult to determine whether a vomiting episode or abdominal pain are due to the medication used or to GERD (27).

Some studies suggest that the use of anti-GERD drugs may result in risks to patient safety (51), such as an increase in respiratory and gastrointestinal infections (3,28). In particular, in ill children with a compromised immune system, acid suppression has been associated with increased rate of nosocomial candidemia (52).

Among the 16,077 UK pediatric patients extracted from THIN database and divided in three cohorts according to their pharmacological treatment (esomeprazole, other PPIs, or H2RAs groups), no safety outcomes occurred in the "esomeprazole cohort". The incidence of adverse

effects resulted higher in the "H2RA cohort" compared to the "other PPIs cohort" (193 *vs.* 92 events). Gastroenteritis was the most common adverse reaction among all children (34.4%), followed by convulsions/seizures (27%) and pneumonia (18.6%) (41).

In a retrospective, observational postauthorization study, safety outcomes were compared in children users of esomeprazole, other PPIs, or H2RAs. Among 23,470 included children, 2,820 were treated with esomeprazole, 13,818 with other PPIs and 6,832 with H2RAs. In total, 504 children (2%) were hospitalized due to 762 adverse events including gastroenteritis, convulsions/seizures, pneumonia, acute interstitial nephritis, failure to thrive, angioneurotic edema, and thrombocytopenia. Significant differences between the cohorts have been found only for failure to thrive (53).

In a review by Cohen *et al.* (27), adverse effects related to GERD treatments in children, between January 2003 and December 2012, were extracted from the analysis of 44 randomized controlled trials (in total, 2,549 pediatric patients). Adverse effects were observed in at least 23% of children who were administered H2RAs and 34% of those receiving PPIs. Headache, diarrhea and nausea were routinely reported in trials of H2RAs and PPIs, whereas constipation was observed in patients treated with PPIs. Usually, adverse effects were mild: the proportion of serious adverse effects was 1.1% in PPI group and 0.88% in H2RA group.

Adverse effects of PPIs/H2RAs in neonates are well documented. Reduced gastric acidity, gut microbiota modification, and interference with neutrophil function lead to increased risk of gastrointestinal infections in full-term neonates and infants (54,55), and necrotizing enterocolitis (NEC) in very low birth weight (VLBW) infants (56,57). This kind of treatment also increases rates of community-acquired pneumonia (58), ventilator-associated pneumonia in Pediatric Intensive Care Unit (PICU) (59), and late-onset sepsis in NICU patients (60). Moreover, gastric pH changes interfere with calcium absorption, resulting in negative effects on bone development, and increasing the risk of fracture (61).

In a retrospective study including 274 VLBW infants exposed (n=91) or unexposed (n=183) to ranitidine, the risks of NEC, nosocomial infection and mortality resulted significantly higher among exposed neonates (P=0.003) (62).

A recent multicenter retrospective cohort study investigated the association between the use of PPIs and the risk of hospital-acquired acute kidney injury (HA-AKI) among hospitalized Chinese children aged 1 month to 18 years. PPI use was found to be associated with a significantly increased risk of HA-AKI as compared to both non-users (odds ratio, 1.37) and H2RA users (odds ratio, 1.24) (63).

Conclusions

In infants, the management of GER should involve an initial non-pharmacological approach, based on a combination of feeding changes and positioning therapy. Feeding changes are free of risk or cost, and thus should be considered before more expensive or risky interventions are decided. Changing the maternal diet in breastfed babies, changing formula in formula-fed infants, reducing feeding volume, and increasing feeding frequency can be effective in most patients. Dietary modifications and positional changes also seem useful in older children. Certain foods, and particularly high-fiber foods such as whole grains, root vegetables, and green vegetables, can also help to prevent heartburn or GERD (17). For each of these non-pharmacological therapies, a minimum trial of 2 weeks is recommended to evaluate symptom improvement before considering alternative therapies.

If there are signs and symptoms suggestive of GERD in older children or adolescents, the pediatrician can start a diagnostic trial of a PPI for 4 to 8 weeks and observe the patient's response. In infants, no evidence supports empirical therapy with PPIs for the diagnosis of GERD. Moreover, based on expert opinion, PPIs or H2RAs should not be used in children with extraesophageal symptoms (usually respiratory symptoms), except in the case of typical GERD symptoms and/or in the presence of diagnostic testing suggesting GERD (7).

H2RAs work faster than PPIs, and therefore they might be a better option for sudden occasional heartburn or acid reflux. However, there is low-quality evidence to support the efficacy and safety of H2RAs in children, and thus these medications should be prescribed with caution and solely if acid-related GERD has been confirmed (64). Finally, the suspension of ranitidine medicines by EMA, for suspected carcinogenicity, has further complicated the therapy of GERD in infants.

PPIs have shown to be the most effective drugs in children older than 1 year, while their efficacy for treatment of GER has not been clearly demonstrated in neonates and infants. These gastric antisecretory drugs do not exhibit the phenomenon of tachyphylaxis, ensure a more stable suppression of gastric acidity, have a simpler dosage regimen

due to their long period of action, but show a higher frequency of adverse events compared to ranitidine. In most cases, adverse effects are related to the alterations of gastric pH that predispose to respiratory and gastrointestinal infections, especially in children with a compromised immune system. Finally, doubts remain on PPI long-term effects, and on the safety profile of these medications, particularly for chronic use.

In conclusion, based on literature data, there is an increasingly compelling reason to limit the empirical utilization of acid suppressive therapy in children (65). A proper differential diagnosis between GER and GERD is essential in this regard.

Further research should be directed towards the development of novel antisecretory drugs, with proven efficacy and good safety profile, for treating pediatric GERD, particularly in newborns and infants.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-22-401/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-22-401/coif). RA serves as an unpaid editorial board member of *Translational Pediatrics* from March 2022 to February 2024. The other authors have no conflicts of interest to declare.

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