Management of Uncomplicated GERD in Pediatric Patients


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Objectives
At the conclusion of this knowledge-based activity, the pharmacist will be able to:
1. Review the pathophysiology and common clinical presentation of gastroesophageal reflux disease (GERD).
2. Describe diagnostic criteria for GERD for pediatric patients and describe current treatment guidelines from the American College of Gastroenterology (ACG).
3. Explain treatment modalities available for the management of uncomplicated GERD in pediatric patients.
4. Recognize the role of the pharmacist in managing GERD in pediatric patients.

Objective: To review the treatment of gastroesophageal reflux disease (GERD) in pediatric patients.

Data sources: PubMed using search terms gastroesophageal reflux disease, diagnosis, erosive esophagitis, antacids, histamine-2 receptor antagonists, proton pump inhibitors, and current treatment guidelines.

Data synthesis: Gastroesophageal reflux disease is a common gastrointestinal disorder for pediatric patients. The reflux of contents from the stomach into the esophagus can lead to common symptoms such as heartburn, regurgitation, and acidic taste. Gastroesophageal reflux disease is divided into esophageal or extraesophageal syndromes, and then further depending on the presence of esophageal injury. Many exacerbating factors have been identified, including certain foods, pregnancy, being overweight or obese, and some medications. There are many treatment options available for use in the medical management of GERD in pediatric patients. These options include antacids, histamine-2 receptor antagonists (H2RAs), and proton pump inhibitors (PPIs). Guidelines for pediatric patients have recently been published to provide guidance on the treatment of GERD in these populations. In pediatric patients, both H2RAs and PPIs may be considered.

Conclusion: Pharmacists, regardless of setting, are likely to encounter pediatric patients who suffer from GERD. It is important to be aware of the updated treatment guidelines, as well as the different medications available, in order to ensure optimal patient care is provided.

Keywords: gastroesophageal reflux symptoms, gastroesophageal reflux disease

Word count: 215 (including keywords)

Introduction
Gastroesophageal reflux disease (GERD) is a relatively common gastrointestinal disorder. In 2009, there were approximately nine million outpatient visits for GERD in the United States (US) alone, and this condition was discussed with pediatricians at approximately 25% of routine six-month well child visits. Gastroesophageal reflux disease is caused by the backwards flow of stomach contents or acid reflux into the esophagus leading to symptoms such as heartburn and potentially esophageal damage. Gastroesophageal reflux symptoms (GERS) such as heartburn or reflux may occur without being classified as GERD.

The reflux of contents back into the esophagus may be due to many factors, including dysfunction in the lower esophageal sphincter (LES). The LES is an area of smooth muscle at the end of the esophagus that protects contents from the stomach, including gastrin and pepsin, from flowing into the esophagus. Backflow of these acidic enzymes can lead to damaged tissue in the esophagus or aspiration. During periods of eating and
swallowing, the LES also acts as a one-way valve to prevent the passage of food or other stomach contents back into the esophagus. The LES does, however, have transient episodes of relaxation in healthy adults where the backflow of stomach contents may occur, but these episodes are usually symptom-free. These episodes also likely occur in approximately 50% of infants on a daily basis.2

Clinical Presentation
When encountering a patient with possible GERD, it is important to thoroughly assess the patient’s symptoms. For a pediatric patient, a parent or caregiver may report signs and symptoms of possible GERD. For an infant, common symptoms include regurgitation, vomiting, irritability, feeding problems, and poor weight gain. A parent or caregiver may also notice apnea or arching of the back during feeds. For a child or adolescent, symptoms may be similar to an infant, but include heartburn, regurgitation, dyspnea, abdominal pain, and extraesophageal manifestations. A child or adolescent may experience nausea and recurrent vomiting after meals; therefore, he or she may refuse to eat. Children and adolescents may also experience supra-esophageal complications, such as chronic cough, apnea, bronchitis, wheezing, asthma, otitis media, sinusitis, hoarseness, dental erosions, or chronic sore throat. For any infant, child, or adolescent with alarming symptoms or failure to thrive, the patient should be referred to a pediatric gastroenterologist for further evaluation.2

Diagnostic Criteria
Table 1 lists possible diagnostic tests for pediatric patients, along with the purpose of each test. For more details, please refer to the specific guidelines for GERD in these patient populations.2,5,6

For a pediatric patient (i.e. infant, child, or adolescent), there is no particular diagnostic test that is the “gold standard” to confirm GERD. A thorough history and physical examination should be completed for each pediatric patient. Laboratory tests may also be obtained for a differential diagnosis and could include a complete blood count, urinalysis, electrolytes, serum creatinine, and urea nitrogen. Celiac screenings are also recommended when suspecting GERD among a pediatric patient.2

Treatment Guidelines
There are several guidelines devoted to the management of GERD in pediatric patients.2,5,7 Of these, two sets of guidelines are used in clinical practice. The joint guidelines by North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) were published in 2009.6 Within the publication, several recommendations – based on the quality of evidence – are provided about diagnosis, treatment options, and management of infants and children with suspected GERD.6 In 2013, the American Academy of Pediatrics (AAP) published recommendations as guidance for the pediatrician.2 The AAP provided treatment algorithms for the stepwise approach with infants and children with suspected GERD. The document also provides details regarding appropriate prescribing of certain drugs based on the patient’s weight and age.2

The sections below review the recommendations within the 2013 ACG and AAP guidelines for pediatric patients.2,5,6

Nonpharmacologic Interventions
The AAP guidelines recommend various nonpharmacologic interventions for pediatric patients.2 Each intervention should be specific for the patient. For an infant, a combination of feeding and positioning changes should be recommended. Specific feeding modifications include changes in the maternal

| Table 1. List of Diagnostic Tests for Gastroesophageal Reflux Disease |
|-------------------------|------------------|
| **Diagnostic Test**     | **Purpose**      |
| Endoscopy               | Observation of epithelium lining and identification of Barrett’s esophagus and complications of GERD |
| Manometry               | Evaluation of peristaltic function of the esophagus in patients with normal endoscopic findings prior to pH testing |
| pH Testing              | Determination of percent time pH is less than 4 in a 24-hour period |
| Gastroesophageal scintigraphy | Evaluation of postprandial reflux and assessment of gastric emptying |

diets or formulas. For example, an infant may have an allergy to milk protein, which can lead to similar symptoms of GERD. A mother who is breastfeeding could exclude milk and eggs from her diet for two to four weeks to determine effectiveness. If an infant is formula-fed, the formula could be changed to a milk-free alternative, such as Enfamil Prosobee. In addition, the volume per feeding can be reduced, while the number of feedings per day can be increased. Thickening strategies are suggested, such as adding rice cereal to the formula but the AAP guidelines mention association between thickened feedings and necrotizing enterocolitis in preterm infants. Following feedings, it is important to keep infants completely upright. For pediatric patients older than one year, prone positioning is acceptable among awake, alert, and observed children.²

For a child or adolescent, nonpharmacologic interventions align with the recommendations for adult patients (e.g., weight loss, smoking and alcohol cessation, elevation of bed).² The AAP guidelines identify potential triggers for GERD in children and adolescents and recommend eliminating them from the diet. Sugarless gum has been shown to reduce the number of episodes related to GERD.²

**Pharmacologic Interventions**

**Infants**

If nonpharmacologic interventions are not successful, then a referral to a pediatric gastroenterologist should be completed. Pharmacologic interventions include gastric acid inhibition or enhanced motility of the gastrointestinal tract. Some infants may be hospitalized for observation; for severe cases, tube feedings may be considered. Please refer to the section General Management of GERD for further details about specific medication for pediatric patients.²

**Children and Adolescents**

Along with nonpharmacologic interventions, a two-week trial of a proton pump inhibitor (PPI) should be initiated. If symptoms improve, then the PPI should be continued at the same dose and frequency for an additional 8 to 12 weeks. Following an extended treatment with a PPI, this agent should be tapered to prevent rebound acid regurgitation. If symptoms do not improve or the patient has a relapse, then a pediatric gastroenterologist should be consulted for further evaluation.²

**General Management**

The main approach is gastric acid inhibition through the use of histamine-2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs). These two options can heal erosive esophagitis, if present, and treat current symptoms. The risks and benefits of H2RAs and PPIs should be assessed before the initiation and continuation of therapy. Famotidine and ranitidine are preferred H2RAs in pediatric patients. Famotidine has safety and efficacy data in patients age one year and older, while ranitidine has data to support use in patients as young as one month old.⁷,⁸ All of the available PPIs are also indicated for use in the pediatric population except for dexlansoprazole and omeprazole with sodium bicarbonate.⁹-¹⁶ In addition, pediatric patients with a high risk of complications should receive aggressive therapy (i.e. H2RA plus PPI). Antacids have been used as-needed for mild esophagitis among children and adolescents. However, these agents are not recommended as chronic therapy and caution should be utilized among infants and younger children due to the risk of toxicities, such as renal failure. With calcium-based antacids, milk alkali syndrome has occurred among pediatric patients; this syndrome can cause hypercalcemia, alkalosis, and renal failure.⁶

Prokinetic agents (i.e. metoclopramide) and surface agents (i.e. sucralfate) can also be used for the management of GERD in pediatric patients. Other prokinetic agents include erythromycin, bethanechol, and baclofen. The NASPGHAN/ESPGHAN guidelines do not recommend this class of agents for the management of GERD.⁶ In clinical practice, some pediatric patients may be prescribed these agents due to refractory GERD, as long as an acid suppressive agent is used concomitantly. Along with sucralfate, sodium alginate is another surface agent; these two products have limited efficacy and safety data among pediatric patients.² However, the NSAPGHAN/ESPGHAN guidelines recommend use as adjunctive therapy for esophagitis.⁶ Table 2 provides general treatment approaches and strategies for a pediatric patient for H2RAs and PPIs. Table 3 provides more information related to specific agents used in the treatment of GERD, including dosing and adverse effects.

**Role of the Pharmacist**

In any clinical setting, a pharmacist will encounter a patient with GERD and can have an impact in patient care for this condition. A pharmacist can help assess
and identify the potential problem, recommend appropriate treatment, or refer the patient for immediate attention. For example, an ambulatory care or community-based pharmacist may be approached by a patient with symptoms of GERD, but a brief, detailed interview can help determine if self-treatment or referral to primary care physician is appropriate. Based on the patient’s complaints and risk factors for GERD, nonpharmacologic interventions can be reviewed and recommended as initial and/or adjunctive treatment for the individual. A pharmacist can discuss the general approach, design an individualized plan from the evidence-based guidelines, and recommend a specific agent based on the symptom frequency, duration, and severity. When a specific agent is selected and recommended, the pharmacist can review the role of the agent and timing of onset, along with education on the appropriate dosing and potential adverse events. If a PPI is chosen, monitoring and education about short- and long-term adverse events should be included in a counseling session. A pharmacist can inform the patient about the potential of rebound hypersecretion if a PPI is discontinued. For a pediatric patient, a pharmacist can calculate the appropriate weight-based dosing and determine the best formulation of an agent. A specialty pharmacist in pediatrics can help design regimens for this patient population due to the limited evidence. For any patient, a pharmacist can assist in the selection of the most cost effective choice and also suggest an alternative agent if a drug shortage occurred. While reviewing cost of a specific agent, review of insurance coverage and completion of prior authorization can be assisted by a pharmacist. A community pharmacist may also be able to compound a product or help find a specialty compounding pharmacy.

**Conclusion**

Gastroesophageal reflux disease is a common condition that will be encountered by pharmacists in any practice setting - community, ambulatory care, and hospital. This disease requires an effective and patient-centered therapeutic plan to achieve symptoms control, prevent complications, and improve quality of life. Guidelines have been published for pediatric and adult patients to guide diagnosis and therapeutic plans. These guidelines supplement clinical judgment. Nonpharmacologic interventions should be specific for each patient. Pharmacotherapy is effective in symptom control based on the frequency and severity of a patient’s clinical features. Further diagnostic tests or referral to a gastroenterologist may be necessary in patients unable to achieve control with specific agents or have refractory GERD.

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**Table 2. General Pharmacologic Management of Gastroesophageal Reflux Disease**

<table>
<thead>
<tr>
<th>Pediatric Patients</th>
<th>Mild esophagitis</th>
<th>Scheduled H2RA</th>
<th>Low-dose PPI, based on weight</th>
<th>Cimetidine has been extensively studied in children. Ranitidine has the fewest drug-drug interactions.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate esophagitis</td>
<td>Low-dose PPI, based on weight</td>
<td>High-dose PPI, based on weight</td>
<td>Initial therapy with a PPI should be for 3 months. A PPI should be tapered to prevent rebound acid hypersecretion.</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: H2RA = histamine-2 receptor antagonist; PPI = proton pump inhibitor

Table 3. Available Treatment Options for Gastroesophageal Reflux Disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Dosage Forms available</th>
<th>Comment</th>
<th>Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proton Pump Inhibitors</strong></td>
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<td></td>
</tr>
<tr>
<td>Dexlansoprazole</td>
<td>Not approved for pediatric population; off-label use</td>
<td>Delayed-release capsules (30, 60 mg)</td>
<td>Approved for use up to 4 weeks for NERD</td>
<td>Atazanavir, Methotrexate, Tacrolimus, Warfarin</td>
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<tr>
<td>(Dexilant)</td>
<td></td>
<td></td>
<td>No generic available</td>
<td></td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>12-17 years: 20-40 mg once daily 1-11 years: 10-20 mg once daily 1 month-&lt;1 year: 2.5-10 mg once daily</td>
<td>Delayed-release capsules (20, 40 mg) and oral powder for suspension (2.5, 5, 10, 20, and 40 mg)</td>
<td>Available OTC: 20 mg Infant dose approved for up to 6 weeks; all others approved up to 8 weeks</td>
<td>Atazanavir, Cilostazol, Clopidogrel, Methotrexate, Nelfinavir, Saquinavir, Tacrolimus</td>
</tr>
<tr>
<td>(Nexium)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Lansoprazole        | 1-11 years old, <30 kg: 15 mg once daily  
<30 kg: 30 mg once daily  
≥30 kg: 30 mg once daily  
12-17 years old, NERD: 15 mg once daily  
Erosive esophagitis: 30 mg once daily | Delayed-release capsules and orally disintegrating tablets (15 mg, 30 mg) | Available OTC: 15 mg                              | Atazanavir, Methotrexate, Tacrolimus, Theophylline, Warfarin |
| (Prevacid)          |                                           |                                                              |                                                   |                                        |
| Omeprazole          | 5-<10 kg: 5 mg once daily  
10-<20 kg: 10 mg once daily  
≥ 20 kg: 20 mg once daily | Delayed-release capsules (10, 20, 40 mg) and oral suspension (2.5, 10 mg) | Available OTC: 20 mg and in combination with sodium bicarbonate (Zegerid OTC is not approved for pediatric population) | Atazanavir, Cilostazol, Clopidogrel, Methotrexate, Nelfinavir, Saquinavir, Tacrolimus |
| (Prilosec)          |                                           |                                                              |                                                   |                                        |
| Pantoprazole        | 15-<40 kg: 20 mg once daily  
≥ 40 kg: 40 mg once daily | Delayed-release tablets (20, 40 mg) and oral powder for suspension (40 mg) | Approved for erosive esophagitis associated with GERD (up to 8 weeks) | Atazanavir, Nelfinavir, Methotrexate, Warfarin |
### Rabeprazole (Aciphex)

<table>
<thead>
<tr>
<th>Age/Dose</th>
<th>Description</th>
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<tbody>
<tr>
<td>≥12 years: 20 mg once daily</td>
<td>Delayed-release tablets (20 mg) and capsules (5, 10 mg)</td>
</tr>
<tr>
<td>1-11 years: &lt;15 kg: 5 mg once daily</td>
<td>Generic available</td>
</tr>
<tr>
<td>&gt;15 kg: 10 mg once daily</td>
<td>Atazanavir, Cyclosporine, Methotrexate, Warfarin</td>
</tr>
</tbody>
</table>

### Histamine-2 Receptor Antagonists

<table>
<thead>
<tr>
<th>Cimetidine (Tagamet)</th>
<th>Not approved for pediatric population; off-label use</th>
<th>Tablets (200, 400 mg)</th>
<th>Available OTC: Numerous; inhibits CYP1A2, 2C9, 2C18, 2D6, 3A3, 3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Famotidine (Pepcid)</td>
<td>&lt;3 months of age: 0.5 mg/kg/dose once daily 3 months-&lt;1 year: 0.5 mg/kg/dose twice daily 1-16 years: 1 mg/kg/day in divided doses up to 40 mg twice daily</td>
<td>Tablets (20, 40 mg) Oral suspension (40 mg/5 ml)</td>
<td>Available OTC alone and with antacids None</td>
</tr>
<tr>
<td>Nizatidine (Axid) (pulvules) (solution)</td>
<td>150 mg twice daily (solution)</td>
<td>Pulvules (150, 300 mg) Oral solution (15 mg/ml)</td>
<td>Available OTC: 75 mg; solution only approved for pediatrics ≥ 12 years old None</td>
</tr>
<tr>
<td>Ranitidine (Zantac)</td>
<td>1 month-16 years: 5-10 mg/kg per day in 2 divided doses</td>
<td>Tablets (150, 300 mg) Effervescent tablets (25 mg) Syrup (15 mg/ml)</td>
<td>Available OTC Atazanavir, Glipizide, Ketoconazole, Triazolam, Warfarin</td>
</tr>
</tbody>
</table>

### Antacids

| aluminum hydroxide, calcium carbonate, magnesium hydroxide, sodium bicarbonate | Not for infants; varies by product for children and adolescents | Chewable tablets, suspension, etc | Doses three to four times per day Take 1 to 3 hours after meals and other medications | Varies by the product, but chelation or increases / decreased absorption may occur |

### Other Options

<p>| Metoclopramide (Reglan) | Not approved for pediatric population; Dispersible | Tablets (5, 10 mg) | May be considered for refractory cases | Anticholinergic agents CNS depressants |</p>
<table>
<thead>
<tr>
<th>Drug</th>
<th>Uses</th>
<th>Formulations</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sucralfate (Carafate)</td>
<td>off-label use</td>
<td>Tablet (5 mg), Solution (1 mg/ml, 5 mg/ml)</td>
<td>Not approved for pediatric population; off-label use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tablet (1 gm), Suspension (1 gm/ml)</td>
<td>Generic not available for suspension</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>May be considered for refractory cases</td>
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<tr>
<td>Cimetidine</td>
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<tr>
<td>Fluoroquinolones</td>
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<td>Digoxin</td>
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<td>Levothyroline</td>
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<tr>
<td>Phenytoin</td>
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<tr>
<td>Ranitidine</td>
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<td>Theophylline</td>
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<tr>
<td>Tetracycline</td>
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</table>

Abbreviations: CNS = central nervous system; CYP = cytochrome; GERD = gastroesophageal reflux disease; gm = gram; mg = milligram; ml = milliliter; NERD = nonerosive reflux disease; OTC = over the counter


References
Self-assessment questions:

1. Which one of the following is a common symptom of GERD for an infant patient?
   a. Chronic sore throat  
   b. Failure to thrive  
   c. Apnea  
   d. Vomiting after meals

2. Which nonpharmacologic intervention has specifically shown to reduce reflux episodes in the pediatric patients?
   a. Chocolate intake  
   b. Fluid intake  
   c. Smoking cessation  
   d. Sugarless gum

3. A 13-year-old child has been diagnosed with GERD and is considered at high-risk of complications. Which one of the following medications would be the best choice?
   a. A PPI with timed, once-daily dosing  
   b. An antacid as needed after meals  
   c. Metoclopramide scheduled with meals  
   d. Sucralfate with scheduled dosing

4. Which one of the following histamine-2 receptor antagonists would be the most effective and safe option for a 6-month-old child?
   a. Famotidine  
   b. Ranitidine  
   c. Cimetidine  
   d. Nizantidine

5. Which statement is true regarding prokinetic agents for GERD management?
   a. These agents are FDA-approved for use among children 6 years or older  
   b. Metoclopramide could be used in refractory cases of GERD.  
   c. Prokinetic agents inhibit pepsin activity, up to 30%.  
   d. Constipation is the most commonly reported adverse event.

6. A pharmacist would counsel the parent or caregiver of a 6-year-old patient on which statement:
   a. Gastroesophageal reflux disease is a short-lived disease and does not require medical intervention.  
   b. Any lifestyle modification or intervention should be initiated for an adequate period of 8 weeks.  
   c. If pharmacologic therapy is required, histamine-2 receptor antagonists or proton pump inhibitors are recommended as acid suppressive therapy.  
   d. Prokinetic agents are a safety option, as long as this class is dosed specifically for the patient.