Lown Right Care

Reducing Overuse and Underuse

Overuse of Antireflux Medications in Infants

Elizabeth R. Wolf, MD, MPH; Naren Vadlamudi, MD; and Matthew Schefft, DO, MSHA

Children's Hospital of Richmond at Virginia Commonwealth University, Richmond, Virginia

Patient perspective by Helen Haskell and John James

Case Scenario

A two-month-old full-term, formula-fed infant presents for the first well-child examination since the newborn period. The child's parents are concerned because the infant spits up at least four times per day. The contents resemble curdled milk (nonbloody, nonbilious), and the spit-up is nonprojectile. The infant is gaining weight and following the 75% weight curve for age. The parents report that the infant gets fussy every day around 5:00 p.m. The mother has a 10-year-old child who was prescribed antireflux medications around this age and is wondering if these medications should be prescribed for her infant.

Clinical Commentary

Gastroesophageal reflux, or the regurgitation of gastric contents, occurs in up to two-thirds of healthy infants.[1] Gastroesophageal reflux begins approximately two to three weeks after birth and peaks between four and five months of age. Physiologic reasons for increased reflux in infants include an underdeveloped angle of His (the angle between the greater curvature of the stomach and esophagus), inadequate gastric accommodation, prolonged supine positioning, and a liquid diet. Symptoms usually resolve completely by one year of age.[2] By one year of age, muscles in the lower esophagus strengthen, the esophagus lengthens, and esophageal and intestinal motility coordination improves. Normal developmental milestones, such as head control, sitting up, and the introduction of solid food, help improve gastroesophageal reflux symptoms. Infants who experience reflux without discomfort or other problems are sometimes referred to as "happy spitters."

The North American Society for Pediatric Gastroenterology, Hepatology & Nutrition has developed guidelines to help clinicians differentiate gastroesophageal reflux from gastroesophageal reflux disease (GERD).[3] The guidelines define GERD as reflux that involves pain, poor weight gain, or mucosal injury on upper endoscopy.[3,4] Although changes in weight and endoscopy findings can be evaluated objectively, the assessment of pain (e.g., crying, grimacing, arching) is subject to parent and clinician interpretation. It can be challenging for parents and clinicians to distinguish manifestations of GERD-related pain from other conditions, such as dyschezia or colic.[5] Clinicians can feel pressure to treat gastroesophageal

TAKE-HOME MESSAGES FOR RIGHT CARE

- Gastroesophageal reflux (i.e., the regurgitation of gastric contents) occurs in up to two-thirds of healthy infants and is considered physiologic.
- GERD can be distinguished from gastroesophageal reflux by pain, poor weight gain, or mucosal injury on upper endoscopy.
- The assessment of GERD-related pain in infants can be challenging because the manifestations (e.g., crying, grimacing, arching) overlap with colic, dyschezia, and other common conditions.
- Long-term use of antireflux medications is associated with an increased risk of fractures and acute and chronic diseases.
- The American Academy of Pediatrics and Choosing Wisely have recommended against the use of antireflux medications in infants with reflux that is effortless, painless, and not affecting growth.

GERD = gastroesophageal reflux disease.

Lown Institute Right Care Alliance is a grassroots coalition of clinicians, patients, and community members organizing to make health care institutions accountable to communities and to put patients, not profits, at the heart of health care.

This series is coordinated by Kenny Lin, MD, MPH, deputy editor.

A collection of Lown Right Care published in *AFP* is available at https://www.aafp.org/afp/rightcare.

CME This clinical content conforms to AAFP criteria for CME. See CME Quiz on page 539.

Author disclosure: No relevant financial relationships.

reflux with medications even though it is a benign condition. One-fourth of parents of infants with gastroesophageal reflux perceive the symptoms as troublesome.[1] Clinicians are subject to commission bias, which is the tendency to act even when inaction leads to an identical or better outcome.[6]

ANTIREFLUX MEDICATIONS

Clinicians may prescribe histamine H_2 receptor antagonists (H2RAs) or proton pump inhibitors (PPIs) to reduce the perceived discomfort associated with gastroesophageal reflux. These medications decrease the acidity in gastric contents but do not improve regurgitation in the absence of GERD.[3,7,8] In many cases, treatments have not been proven more effective than placebo.[8-10]

Although the medical community once viewed H2RAs and PPIs as benign medications, there are now concerns about the short- and long-term effects.[11,12] In the short term, these medications have been linked to necrotizing enterocolitis and sepsis in preterm and low-birth-weight infants.[13-20] Full-term and normal-birth-weight infants are at increased risk of lower respiratory tract and gastrointestinal infections.[8,21] In the long term, there is a link between acid suppression and alteration in the microbiome and higher rates of allergies, asthma, and obesity.[22-25] PPI and combination H2RA/PPI therapy have been linked to a higher risk of fractures in children, with earlier initiation and longer duration of treatment associated with the highest risk.[26] Patients treated with acid-suppressing medication incur more than $2,300 in additional health care costs compared with healthy patients.[27]

CHOOSING WISELY

The American Academy of Pediatrics and Choosing Wisely have recommended against the use of antireflux medications for infants with reflux that is effortless, painless, and not affecting growth.[12,28] Antireflux medications are listed in the Choosing Wisely top five lists from the American Academy of Pediatrics section on perinatal medicine and the Society of Hospital Medicine.[12,28]

ALTERNATIVE TREATMENT

Because some parents perceive gastroesophageal reflux as problematic, nonpharmacologic alternatives may be offered. Burping the infant at regular intervals, offering smaller and more frequent feedings, and keeping the infant upright for 30 minutes after a feed may be helpful. However, it can be logistically challenging to keep an infant upright for an extended period when feeding every two to four hours.

Parents may consider thickening formula or expressed breast milk with an infant oat cereal. Rice cereal was historically used for this purpose, but concerns about arsenic contamination have limited its use.[29] Thickening has been shown to decrease the frequency of reflux episodes.[30] Adding a thickener to formula increases the caloric density of the milk, which can be helpful in underweight infants but can cause excessive weight gain in normal-weight and overweight infants. The effort required to thicken expressed breast milk instead of breastfeeding may not be worthwhile because of the benign nature of gastroesophageal reflux. Antireflux formulas that are made with rice starch work by becoming more viscous once they encounter stomach acid. Xanthan gum (e.g., SimplyThick) has been associated with necrotizing enterocolitis and is not recommended as a thickener for infants.[31]

Patient Perspective

Overmedication is a cause for concern, especially when it affects the youngest and most vulnerable. Almost all babies spit up (in our experience, at least), but new parents may be alarmed when their baby exhibits symptoms they did not expect. Parents habituated to television advertisements or those who, as in this scenario, experienced antireflux medications freely given to infants in years gone by may reasonably expect a pharmacologic solution. Parents want the best for their children.

Many parents quickly retract their request for a prescription when advised that antireflux medications have not shown effectiveness for infants and could increase the risk of infections, bone fractures, and other unknown effects. But even new parents know their children best, and their concerns should never be taken lightly. Parents often crave information; clear and detailed explanations can go a long way toward creating a positive relationship between the family and physician. Families are more likely to feel heard and supported if they can leave the office with a plan to help control reflux episodes, an understanding that this is a common and usually transitory phase of infant development, and knowledge of signs that could indicate a more serious condition and should precipitate a return visit.

Resolution of Case

A thorough history finds that the infant's crying is not associated with the spit-up episodes and tends to occur in the afternoons and evenings. The likely cause is colic, which peaks around six weeks of life. The parents are reassured that their child is healthy with normal growth and development, and that reflux is common and often self-resolves. The parents are informed that frequent burping, upright positioning, and thickened feedings may decrease the frequency of spit-ups, and antireflux medications, such as H2RAs or PPIs, are not needed, do not prevent spit-ups, and may cause short- and long-term health problems.

Address correspondence to Elizabeth R. Wolf, MD, MPH, at elizabeth.wolf@vcuhealth.org. Reprints are not available from the authors.

References

1. Nelson SP, Chen EH, Syniar GM, et al.; Pediatric Practice Research Group. Prevalence of symptoms of gastroesophageal reflux during infancy. A pediatric practice-based survey. *Arch Pediatr Adolesc Med*. 1997;151(6):569-572.
2. Campanozzi A, Boccia G, Pensabene L, et al. Prevalence and natural history of gastroesophageal reflux: pediatric prospective survey. *Pediatrics*. 2009;123(3):779-783.
3. Rosen R, Vandenplas Y, Singendonk M, 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):516-554.
4. Quitadamo P, Urbonas V, Papadopoulou A, et al. Do pediatricians apply the 2009 NASPGHAN-ESPGHAN guidelines for the diagnosis and management of gastroesophageal reflux after being trained? *J Pediatr Gastroenterol Nutr*. 2014;59(3):356-359.
5. Barr RG, Rajabali F, Aragon M, et al. Education about crying in normal infants is associated with a reduction in pediatric emergency room visits for crying complaints. *J Dev Behav Pediatr*. 2015;36(4):252-257.
6. Musiienko A. Commission bias. In: Raz M, Pouryahya P, eds. *Decision Making in Emergency Medicine. Biases, Errors and Solutions*. Springer Singapore; 2021:77-82.
7. Simeone D, Caria MC, Miele E, et al. Treatment of childhood peptic esophagitis: a double-blind placebo-controlled trial of nizatidine. *J Pediatr Gastroenterol Nutr*. 1997;25(1):61-55.
8. Orenstein SR, Hassall E, Furmaga-Jablonska W, et al. Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. *J Pediatr*. 2009;154(4):514-520.e4.
9. van der Pol RJ, Smits MJ, van Wijk MP, et al. Efficacy of proton-pump inhibitors in children with gastroesophageal reflux disease: a systematic review. *Pediatrics*. 2011;127(5):925-935.
10. Higginbotham TW. Effectiveness and safety of proton pump inhibitors in infantile gastroesophageal reflux disease. *Ann Pharmacother*. 2010;44(3):572-576.
11. Boruta M, Boruta R, Li J. Acid suppression therapy and symptom improvement (or lack thereof) in children. *Pediatrics*. 2019;144(1):e20190909.
12. Quinonez RA, Garber MD, Schroeder AR, et al. Choosing wisely in pediatric hospital medicine: five opportunities for improved healthcare value. *J Hosp Med*. 2013;8(9):479-485.
13. Santana RNS, Santos VS, Ribeiro-Júnior RF, et al. Use of ranitidine is associated with infections in newborns hospitalized in a neonatal intensive care unit: a cohort study. *BMC Infect Dis*. 2017;17(1):375.
14. Terrin G, Passariello A, De Curtis M, et al. Ranitidine is associated with infections, necrotizing enterocolitis, and fatal outcome in newborns. *Pediatrics*. 2012;129(1):e40-e45.
15. Chung EY, Yardley J. Are there risks associated with empiric acid suppression treatment of infants and children suspected of having gastroesophageal reflux disease? *Hosp Pediatr*. 2013;3(1):16-23.
16. Guillet R, Stoll BJ, Cotten CM, et al.; National Institute of Child Health and Human Development Neonatal Research Network. Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. *Pediatrics*. 2006;117(2):e137-e142.
17. Beck-Sague CM, Azimi P, Fonseca SN, et al. Bloodstream infections in neonatal intensive care unit patients: results of a multicenter study. *Pediatr Infect Dis J*. 1994;13(12):1110-1116.
18. Rojas MA, Efird MM, Lozano JM, et al. Risk factors for nosocomial infections in selected neonatal intensive care units in Colombia, South America. *J Perinatol*. 2005;25(8):537-541.
19. Graham PL III, Begg MD, Larson E, et al. Risk factors for late onset gram-negative sepsis in low birth weight infants hospitalized in the neonatal intensive care unit. *Pediatr Infect Dis J*. 2006;25(2):113-117.
20. Bianconi S, Gudavalli M, Sutija VG, et al. Ranitidine and late-onset sepsis in the neonatal intensive care unit. *J Perinat Med*. 2007;35(2):147-150.
21. Canani RB, Cirillo P, Roggero P, et al.; Working Group on Intestinal Infections of the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition. Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. *Pediatrics*. 2006;117(5):e817-e820.
22. Jackson MA, Goodrich JK, Maxan M-E, et al. Proton pump inhibitors alter the composition of the gut microbiota. *Gut*. 2016;65(5):749-756.
23. Mitre E, Susi A, Kropp LE, et al. Association between use of acid-suppressive medications and antibiotics during infancy and allergic diseases in early childhood. *JAMA Pediatr*. 2018;172(6):e180315.
24. Wang Y-H, Wintzell V, Ludvigsson JF, et al. Association between proton pump inhibitor use and risk of asthma in children. *JAMA Pediatr*. 2021;175(4):394-403.
25. Stark CM, Susi A, Emerick J, et al. Antibiotic and acid-suppression medications during early childhood are associated with obesity. *Gut*. 2019;68(1):62-69.
26. Malchodi L, Wagner K, Susi A, et al. Early acid suppression therapy exposure and fracture in young children. *Pediatrics*. 2019;144(1):e20182625.
27. Kothari S, Nelson SP, Wu EQ, et al. 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):2703-2709.
28. Ho T, Dukhovny D, Zupancic JAF, et al. Choosing Wisely in newborn medicine: five opportunities to increase value. *Pediatrics*. 2015;136(2):e482-e489.
29. Karagas MR, Punshon T, Sayarath V, et al. Association of rice and rice-product consumption with arsenic exposure early in life. *JAMA Pediatr*. 2016;170(6):609-616.
30. Kwok TC, Ojha S, Dorling J. Feed thickener for infants up to six months of age with gastro-oesophageal reflux. *Cochrane Database Syst Rev*. 2017;(12):CD003211.
31. Beal J, Silverman B, Bellant J, et al. Late onset necrotizing enterocolitis in infants following use of a xanthan gum-containing thickening agent. *J Pediatr*. 2012;161(2):354-356. ■