PERSPECTIVE

Acid Suppression in Neonates: Friend or Foe?

PRASHANTH MURTHY[1], ALIYAH DOSANI[2,3] AND ABHAY LODHA[1,2]

From Departments of [1]Pediatrics and [2]Community Health Sciences, University of Calgary; and [3]School of Nursing and Midwifery, Mount Royal University; Calgary, Canada.

Correspondence to: Dr Abhay Lodha, Associate Professor, Department of Pediatrics, and Community Health Sciences, Foothills Medical Centre, C211, 29th Street NW Calgary, Alberta, Canada, T2N 2T9. aklodha@ucalgary.ca

Medications that reduce gastric acid secretion are commonly prescribed for treating gastroesophageal reflux disease. However, several studies have shown that these medications are not very effective, and are associated with adverse effects. This article discusses the physiology of gastric acid secretion, clinical indications and pharmacology of acid suppressing medications, and possible adverse effects of these medications.

Keywords: *Gastroesophageal reflux disease (GERD), Low birth weight infants, Management, Neonatal intensive care unit (NICU).*

Gastroesophageal reflux (GER) is defined as the retrograde flow of gastric contents into esophagus. GER is difficult to define and diagnose in newborns [1]. GER is a physiological event that occurs in all infants. Studies on healthy infants demonstrated episodes of reflux as high as 73 times per day [2]. Reflux of gastric contents into the esophagus in infants may result in various symptoms such as irritability and crying with regurgitation, oxygen desaturation, or bradycardia. These infants are diagnosed as having gastroesophageal reflux disease (GERD) after other potential causes have been ruled out [1]. GERD can lead to esophagitis and vomiting, and has been attributed to other symptoms like apnea, aspiration, poor feeding, and failure to thrive, resulting in longer hospital stays. In infants, reflux of acidic contents is likely to be the main pathophysiological influence for symptoms associated with GERD. Clinicians struggle to manage this condition in daily practice in the absence of definitive diagnostic tests and medications. Treatment of GERD in neonates can include both non-pharmacological and pharmacological approaches [1]. Pharmacological approaches to GERD include acid suppression and prokinetic agents. Acid suppressant medications are among the most commonly prescribed medications in neonatal intensive care units (NICUs) [3]. However emerging evidence casts doubts regarding the safety of these medications [1]. This write-up is based on the following question: In premature neonates (**P**opulation), are acid inhibitors (**I**ntervention) compared to no acid inhibitors (**C**omparisons) useful and safe for the treatment of GERD (**O**utcome)?

PHYSIOLOGY AND SYMPTOMS OF GERD

The lower esophageal sphincter (LES) and crural diaphragm play a major role in GER. A ring of thickened and tonically contracted smooth muscle that generates high pressure constitutes the LES. Additionally, the right crus of the diaphragm circumscribes the LES and provides extra muscular support. The LES in conjunction with the diaphragm creates a high-pressure zone in the distal esophagus that prevents reflux of gastric contents into the esophagus. ***Fig.* 1** shows physiological reasoning of GERD in neonates. Presence of an indwelling feeding tube across the LES increases GER. This effect is most prominent during the first post prandial hour. Feeding tubes may impair competence of LES, thereby causing reflux [4]. Mechanical and chemical stimulation of acid production accounts for the majority of acid production. This begins with distension of the stomach that follows ingestion of food, which stimulates the stretch receptors, resulting in gastrin release by G cells [5].

Symptoms of GERD occur due to regurgitation of acid and related esophagitis. The most common clinical manifestation of GERD is related to regurgitation ranging from drooling and spitting to overt projectile vomiting. Regurgitation and vomiting can lead to loss of nutrients and calories, and, subsequently lead to inadequate weight gain, weight loss, and failure to thrive [6]. Symptoms like aspiration, apnea, and bradycardia are a result of the physical presence of refluxate, and vary with the nature of reflux contents. The presence of acid in combination with pepsin is most likely to result in

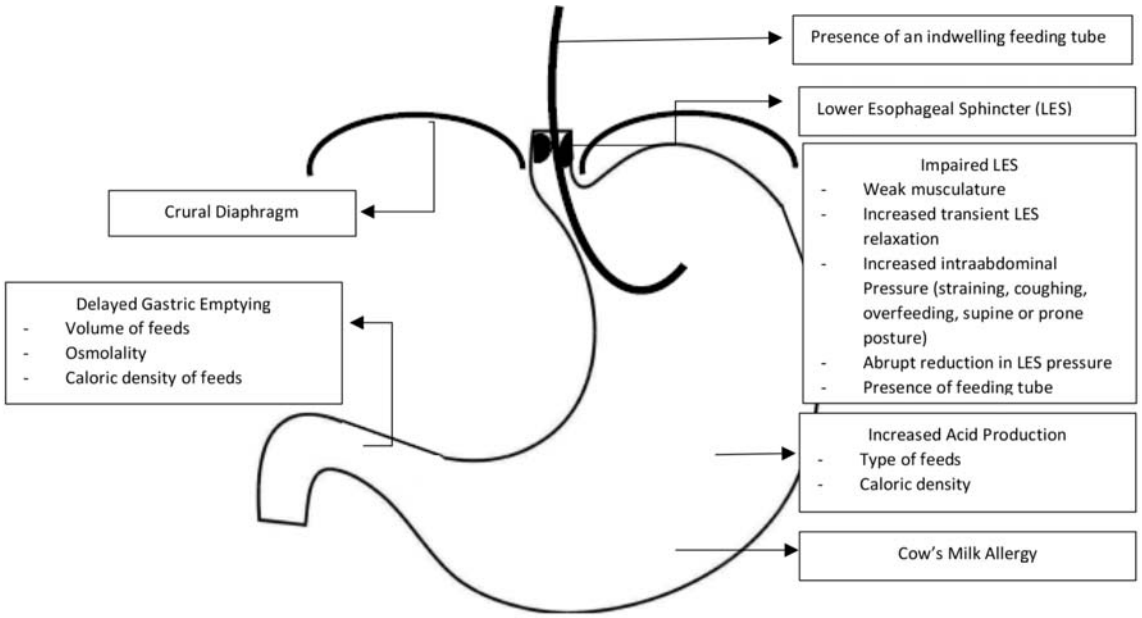

FIG. 1 *Mechanism of Gastroesophageal Reflux*.

mucosal injury. Prolonged exposure of acidic gastric contents can lead to mucosal inflammation, excoriation and ulceration leading to painful esophagitis. Symptoms of esophagitis include increased crying and irritability, feeding difficulties, hematemesis, and failure to thrive [1,7]. Sleep disturbance and swallowing dysfunction also occur more frequently in infants with GERD [8,9].

DIAGNOSIS OF GERD

There is no gold standard investigation for diagnosing GERD in infants. Often the diagnosis is inferred from a positive response to a therapeutic trial in children, but the same is not true for infants or neonates. In neonates, detailed history and examination are useful tools in diagnosing GERD. There are several methods to diagnose GER in the preterm infants: contrast fluoroscopy, pH monitoring and multi-channel intra-esophageal impedance (MII) monitoring [1]. However, none of these diagnostic tools are routinely used in clinical practice. Contrast fluoroscopy can be used to detect GER, but has a poor sensitivity, and pH probe monitoring will calculate the reflux index (RI) determining abnormal *versus* normal reflux. Reflux index is defined as percent of time the gastric pH is <4.0 for more than 10% of time in infants <1 year of age [10]. However, measurement of pH is not an accurate method to diagnose GER in premature infants because their stomach pH is rarely below 4.0 owing to frequent milk feedings and higher baseline pH [1]. Presently, combining MII with the pH probe method has a better accuracy to detect GER. MII can be used to estimate the movement of fluids, solids and air in the esophagus by alterations in electric impedance between multiple electrodes [1].

THERAPEUTIC APPROACH

The diagnostic approach and treatment of GERD should be based on evidence-informed guidelines such as those developed by the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) [11]. Infants with uncomplicated GER do not require any treatment. Management of GERD should include non-pharmacological approaches aimed to prevent and alleviate symptoms, promote normal growth, and resolve inflammatory changes in the esophagus [12]. A stepwise approach to treatment is used. Firstly, non-pharmacological therapies such as post-feeding positioning and dietary modifications, including feed thickeners and a trial of hypoallergenic formula are used. Pharmacological management is attempted only after non-pharmacological therapies fail (***Fig.* 2**). Finally surgical intervention is reserved for severe cases of proven and severe GERD not responding to medical therapies [13,14].

Non-Pharmacological Management

Non-pharmacological management mainly involves infant positioning, feed thickeners, altering feed volumes and feed duration, and avoidance of cow's milk protein

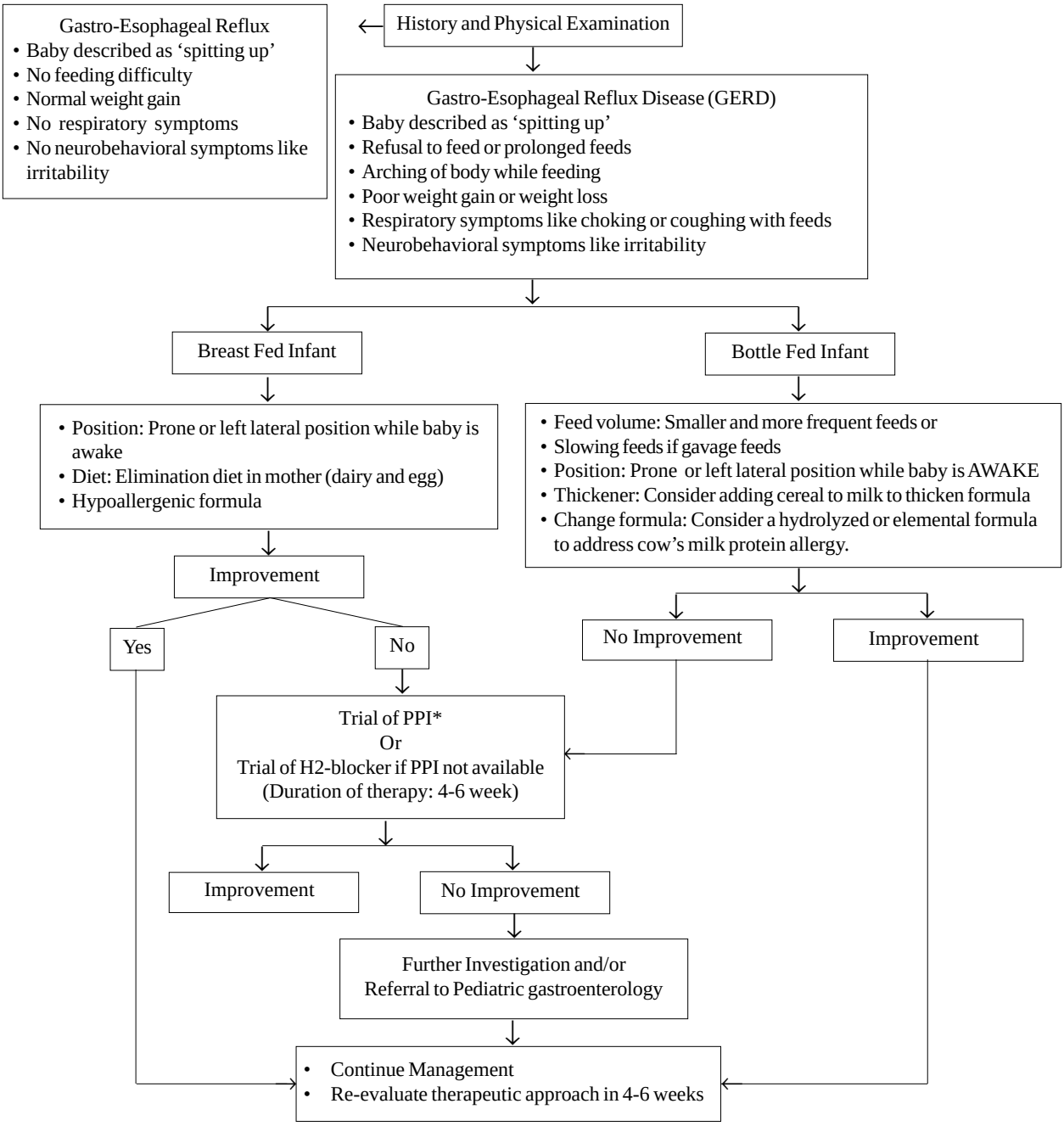

FIG. 2 *Approach to treatment of gastroesophageal reflux disease in infants.*

based feeding formulas. Reduction of feeding volume is often employed for symptomatic relief of reflux; however, there is no evidence in the literature to support this intervention. Hydrolyzed milk formulas have been reported to reduce GER by reducing gastric transit time [15]. Non-pharmacological strategies for GERD are often the first line of management in the treatment of reflux.

Pharmacological Management

The main focus of the pharmacotherapy of GERD is reducing the esophageal exposure to gastric acid. This is achieved either by buffering secreted acid or reducing acid production. Oral antacids are effective in neutralizing gastric acid, but their use is poorly studied in preterm

infants. The drawback to using antacids is that they contain heavy metals like aluminum, which can lead to encephalopathy, anemia, and osteomalacia [13]. Therefore, antacid use in preterm infants is not recommended [12]. Prokinetics agents – metoclopramide, domperidone, and erythromycin – also have a limited role in the treatment of GERD in infants. These drugs appear to increase gastric emptying, reduces the regurgitation episodes, and increase the LES tone. There is little evidence to support the use of metoclopramide and other prokinetics agents [1,7]. Using either domperidone or cisapride is not recommended due to various cardiac side effects, especially prolonged QTc and arrhythmia. Erythromycin increases antral contractility, and is used in preterm infants for gastric emptying. However, its use is associated with hypertrophic pyloric stenosis and cardiac arrhythmias [16]. In a recent randomized controlled trial, erythromycin did not decrease GER events in 24 hours pH-MII, and its role remained ineffective in the treatment of GERD in premature neonates [17]. Baclofen, a GABA agonist, reduces the frequency of lower esophageal sphincter relaxation, decreases acid reflux, and accelerates gastric emptying. However, its use is associated with significant central nervous system adverse effects [1,7]. Therefore, the mainstay of treatment for GERD has remained acid suppression.

Acid suppressant medications

These medications are rampantly used in the newborn population, often without much efficacy in controlling reflux symptoms in neonates. Their use may be effective only in infants with erosive esophagitis. Indiscriminate use of these medications in all cases of GERD is unwarranted and could be harmful to infants. The primary action of these medications is acid reduction and thereby symptomatic relief from esophageal inflammation. There are two class of medications, histamine (H_2) receptors antagonists and proton pump inhibitors (PPIs). ***Table*** I compares H_2 blockers with proton pump inhibitors.

Compared to placebo, H_2 receptors inhibitors are effective in reducing symptoms [18]. However, available evidence does not demonstrate any advantage of H_2 blockers over PPIs [3]. PPIs are more potent than H_2 blockers in increasing gastric pH and can also reduce gastric secretory volumes. Esophagitis not responding to H_2 receptor antagonists has been shown to respond to omeprazole therapy. In a double-blinded randomized controlled trial (RCT) of patients with age range of 6 months to 13.4 years, omeprazole was shown to be effective in reducing clinical symptoms of GERD refractory to ranitidine, reduce acid exposure as noted on pH probe, and improve esophagitis [19]. However, the evidence in favor of PPIs is inconsistent. Two RCTs of omeprazole in preterm and term infants failed to demonstrate improvement in GERD symptoms despite showing reduced esophageal acidity [20,21]. In contrast, a systematic review on effectiveness of PPI concluded that they were effective in reducing gastric acidity or acid reflux but not in relieving GERD symptoms [3]. There is no evidence supporting use of PPIs in functional reflux [3].

There is a lack of evidence supporting efficacy of acid-reducing drugs for GERD symptoms in the neonatal population. Currently there are no established guidelines for using acid reducing drugs in neonates. Despite the

TABLE I A COMPARISON BETWEEN H_2 BLOCKERS AND PROTON PUMP INHIBITORS

	H_2 Blockers	*Proton Pump Inhibitors*
Mechanism of action	Selectively and reversibly inhibit histamine-2 receptor in the gastric parietal cell, resulting in decreased production of gastric acid and pepsin	Block the final common pathway of acid secretion in parietal cells by blocking Na^+ K^+ ATPase, often referred to as the proton pump Gastric acid production is blocked despite parietal cell stimulation.
Onset of action	Rapid onset of action acting within 30 min and reach peak levels in 1 to 3 h with a duration of action varying between 4 to 12 h.	Onset of action varying from 1 hour to 90 min and a half-life of 0.5 to 2 h. The time taken to reach the maximum concentration for omeprazole is 2 hours. In spite of a relatively quick onset of action, PPIs take time to reach their maximum effect taking up to 4 d.
Acid suppression	Incomplete with approximately 70% of acid being suppressed.	Nearly complete (80-95%).
Metabolism	Metabolized in the liver by the cytochrome P450 system. Elimination is mainly attributable to renal excretion,	Metabolized in the liver by cytochrome enzymes CYP2C19 and CYP3A4. Hepatic insufficiency significantly prolongs plasma clearance and increases plasma concentrations
Common medications	Ranitidine and Famotidine	Omeprazole, Lansoprazole and Pantoprazole

fact that none of the currently available PPIs are approved for use in children less than 1 year of age, they continue to be used in the treatment of GERD [22]. Efficacy, dosing, and duration of PPI in infants is not well studied and unclear [7]. The duration of the treatment must be between 4 and 6 weeks following which a trial off medications must be undertaken. Since these medications reach maximal effect close to 4 days after initiation, PPIs must be tried for a longer duration (at least 1 week) before being deemed ineffective. We recommend that utmost caution be exercised when using these medications to suppress acid production, because they are not always effective and they are associated with several adverse effects.

Adverse effects of acid suppression

There are some potential adverse effects associated with these medications. Exposure to ranitidine was associated with a seven-fold increase in late-onset sepsis in infants, especially from gram-negative infections, and included death [1,3,7]. The proposed mechanism is loss of gastric acidity leading to increased gastrointestinal colonization. A retrospective study linked ranitidine use to a 6.6-fold increase in necrotizing enterocolitis and a higher mortality rate [1,3,7]. Acid suppression has been associated with increased risk of acute gastroenteritis, community-acquired pneumonia, and Clostridium difficile, Salmonella and Campylobacter infections [1,3,7]. There are no studies that have looked at long-term effects, especially with respect to calcium turnover and bone loss in neonates.

CONCLUSIONS

Acid suppression, in general, has little or no beneficial effects on functional reflux when considering the risk of possible adverse effects. Acid-suppression medications provide symptomatic relief only in a subset of neonates, especially those with erosive esophagitis. Thus, the use of acid suppression medication in neonates is neither friend nor foe. Indiscriminate use of acid suppressant agents for all neonates with GERD symptoms is dangerous, having the potential for serious side effects. Occasionally, PPIs must be considered as a first line of therapy for a small subset of infants with erosive esophagitis. Emerging evidence of harmful effects of acid suppression is a reminder for all clinicians to exercise utmost caution when using these medications. Even when H_2 blockers or PPIs are used, they should be used for a limited duration with constant vigilance for potential adverse effects. We suggest that discontinuing treatment with acid suppressing medication be considered between 4-6 weeks, even in infants where they have been shown to be effective.

Contributors: PM: drafted and revised the manuscript, AKL: conceptualized the manuscript, drafted, reviewed, and revised the final manuscript, PM, AD, AKL: revised and reviewed the final draft before submission

Funding: None; *Competing interests*: None stated.

REFERENCES

1. Eichenwald EC; Committee on Fetus and Newborn. Diagnosis and management of gastroesophageal reflux in preterm infants. Pediatrics. 2018;142: pii:e20181061.
2. Winter H, Kum-Nji P, Mahomedy SH, Kierkus J, Hinz M, Li H, *et al*. Efficacy and safety of pantoprazole delayed-release granules for oral suspension in a placebo-controlled treatment-withdrawal study in infants 1-11 months old with symptomatic GERD. J Pediatr Gastroenterol Nutr. 2010;50:609-18.
3. Tighe M, Afzal NA, Bevan A, Hayen A, Munro A, Beattie RM. Pharmacological treatment of children with gastro-oesophageal reflux. Cochrane Database Syst Rev. 2014;11:CD008550.
4. Peter CS, Wiechers C, Bohnhorst B, Silny J, Poets CF. Influence of nasogastric tubes on gastroesophageal reflux in preterm infants: A multiple intraluminal impedance study. J Pediatr. 2002;141:277-9.
5. Richardson CT, Walsh JH, Cooper KA, Feldman M, Fordtran JS. Studies on the role of cephalic-vagal stimulation in the acid secretory response to eating in normal human subjects. J Clin Invest. 1977;60:435-41.
6. Frakaloss G, Burke G, Sanders MR. Impact of gastroesophageal reflux on growth and hospital stay in premature infants. J Pediatr Gastroenterol Nutr. 1998;26:146-50.
7. El-Mahdy MA, Mansoor FA, Jadcherla SR. Pharmacological management of gastroesophageal reflux disease in infants: current opinions. Curr Opin Pharmacol. 2017;37:112-7.
8. Ghaem M, Armstrong KL, Trocki O, Cleghorn GJ, Patrick MK, Shepherd RW. The sleep patterns of infants and young children with gastro-oesophageal reflux. J Paediatr Child Health. 1998;34:160-3.
9. Mercado-Deane MG, Burton EM, Harlow SA, Glover AS, Deane DA, Guill MF, *et al*. Swallowing dysfunction in infants less than 1 year of age. Pediatr Radiol. 2001;31:423-8.
10. Da Dalt L, Mazzoleni S, Montini G, Donzelli F, Zacchello F. Diagnostic accuracy of pH monitoring in gastro-oesophageal reflux. Arch Dis Child. 1989;64:1421-6.
11. 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;66:516-54.
12. Rudolph CD, Mazur LJ, Liptak GS, Baker RD, Boyle JT, Colletti RB, *et al*. Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children:

recommendations of the North American Society for Pediatric Gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr. 2001;32:S1-31.
13. Tsou VM, Young RM, Hart MH, Vanderhoof JA. Elevated plasma aluminum levels in normal infants receiving antacids containing aluminum. Pediatrics. 1991;87:148-51.
14. Tsou VM, Bishop PR. Gastroesophageal reflux in children. Otolaryngol Clin North Am. 1998;31:419-34.
15. Mihatsch WA, Hogel J, Pohlandt F. Hydrolysed protein accelerates the gastrointestinal transport of formula in preterm infants. Acta Paediatr. 2001;90:196-8.
16. Chicella MF, Batres LA, Heesters MS, Dice JE. Prokinetic drug therapy in children: a review of current options. Ann Pharmacother. 2005;39:706-11.
17. Ballengee CR, Davalian F, Conaway MR, Sauer CG, Kaufman DA. Erythromycin and Reflux Events in Premature Neonates: A Randomized Clinical Trial. J Pediatr Gastroenterol Nutr. 2018;67:720-5.
18. Orenstein SR, Shalaby TM, Devandry SN, Liacouras CA, Czinn SJ, Dice JE, *et al*. Famotidine for infant gastro-oesophageal reflux: a multi-centre, randomized, placebo-controlled, withdrawal trial. Aliment Pharmacol Ther. 2003;17:1097-107.
19. Cucchiara S, Minella R, Iervolino C, Franco MT, Campanozzi A, Franceschi M, *et al*. Omeprazole and high dose ranitidine in the treatment of refractory reflux oesophagitis. Arch Dis Child. 1993;69:655-9.
20. Moore DJ, Tao BS, Lines DR, Hirte C, Heddle ML, Davidson GP. Double-blind placebo-controlled trial of omeprazole in irritable infants with gastroesophageal reflux. J Pediatr. 2003;143:219-23.
21. Omari TI, Haslam RR, Lundborg P, Davidson GP. Effect of omeprazole on acid gastroesophageal reflux and gastric acidity in preterm infants with pathological acid reflux. J Pediatr Gastroenterol Nutr. 2007;44:41-4.
22. Barron JJ, Tan H, Spalding J, Bakst AW, Singer J. Proton pump inhibitor utilization patterns in infants. J Pediatr Gastroenterol Nutr. 2007;45:421-7.