Evaluation and Management of the Pediatric Patients with Suspected Gastroesophageal Reflux Diseases

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ABSTRACT

Gastroesophageal reflux is a normal physiologic process occurring in healthy infants. Symptoms due to gastro-esophageal reflux diseases (GERD) are troublesome when they have adverse effects on the well-being of the patient. A thorough history and physical examination is generally sufficient to establish a clinical diagnosis of uncomplicated infant with gastroesophageal reflux. Poor weight gain is a warning sign. Irritability and regurgitation are associated with a wide range of physiologic and pathologic conditions. Heartburn or substernal burning is a reliable indicator for GERD in adolescents. Barrett esophagus does occur in children with severe chronic reflux. GERD is commonly cited as a cause of dysphagia; however, there are no strong pediatric data demonstrating this relationship. An etiologic role for reflux in reactive airways disease, such as asthma, has not been established. No test can determine whether reflux is causing recurrent pneumonia.

Data showing the correlation between reflux and upper airway disease is weak, consisting mainly of case descriptions. Sandifer syndrome is an uncommon, but specific manifestation of GERD. Children with cerebral palsy are at particularly high risk of GERD. Similarly, children with certain genetic syndromes such as Cornelia de Lange and Down syndrome are prone to GERD. A higher prevalence of GERD and its complications has been reported in patients with a variety of chronic respiratory disorders including bronchopulmonary dysplasia and cystic fibrosis. GERD treatment is frequently administered to premature infants. However, the true prevalence of GERD is unknown.

***Keywords**: gastroesophageal reflux diseases, infants, children*

ABSTRAK

Gastroesofageal refluks (GER) merupakan proses fisiologis pada bayi. Gejala klinis yang disebabkan oleh penyakit gastroesofageal refluks merupakan masalah bila memberikan efek buruk pada anak. Anamnesis dan pemeriksaan fisis, umumnya cukup untuk menegakkan diagnosa GER tanpa komplikasi secara klinis pada bayi. Kenaikan berat badan yang tidak adekuat merupakan tanda peringatan. Iritabilitas dan regurgitasi berhubungan dengan berbagai kondisi fisiologis dan patologis. Nyeri dada atau rasa terbakar pada daerah substernum merupakan indikator penyakit GER pada remaja. Esofagus 'Barrett' terjadi pada keadaan yang berat dan kronis. Penyakit GER sering sebagai penyebab disfagia, meskipun tidak terdapat data yang kuat untuk menunjukkan hubungan tersebut pada anak. Refluks sebagai penyebab asma tidak dapat dibuktikan. Tidak ada pemeriksaan penunjang yang dapat menunjukkan refluks sebagai penyebab pneumonia berulang.

Data menunjukkan hubungan lemah antara refluks dan penyakit saluran napas atas. Sindrom Sandifer jarang ditemukan, tetapi merupakan manifestasi klinis spesifik penyakit GER. Anak dengan palsi serebral sangat berisiko mengalami penyakit GER. Hal yang sama, anak dengan sindrom genetik tertentu seperti 'Cornelia de Lange' dan Sindrom 'Down' cenderung mengalami penyakit GER. Prevalens penyakit GER dan komplikasi yang tinggi dilaporkan pada beberapa gangguan pernapasan kronis, termasuk displasia bronkopulmonalis dan 'cystic fibrosis'. Terapi penyakit GER sering diberikan untuk bayi prematur. Walaupun demikian, prevalensi penyakit GER sebenarnya tidak diketahui.

***Kata kunci**: penyakit gastroesofageal refluks, bayi, anak*

INTRODUCTION

Gastroesophageal reflux (GER) is the passage of gastric contents into the esophagus with or without regurgitation and vomiting. Gastroesophageal reflux is a normal physiologic process occurring several times per day in healthy infants. Most episodes of GER in healthy infants last < 3 minutes, occur in the postprandial period, and cause few or no symptoms. Regurgitation is defined as the passage of refluxed gastric contents into the pharynx or mouth and sometimes expelled out of the mouth.[1] Although most infants presenting with regurgitation have a normal physical examination, it is now recognized that infants may also present a wide variety of symptoms.

Gastroesophageal reflux diseases (GERD) is defined when reflux of gastric contents is the cause of troublesome symptoms and/or complications. Symptoms due to GER are troublesome when they have adverse effects on the well-being of pediatric patients. Symptoms of GERD vary by age. Clinical presentations that should be considered as possibly related to GERD are regurgitation with weight loss, irritability, chronic crying, feeding refusal or dysphagia. Chronic respiratory symptoms may also be consequences of GERD. Neurological diseases associated with hypertonia, spasticity, hypotonia, myopathy or congenital anomalies noted to cause more GER than in general population.[2]

INFANT WITH UNCOMPLICATED RECURRENT REGURGITATION

The practitioner's challenge is to distinguish regurgitation and vomiting caused by reflux or reflux disease from vomiting caused by numerous other disorders (Table 1). In the infant with recurrent regurgitation or spitting, a thorough history (Table 2) and physical examination with attention to warning signals suggesting other diagnoses (Table 3) is generally sufficient to establish a clinical diagnosis of uncomplicated infant GER-the so-called "happy spitter".[3,4] Intermittently, an episode of vomiting, even forceful vomiting may occur. Irritability may accompany regurgitation and vomiting; however, in the absence of other warning symptoms, it is not an indication for extensive diagnostic testing.[4]

Generally, parental education, anticipatory guidance, and optimalisation of feeding composition, frequency and volume are recommended in infants with uncomplicated GER. Many infants are overfed. In infants with persistent regurgitation, a thickened, by preference commercial anti-regurgitation formula, decreases the frequency and volume of regurgitation. Since regurgitation is sometimes the sole manifestation of cow's milk protein allergy in healthy looking infants, a two-week trial of (thickened) protein hydrolysate or a trial of milk-free diet for the breast feeding mother is appropriate.[3] Prone positioning cannot be recommended because of its association with sudden infant death syndrome (SIDS). One pilot trial suggested that the 40° supine position is effective in a subgroup of infants presenting with frequent regurgitation and irritability.[4] Left lateral decubitus may also decrease the number of refluxes. There is no evidence that anti-secretory or pro-motility agents improve infant regurgitation.

Table 1. Differential diagnosis of vomiting in infants and children[2]

Gastrointestinal obstruction	Pyloric stenosis Malrotation with intermittent volvulus Intestinal duplication Hirschsprung disease Antral/duodenal web Foreign body Incarcerated hernia
Other gastrointestinal disorders	Achalasia Gastroparesis Gastroenteritis Peptic ulcer Eosinophilic esophagitis/ gastroenteritis Food allergy Inflammatory bowel disease Pancreatitis Appendicitis
Neurologic	Hydrocephalus Subdural hematoma Intracranial hemorrhage Intracranial mass Infant migraine Chiari malformation
Infectious	Sepsis Meningitis Urinary tract infection Pneumonia Otitis media Hepatitis
Metabolic/endocrine	Galactosemia Hereditary fructose intolerance Urea cycle defects Amino and organic acidemias Congenital adrenal hyperplasia
Renal	Obstructive uropathy Renal insufficiency
Toxic	Lead Iron Vitamin A and D Medications–ipecac, digoxin, theophylline, etc
Cardiac	Congestive heart failure Vascular ring
Others	Pediatric falsification disorder (Munchausen syndrome by proxy) Child neglect or abuse Self induced vomiting Cyclic vomiting syndrome Autonomic dysfunction

Table 2. History of children with suspected gastroesophageal reflux disease[2]

Feeding and dietary history	Amount/frequency (overfeeding) Preparation of formula Recent changes in feeding type or technique Position during feeding Burping Behavior during feeding: choking, gagging, cough, arching, discomfort, refusal
Pattern of vomiting	Frequency/amount Pain Forceful Blood or bile Associated fever, lethargy, diarrhea
Past medical history	Prematurity Growth and development Past surgery, hospitalizations Newborn screen results Recurrent illnesses, especially croup, pneumonia, asthma Symptoms of hoarseness, fussiness, hiccups, apnea Previous weight and height gain Other chronic conditions
Medications	Current, recent, prescription, non-prescription
Family psycho-social history	Sources of stress Maternal or paternal drug use Post partum depression
Family medical history	Significant illnesses Family history of gastrointestinal disorders Family history of atopy
Growth chart including height, weight and head circumference	Warning signals (see Table 3)

Table 3. Warning signals requiring investigation in infants with regurgitation or vomiting[2]

Bilious vomiting	Lethargy
Gastrointestinal bleeding: hematemesis, hematochezia	Hepatosplenomegaly
Consistently forceful vomiting	Bulging fontanelle
Onset of vomiting after 6 months of life	Macro/microcephaly
Failure to thrive	Seizures
Abdominal tenderness or distension	Diarrhea
Constipation	Fever
Documented or suspected genetic/metabolic syndrome	

INFANT WITH RECURRENT REGURGITATION AND POOR WEIGHT GAIN

While the history and physical examination may be identical, poor weight gain is a warning sign. A feeding history should be obtained that includes an estimate of calories ingested per day. Among infants, possible etiologies are infections (especially urinary tract infection), food allergy, anatomic abnormalities, neurologic disorders, metabolic disease and child neglect or abuse. A two- to four-week trial of extensively hydrolyzed or amino acid based formula is appropriate. Hospitalization for observation and testing may also appropriate. Nasogastric or nasojejunal feeding is occasionally necessary to achieve weight gain in the infant with no other clear explanation for poor weight gain.

INFANT WITH UNEXPLAINED CRYING AND/OR DISTRESSED BEHAVIOR

Irritability and regurgitation are non-specific symptoms that occur in normal infants and are associated with a wide range of physiologic and pathologic conditions. For example, exposure to environmental factors such as tobacco smoke may result in irritability in infants. Normal young infants fuss or cry an average of two hours daily. There is substantial individual variation and some healthy infants cry as much as six hours per day. Likewise there is variation in parental perceptions regarding the severity and duration of crying and its importance. The amount of daily crying typically peaks at six weeks of age.[5] A symptom diary or hospital observation may be useful. Although one study in infants showed a correlation between infant grimacing and episodes of reflux, multiple other studies have shown no relationship between crying and GERD or the presence of esophagitis.[6] The available evidence does not support an empiric trial of acid suppression in infants with unexplained crying, irritability or sleep disturbance. One pilot study showed decreased irritability in the 40° supine sleeping position.[4]

Disorders other than GERD which are likely to cause irritability include cow's milk protein allergy, infections (especially of the urinary tract), constipation, respiratory disorders, congenital or acquired neurologic abnormalities, metabolic disease, surgical emergencies (such as intermittent volvulus or ovarian torsion), cardiac disease, corneal abrasion, bone fractures, hair tourniquet syndrome, tobacco smoke exposure, hunger, abuse or neglect.[6,7] An empiric 2- to 4-week trial of a thickened or extensively hydrolysed formula or amino acid based formula might be indicated in irritable infants after diagnostic evaluations have been performed for other conditions causing irritability.

Reflux is an uncommon cause of irritability or unexplained crying in otherwise healthy infants. However, if irritability persists with no explanation other than suspected GERD, expert opinion suggests the following options. The practitioner may continue anticipatory guidance and training of parents in the management of such infants with the expectation of improvement with time. Further investigations to ascertain the relationship between reflux episodes and

symptoms, or to diagnose reflux or other causes of esophagitis may be indicated (pH monitoring positive/negative impedance monitoring, endoscopy). The risk/benefit ratio of anti-secretory therapy is not clear.[7]

HEARTBURN

Heartburn or substernal burning pain is a symptom of GERD with or without esophagitis. Recent consensus statements suggest that typical heartburn is a reliable indicator for GERD in adolescents and adults. If improvement follows lifestyle changes and proton pump inhibitor (PPI) therapy, treatment can be continued for two to three months. In some patients, abrupt discontinuation of treatment may result in acid rebound that precipitates symptoms.[8] If symptoms recur when therapy is weaned or discontinued, upper endoscopy may be helpful to determine the presence and severity of esophagitis and differentiate reflux-related esophagitis from non-reflux pathologies such as infection or eosinophilic esophagitis that may present with heartburn. Because chronic heartburn can have a substantial negative impact on quality of life, long-term therapy with PPI may be required, even in the absence of esophagitis.[8]

REFLUX ESOPHAGITIS

In open-label studies in children with erosive esophagitis, PPIs resulted in healing in 78-95% with 8 weeks of therapy and in 94-100% with 12 weeks of therapy. Symptoms improved in 70-80% of the group treated for 12 weeks.[9]

Proton pump inhibitors are recommended as initial therapy for 3 months in children with erosive esophagitis. If adequate control of symptoms is not achieved within 4 weeks, the dose of PPI can be increased. In most cases, efficacy of therapy can be monitored by extent of symptom relief without routine endoscopic follow-up. Endoscopic monitoring of treatment efficacy may be useful in patients whose presenting signs and symptoms are atypical, who have persistent symptoms while taking adequate acid suppressive drugs or who had higher grades of esophagitis or esophageal stricture at presentation. The optimum dosage regimen is a single dose given 15-30 minutes before the first meal of the day. It is not necessary make patients achlorhydric to relieve symptoms or heal esophagitis, and, in light of the data on infectious and other complications of acid suppression, it is probably not desirable to do so. Not all reflux esophagitis is chronic or relapsing and therefore, trials of reduction of dose and withdrawal of PPI therapy should be performed after the patient has been asymptomatic for some time, e.g., after 3-6 months on treatment. PPI should be tapered over at least 4 weeks. Recurrence of symptoms and/or esophagitis after repeated trials of PPI withdrawal usually indicates that chronic, relapsing GERD is present, if other causes of esophagitis have been ruled out. At this point, therapeutic options include long-term PPI therapy or anti-reflux surgery.[9]

BARRETT ESOPHAGUS

The prevalence of Barrett esophagus (BE) is much lower in children than adults, but it does occur in children with severe chronic GERD. Dysplasia is managed according to adult guidelines. Barrett esophagus per se is not an indication for antireflux surgery.[10]

DYSPHAGIA AND FOOD REFUSAL

Dysphagia, or difficult swallowing, occurs in association with oral and esophageal anatomic abnormalities, neurologic and motor disorders, oral and esophageal inflammatory diseases and psychological stressors or disorders. GERD is commonly cited as a cause of dysphagia or odynophagia, and although it may be causal in some patients, there are no pediatric data demonstrating this relationship. Dysphagia is a prominent symptom in up to 80% of adults and children with eosinophilic esophagitis. Feeding refusal and feeding difficulty are terms used mainly to describe the following infant symptoms such as refusal to eat, uncoordinated sucking and swallowing, gagging, vomiting, and irritability during feeding.[11]

INFANT WITH APNEA OR ALTE

The literatures on the relationship between apnea, respiratory pauses, apparent life-threatening events (ALTEs) or SIDS and reflux are conflicting, it is mostly because of the different criteria used to define apnea, the various methods used to measure reflux and respiratory pauses, and the different populations studied. ALTEs are frightening episodes in infants characterized by a combination of apnea, color change (cyanosis, pallor, plethora), abnormal muscle tone (limpness, stiffness), choking and gagging that require intervention by the observer.[1]

The available evidence suggests that in the vast majority of infants, GER is not related to pathologic

apnea or to ALTE, although there is a clear temporal correlation based on history, observation or testing occurs in individual infants. Impedance-pH recording in combination with polysomnographic recording is recommended to demonstrate such correlation in these infants.[1,2]

REACTIVE AIRWAYS DISEASE

The etiologic role for reflux in reactive airways disease, such as asthma, has not been established. However, animal and human studies have suggested that reflux may exacerbate the existing asthma. Proposed mechanisms explaining why reflux may aggravate asthma include direct production of airway inflammation by aspirated gastric contents, airway hyper-responsiveness triggered by lower airway aspiration of minute amounts of acid, vagally-mediated bronchial or laryngeal spasm, and neurally-mediated inflammation. Esophageal acidification in healthy adults has minimal effect on pulmonary function; however, esophageal acidification in asthmatic patients can produce airway hyper-responsiveness and airflow obstruction.[12]

Few studies have evaluated the impact of asthma on the severity of GERD. Chronic hyperinflation caused by asthma can flatten the diaphragms, alter crural function and displace the lower esophageal sphincter into the negative atmosphere of the chest, effectively reducing resting lower esophageal sphincter (LES) pressure and causing disappearance of the acute esophago-gastric angle of His. Lung hyperinflation and airflow obstruction may produce increased negative intra-thoracic pressure that effectively increasing the pressure gradient across the diaphragm and promoting reflux. Although theophylline and β-receptor antagonists cause a reduction of resting LES pressure, these drugs have not been linked to the development of GERD in treated asthmatics.[12]

Many studies have demonstrated an association between asthma and measurements of reflux by pH probe or pH/multichannel intraluminal impedance (MII). These studies have shown that over half of the children with asthma have abnormal pH or pH/MII recordings.[12] No studies to date have shown that pH/MII studies are useful in identifying those patients whose asthma might respond to anti-reflux therapy. Although adult studies show only limited if any benefit from PPI or surgical therapy, it is possible that selected patients with heartburn, nocturnal asthma, or steroid-dependent, difficult-to-control asthma may derive some benefit. Symptom reporting is less reliable in infants and children than in adults. There is no strong evidence to support empiric PPI therapy in unselected pediatric patients with wheezing or asthma.

RECURRENT PNEUMONIA

No test can determine whether reflux is causing recurrent pneumonia. An abnormal esophageal pH test may increase the probability that reflux is a cause of recurrent pneumonia but is not proof thereof. A normal esophageal pH test cannot exclude reflux as a cause of pneumonia because if airway protection mechanisms are compromised, even brief reflux episodes that are within the normal range, may be associated with aspiration. Lipid-laden alveolar macrophages (LLAM) have been used as an indicator of aspiration but the sensitivity and specificity as an indicator of GER-related lung disease is poor. Pepsin content of pulmonary lavage fluid has also been used to document aspiration of gastric contents. Pepsin concentration is elevated in pulmonary lavage from patients with reflux, but there is substantial overlap with controls.[13] Nuclear scintigraphy can detect aspirated gastric contents when images are obtained for 24 hours after enteral administration of a labelled meal. One study reported that 50% of patients with a variety of respiratory symptoms had aspiration on scintigraphy, but such finding has not been replicated elsewhere.[14] It is important to recognize that aspiration also occurs in healthy subjects, especially during sleep so the threshold for pathologic aspiration of saliva or gastric contents is not established.[15,16]

Although medical and surgical therapy of GERD have been reported to reduce pulmonary symptoms in certain populations of children with recurrent pneumonia, no data are available regarding the predictive value of any diagnostic test for determining which patients will respond to either medical or surgical therapy for GERD. In patients with severely impaired lung function, it may be necessary to proceed with anti-reflux surgery in an attempt to prevent further pulmonary damage despite lack of definitive proof that reflux is a cause of pulmonary disease. Alternatively, if minimal pulmonary disease is present, consideration of medical therapy with careful follow-up of pulmonary function may be instituted although the potential benefits versus risks of proton-pump inhibitor therapy are unclear.

UPPER AIRWAY SYMPTOMS

Data showing the correlation between reflux and upper airway disease are weak, consisting mainly

of case descriptions. Airway symptoms attributed to reflux in adults include hoarseness, chronic cough and the sensation of a lump in the throat (globus sensation). Upper airway edema, erythema, cobblestoning and granulomas are neither sensitive nor specific for the diagnosis of GERD. Criteria used for assessing laryngeal findings are variable as the criteria for diagnosing GERD in published reports. Laryngoscopy is indicated in some of these children to rule out anatomic abnormalities such as laryngeal cleft and functional abnormalities such as vocal fold dysfunction.[16] Data are insufficient to allow recommending a standard approach to diagnosis, treatment and follow-up. Extrapolation from adult studies suggests that PPI will not benefit most children with upper airway symptoms. Reflux has been suggested as a factor contributing to recurrent sinus disease, pharyngitis and otitis media.

DENTAL EROSIONS

Case reports and a systematic review report a causative association between GERD and dental erosion.[17] One study in adolescents showed that reflux was associated with an increased incidence of erosion of enamel on the lingual surfaces of the teeth.[18] Factors other than reflux may also cause similar dental erosions; these include juice drinking, bulimia, and racial and genetic factors that affect the characteristics of enamel and saliva. The inspection of the oral cavity in search for dental erosions is advisable in patients with known GERD.

DYSTONIC HEAD POSTURING (SANDIFER'S SYNDROME)

Sandifer syndrome, the spasmodic torsional dystonia with arching of the back and opisthotonic posturing, mainly involving the neck and back, is an uncommon but specific manifestation of GERD, that must be differentiated from other causes of abnormal movements including seizures, infantile spasms and dystonia.[19] The mechanisms underlying this disorder are unproven, but it may be a vagally mediated reflex response to esophageal acid exposure. It resolves with antireflux treatment.

GROUPS AT INCREASED RISK FOR SEVERE AND CHRONIC GERD

Children with certain underlying disorders are at high risk of developing severe and chronic GERD, compared to those who are otherwise healthy.

NEUROLOGIC IMPAIRMENT

Children with cerebral palsy are at particularly high risk of GERD. Similarly, children with certain genetic syndromes such as Cornelia de Lange and Down syndrome are prone to GERD.[20] Contributing factors that increase reflux frequency and delay esophageal clearance are chronic supine positioning, abnormal swallowing, heightened gag reflex, abnormal sensory integration, delayed gastric emptying, constipation, obesity but also undernutrition, skeletal abnormalities, abnormal muscle tone and medication side effects. Severe GERD may result from poor self-protective mechanisms and delayed diagnosis caused by difficulties in obtaining an accurate history of symptoms. Positional changes and control of muscular tonus may be as important as control of acid reflux. Long-term treatment with PPIs is often effective for symptom control and maintenance of remission of esophagitis.

Descriptive studies suggest that placement of feeding gastrostomy in children with neurologic impairment, may increase the risk of subsequent GERD.[21] Recent surgical studies comparing open and laparoscopic gastrostomy placement suggest that post-operative development of GERD is less common after laparoscopic and percutaneous endoscopic procedures than open surgical procedures.[22]

Given the morbidity and high failure rates of anti-reflux surgery in this group, patients whose symptoms are well-controlled on medical therapy may not derive additional benefit from anti-reflux surgery. The relative risks versus benefit of anti-reflux surgery in children with persistent symptoms despite optimized medical therapy have not been clearly defined.

CHRONIC RESPIRATORY DISORDERS

A higher prevalence of GERD and its complications has been reported in patients with a variety of respiratory disorders including bronchopulmonary dysplasia and cystic fibrosis (CF). In one study, 27% of CF patients < 5 years old reported gastrointestinal symptoms suggestive of reflux (heartburn or regurgitation), compared with only 6% of their normal siblings.[23] However, pH studies in children with CF detect a much higher prevalence of pathologic GER, i.e., reflux is silent in the majority. Reflux may be silent because gastrointestinal symptoms are truly absent, or symptoms may be relatively ignored by CF patients because of their plethora of other problems. Especially acid reflux is prominent in CF patients.

Bronchopulmonary dysplasia, a chronic lung disease of infancy with varying degrees of alveolar growth arrest, airway branching abnormalities and peribronchiolar fibrosis, has been associated with GERD. However, more recent studies have not confirmed this association. Since most studies have cross-sectional or case-control design, a cause-effect relationship remains to be defined. Severe GERD is common in patients presenting for transplantation, and a high incidence of GERD occurs following lung transplantation in children and adults.[24]

THE PREMATURE INFANT

GERD treatment is frequently administered to premature infants. In a recent study, 25% of infants with birthweights < 1,000 grams were discharged on medications to treat reflux. However, the true frequency of GERD is unknown. Behaviors often interpreted as signs of reflux disease in the preterm infant are non-specific and not predictive of esophagitis.[25]

Although reflux episodes may be more common in infants with bronchopulmonary dysplasia, there is no evidence that GERD therapy impacts upon the clinical course or outcome. One study reported a greater than 11-fold increase in the incidence of esophageal adenocarcinoma in adults who were born preterm or small for gestational age.[26] However, a subsequent nested case-control study did not confirm a strong association between risk of esophageal cancer and birth weight.

CONCLUSION

Gastroesophageal reflux disease is defined when reflux of gastric contents is the cause of troublesome symptoms and/or complications. Symptoms of GERD vary by age. Clinical presentations that should be considered as possibly related to GERD are regurgitation with weight loss, irritability, chronic crying, feeding refusal or dysphagia, and chronic respiratory symptoms. Neurological diseases associated with hypertonia, spasticity, hypotonia, myopathy or congenital anomalies noted to cause more GER than in general population.

REFERENCES

1. Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr 2009;49:498-547.
2. Sherman PM, Hassall E, Fagundes-Neto U, Gold BD, Kato S, Koletzko S, et al. A global, evidence-based consensus on the definition of gastroesophageal reflux disease in the pediatric population. Am J Gastroenterol 2009;104:1278-95.
3. Cavataio F, Carroccio A, Iacono G. Milk-induced reflux in infants less than one year of age. J Pediatr Gastroenterol Nutr 2000;Suppl 30:S36-44.
4. Vandenplas Y, De Schepper J, Verheyden S, Devreker T, Franckx J, Peelman M, et al. A preliminary report on the efficacy of the multicare AR-Bed in 3-week-3-month-old infants on regurgitation, associated symptoms and acid reflux. Arch Dis Child 2010;95:26-30.
5. Barr RG. The normal crying curve: what do we really know? Dev Med Child Neurol 1990;32:356-62.
6. Feranchak AP, Orenstein SR, Cohn JF. Behaviors associated with onset of gastroesophageal reflux episodes in infants: prospective study using split-screen video and pH probe. Clin Pediatr (Phila) 1994;33:654-62.
7. Vandenplas Y, Koletzko S, Isolauri E, Hill D, Oranje AP, Brueton M, et al. Guidelines for the diagnosis and management of cow's milk protein allergy in infants. Arch Dis Child 2007;92:902-8.
8. Bjornsson E, Abrahamsson H, Simren M, Mattsson N, Jensen C, Agerforz P, et al. Discontinuation of proton pump inhibitors in patients on long-term therapy: a double-blind, placebo-controlled trial. Aliment Pharmacol Ther 2006;24:945-54.
9. Fiedorek S, Tolia V, Gold BD, Huang B, Stolle J, Lee C, et al. Efficacy and safety of lansoprazole in adolescents with symptomatic erosive and non-erosive gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr 2005;40:319-27.
10. Wang KK, Sampliner RE. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. Am J Gastroenterol 2008;103:788-97.
11. Pasha SF, Di Baise JK, Kim HJ, De Petris G, Crowell MD, Fleischer DE, et al. Patient characteristics, clinical, endoscopic, and histologic findings in adult eosinophilic esophagitis: a case series and systematic review of the medical literature. Dis Esophagus 2007;20:311-9.
12. Scarupa MD, Mori N, Canning BJ. Gastroesophageal reflux disease in children with asthma: treatment implications. Pediatr Drugs 2005;7:177-86.
13. Farhath S, Aghai ZH, Nakhla T, Saslow J, He Z, Soundar S, et al. Pepsin, a reliable marker of gastric aspiration, is frequently detected in tracheal aspirates from premature ventilated neonates: relationship with feeding and methylxanthine therapy. J Pediatr Gastroenterol Nutr 2006;43:336-41.
14. Ravelli AM, Panarotto MB, Verdoni L, Consolati V, Bolognini S. Pulmonary aspiration shown by scintigraphy in gastroesophageal reflux-related respiratory disease. Chest 2006;130:1520-6.
15. Gleeson K, Eggli DF, Maxwell SL. Quantitative aspiration during sleep in normal subjects. Chest 1997;111:1266-72.
16. Huxley EJ, Viroslav J, Gray WR, Pierce AK. Pharyngeal aspiration in normal adults and patients with depressed consciousness. Am J Med 1978;64:564-8.
17. Bartlett DW, Evans DF, Smith BG. Oral regurgitation after reflux provoking meals: a possible cause of dental erosion? J Oral Rehabil 1997;24:102-8.
18. Bartlett DW, Coward PY, Nikkah C, Wilson RF. The prevalence of tooth wear in a cluster sample of adolescent

school children and its relationship with potential explanatory factors. Br Dent J 1998;184:125-9.
19. Cerimagic D, Ivkic G, Bilic E. Neuroanatomical basis of Sandifer's syndrome: a new vagal reflex? Med Hypotheses 2008;70:957-61.
20. Luzzani S, Macchini F, Valade A, Milani D, Selicorni A. Gastroesophageal reflux and Cornelia de Lange syndrome: typical and atypical symptoms. Am J Med Genet A 2003;119:283-7.
21. Sleigh G, Sullivan PB, Thomas AG. Gastrostomy feeding versus oral feeding alone for children with cerebral palsy. Cochrane Database Syst Rev 2004:2:CD003943.
22. Catto-Smith AG, Jimenez S. Morbidity and mortality after percutaneous endoscopic gastrostomy in children with neurological disability. J Gastroenterol Hepatol 2006;21:734-8.
23. Scott RB, O'Loughlin EV, Gall DG. Gastroesophageal reflux in patients with cystic fibrosis. J Pediatr 1985;106:223-7.
24. Young LR, Hadjiliadis D, Davis RD, Palmer SM. Lung transplantation exacerbates gastroesophageal reflux disease. Chest 2003;124:1689-93.
25. Malcolm WF, Gantz M, Martin RJ, Goldstein RF, Goldberg RN, Cotten CM. Use of medications for gastroesophageal reflux at discharge among extremely low birth weight infants. Pediatrics 2008;121:22-7.
26. Kaijser M, Akre O, Cnattingius S, Ekbom A. Preterm birth, low birth weight, and risk for esophageal adenocarcinoma. Gastroenterology 2005;128:607-9.

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