REVIEW ARTICLE

Gastroesophageal reflux disease in children

CME

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Reflux of gastric contents is common in young infants but usually self-limiting and not pathological. Gastroesophageal reflux disease refers to persistent reflux due to pathological factors that results in significant symptoms. Patients may exhibit oesophagitis, bleeding, nutritional failure, or respiratory problems. A high index of suspicion must thus be maintained for all patients. The aim of this article was to provide a concise review of the understanding of this disease, and also to discuss current diagnosis and management strategies for children with gastroesophageal reflux disease.

Introduction

Gastroesophageal reflux (GER) is a common physiological process in young infants, which is characterised by the involuntary passage of gastric contents into the lower oesophagus.[1] In neonates, physiological GER is often noted due to the immaturity of lower oesophageal sphincter (LOS). Previous studies have indicated that 'physiological reflux' occurs in up to 85% of infants with a male-to-female preponderance of 1.6:1.[2,3] The features of physiological GER in infants are that the reflux usually begins at the age of 2 to 3 months, mostly occurring post-prandially, and entails regurgitation of milk. There are no known predisposing factors for physiological GER, which improves with age (47% at the age of 2 months and 4% at 6 months).[4] As this is a self-limiting event with very little impact on development and growth, usually no medical or surgical intervention is needed.

Persistent reflux due to various pathological factors often results in overt clinical symptoms and signs, which are then termed gastroesophageal reflux disease (GERD). Affected children may present with failure to thrive, recurrent pneumonia, or apnoea.[5] Overall, children who are at high risk of having GERD are those who are neurologically impaired. Indeed, up to 70% of these children are said to have GERD, of whom 44 to 67% benefit from anti-reflux surgery.[6] In addition, children with chronic lung disease, as well as those who have had corrective surgery for oesophageal atresia with anatomical transformation at the oesophago-gastric junction, and hiatus hernia, are more likely to be at risk. Typically, in children GERD presents with frequent emesis or feeding intolerance. Symptoms are usually aggravated at night, especially when patients are supine. In infants, long-standing GERD causes failure to thrive due to calorie deprivation. Furthermore, once gastric contents reflux into the airways, symptoms such as coughing and choking ensue. Chronic aspiration may cause apnoeic and bradycardic spells, stridor, or pneumonia.[1] Recent studies suggest that GERD might be related to recurrent pneumonia, asthmatic bronchitis, or even sudden infant death syndrome.[7] As GERD has a serious negative impact on development, growth, and the physical and mental health of children, early diagnosis and effective treatment can significantly reduce morbidity and mortality. The present review aimed to summarise the pathogenesis, clinical features, diagnostic approaches, and treatment of GERD in children.

Anti-reflux mechanism of the lower oesophageal sphincter

The pressure on the LOS acts as a barrier to acid reflux from the stomach. The sphincter is not a simple anatomical valve at a single point, but a physiological sphincter ranging in length from 3 to 7 cm. The length of the sphincter can be determined more accurately using oesophageal manometry.[8] The control of the LOS is via the coordination of various closing and opening mechanisms (Fig 1). Several closing mechanisms contribute towards the proper function of the LOS. First, the crux of the diaphragm creates a pinch cork action and functions to increase the pressure. This action can be easily demonstrated during upper gastro-intestinal endoscopy.[9] Second, the intra-abdominal portion of the oesophagus is a vital aspect of the anti-reflux barrier. The greater the length of this portion, the more valve-like an effect there is.[10] Third, the angle between the stomach and the oesophagus (the angle of His) also helps to prevent reflux.[11] Conversely, forces that tend to increase opening pressure mechanisms oppose the closing mechanisms. Increased intra-

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Child; Fundoplication; Gastroesophageal reflux; Laparoscopy; Treatment outcome

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小兒的胃食道反流病

胃內容物反流在嬰兒期很常見，但它往往只是自限性，並非是病理變化所引致。胃食道反流病是指由病理因素所致的反流情況而引致嚴重的症狀。患者會出現食道炎、食道出血、營養不良或呼吸道疾病。因此，醫生必須對此症保持高度警覺。本文對胃食道反流病展開綜述，並探討目前對小兒患者的診斷方法及處理對策。

abdominal pressure (eg from abdominal tumours, coughing, and constipation) increases intra-gastric pressure and thus potentiates the risk of GERD.[12,13]

Pathogenesis and risk factors of gastroesophageal reflux disease in children

Once there is an imbalance between the opening and closing pressures, GERD will occur. Factors that have been proven to alter the pressure balance and lead to GERD are: (1) poor function of LOS which is more likely to be seen in children who suffer from neuronal/muscular dysfunction[14,15]; (2) oesophageal dysmotility resulting in reduced clearance—due to drugs (eg antihistamines) and hormones, as well as the neuronal disability can weaken oesophageal motility. Wenzl et al[16] reported that the occurrence rate of GERD was associated with the duration of gastric content staying in oesophagus and not the frequency of reflux; (3) abnormal anatomy—including congenital malformation (eg short intra-abdominal oesophagus) or acquired diseases (eg oesophageal atresia repair); and (4) higher intra-gastric pressure and delayed gastric emptying.

Overall, children who are at risk of GERD are those who are neurologically impaired (eg with cerebral palsy), and those who have undergone corrective surgery for oesophageal atresia which leads to altered anatomy of the oesophago-gastric junction. For those who suffer from chronic lung disease and are known to have hiatus hernia are also at risk.[17] In this regard, up to 15% of neurologically impaired children have GERD symptoms. The underlying neurological impairment could be part of a global neurological disease burden, which results in oesophageal and gastroduodenal dysmotility, leading to LOS dysfunction.[18] Furthermore, these children often have physical deformities like scoliosis that affect the anatomy of the gastroesophageal junction and oesophagus. In children, seizures also increase intra-abdominal pressure and thereby reinforce the opening mechanisms of the LOS.[19]

Clinical symptoms and signs in children with gastroesophageal reflux disease

Clinical features of GERD vary in children of different ages. In infants, emesis and aspiration are the most common; emesis ensues in 90% of those afflicted.[20] Frequent emesis may give rise to malnutrition and failure to thrive in this age-group. In older children, the commonest symptoms are acid regurgitation (especially post-prandially), and retrosternal discomfort (oesophagitis). Acid-suppressing drugs can reduce these symptoms.[21] However, once inflammatory oesophageal stricture occurs they may have dysphagia. Furthermore, GERD has been reported to induce asthma, recurrent pneumonia, and chronic cough.[22]

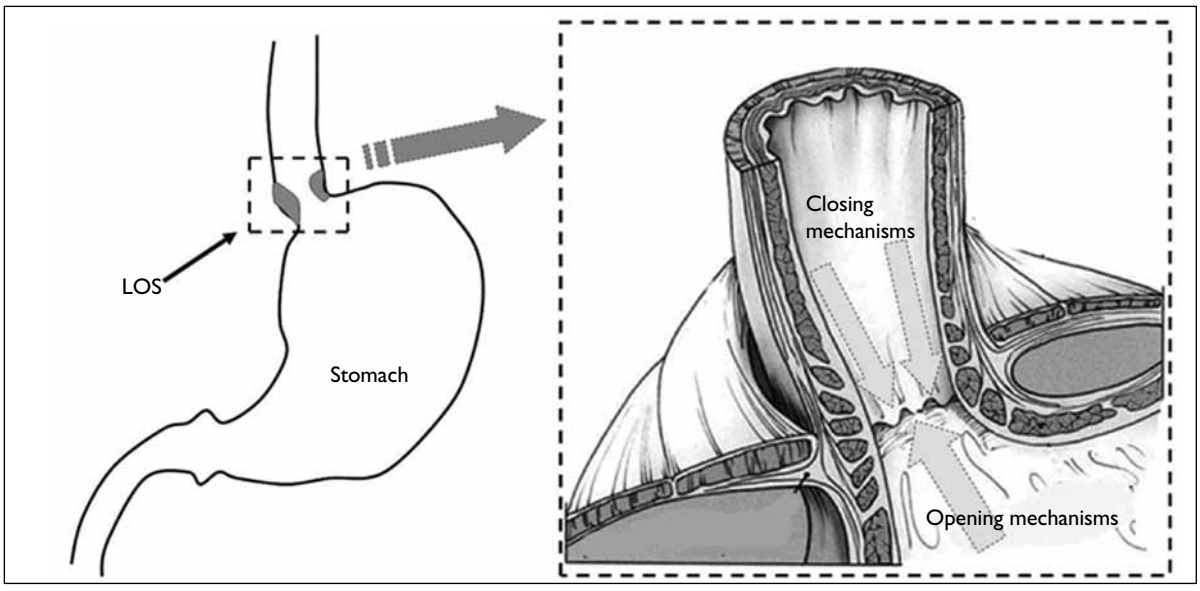

FIG 1. A schematic diagram showing opposing opening and closing mechanisms in maintaining the physiological lower oesophageal sphincter (LOS)

Diagnosis of gastroesophageal reflux disease in children

Diagnosing GERD is similar to the diagnosing of any other diseases. A carefully taken history is paramount to discern the nature and frequency of emesis, any evidence of predisposing conditions, and the presence of complications. The most important goal is to ensure that normal infants are not subjected to unnecessary treatments and operations. In patients with clinically suspected GERD, further investigations can be conducted to confirm the diagnosis.

Contrast meal

A contrast meal can be used to demonstrate the functional status of the oesophagus, as well as its anatomical morphology, such as the angle of His between the stomach and oesophagus, oesophageal dysmotility, mucosal irregularity (suggesting inflammation), stricture, and hiatus hernia.[23] However, contrast studies are relatively insensitive and give rise to many false positives and negatives. They are most useful in ruling out underlying obstruction such as that due to achalasia.

Scintiscan

Nuclear imaging can be a useful tool in the evaluation of delayed gastric emptying. Furthermore, if the radioactive tracer can be found in the lung, silent aspiration can be confirmed.[24] If delayed gastric emptying is evident, pyloroplasty may be needed at the time of fundoplication.

Oesophagogastroduodenoscopy

Oesophagogastroduodenoscopy is ideal for assessing the status of the oesophagus, especially in persons with symptoms of dysphagia.[25] Hiatus hernia can also be identified at the same time. Direct visualisation of the oesophagus can also accurately assess the degree of oesophagitis.

24-Hour oesophageal pH study

In the past, the clinical investigation and diagnosis of GERD was hindered due to the lack of a widely accepted and accurate definition. In this regard, a simple investigation relying on assessing the 'refluxed' hydrogen ions into the oesophagus formed the basis of the pH study. Indeed, a 24-hour pH study has now become the gold standard for the diagnosis of GERD, with both the sensitivity and specificity values of more than 90%.[26] This technique measures the duration and frequency of episodes in which the pH falls below 4 and data are collected and analysed using computer software. A portable pH and pressure meter can also be used to examine various physical conditions in oesophagus, involving parameter variation in the day or at night and before or after meals. Meanwhile, it can help to distinguish false reflux, caused by oral or oesophageal secretions.[27] A reflux episode is defined as the oesophageal pH dropping below 4. Oesophageal pH monitoring is performed for 24 or 48 hours and at the end of recording, the patient's tracing is analysed and the results are expressed using six standard components:

- Percent total time with a pH <4.0
- Percent upright time with a pH <4.0
- Percent supine time with a pH <4.0
- Number of reflux episodes
- Number of reflux episodes lasting ≥5 minutes
- Longest reflux episode (mins)

From these six parameters an eventual DeMeester score is calculated, and constitutes a global measure of oesophageal acid exposure.[28-30] The scoring system was originally derived from 24-hour pH studies in 50 normal subjects in which the standard deviation of the mean of each of the six components was measured. An artificial 0 point was established 2 standard deviations below the mean value of the normal subjects for each component. The resulting scoring system was built around the standard deviation as a weighting unit. Any measured value from a given patient could be referenced to this 0 point and be awarded points based on dividing the measured value by the standard deviation of the mean of the normal value.

The threshold for diagnosing reflux is thus defined by either of the following:

(1) DeMeester score >14.72;

(2) (a) pH <4.0 for more than 5.5% of the total time;

(b) pH <4.0 for more than 8.3% of all the time spent in an upright position; or

(c) pH <4.0 for more than 3% of all the time spent in a supine position.

However, the DeMeester score is not the only parameter for deciding whether a patient should undertake a surgical operation. Other factors, including the effectiveness of medical management, associated diseases, and abnormal anatomy also have to be considered.

The 24-hour oesophageal pH monitoring is the most important way to predict abnormal acid exposure, and to rule out the primary motility disorder in patients presenting with dysphagia. It can be utilised to monitor the efficacy of medical treatment, and provide detailed clinical information to assess LOS function. Furthermore, it particularly contributes to the evaluation of patients with recurrent symptoms after fundoplication.

Multi-channel intraluminal impedance study

Multi-channel intraluminal impedance (MII) has been recently introduced to study electrical impedance when substances pass through the oesophagus. Using a series of impedance sensors lying 1 cm apart on a probe, the direction of substance flow in the oesophagus can be measured (Fig 2). The main advantage of MII over conventional 24-hour pH monitoring is that an impedance probe can simultaneously detect both acid and non-acid GERD and to discern between liquid and gas.[31] In contrast, a 24-hour pH study can only identify acid reflux with a pH lower than 4.0, but can give false-negative results in patients who suffer non-acid reflux. This limitation of traditional pH monitoring has become even more important as primary care doctors routinely prescribe H_2 antagonists or proton pump inhibitors on an empirical basis. Thus, the use of MII represented a paradigm shift in the GERD diagnosis. Combined impedance-pH testing thus provides essential information about the acidity of a reflux event that can be gathered and categorised.[32] Furthermore, through the combination of MII with manometry, thorough oesophageal function through evaluation of oesophageal pressures and acid flow can also be studied. Indeed, a prospective study published in 1999 combining a pH probe and MII probe in infants concluded that impedance was a sensitive procedure for detection of acid and non-acid GER, which provided important information in the evaluation of reflux.[33] Findings of this initial study were further corroborated by another study.[16]

As in adults, the most important parameter in interpreting the results of multi-channel impedance/pH monitoring in children was in the evaluation of the relationship between symptoms and acid versus non-acid reflux.[34,35] In this population, MII recording along with pH monitoring doubled the probability of documenting an association between symptoms and reflux as compared to pH monitoring alone.[36] Despite the increase in diagnostic sensitivity, the drawback of the MII probe was the lack of normative values in children, which still need to be worked. Since last year, our unit has also been able to provide impedance monitoring in addition to traditional 24-hour pH studies.

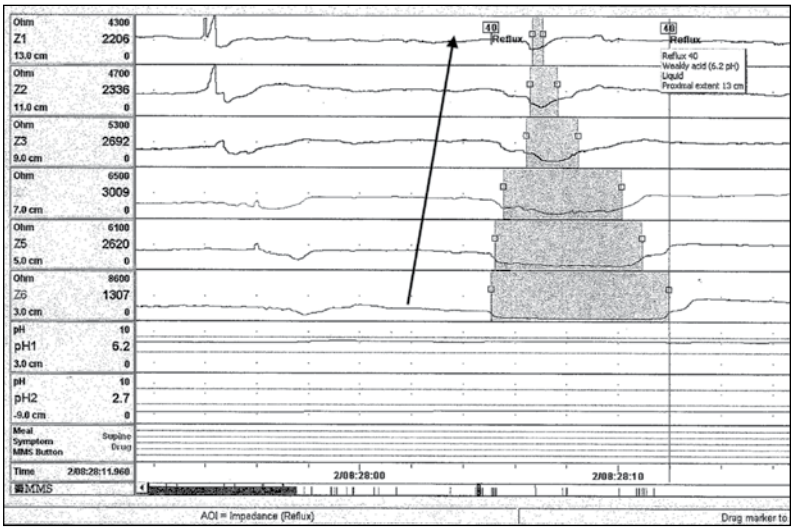

FIG 2. A representative recording from multi-channel intraluminal impedance study on a child with non-acid reflux

The arrow shows the direction of the gastric liquid from distal (Z6) to proximal oesophagus (Z1)

Treatment of gastroesophageal reflux disease in children

The aim of GERD treatment lies in improving anti-reflux function of the oesophagus and reducing gastric reflux, relieving symptoms, treating the complications, and preventing recurrence. Early accurate diagnosis and treatment achieves satisfactory improvement in symptoms and a good prognosis. Indeed, it was reported that symptoms would vanish in 50 to 90% of GERD children after receiving treatment for a period of months.[20] The treatment algorithm was a stepwise process. For small babies with physiological reflux only, conservative management needs to be considered. The regurgitation of milk after feed is due to immature development of the oesophageal sphincter, which disappears with time. Lifestyle modifications such as frequent small meals, minimising air swallowing during feeding, and propping up the baby after food, can all help alleviate reflux. For older children, modifications include weight loss, adjustment of the sleeping position, smoking cessation, and avoidance of caffeine and spicy foods.

Medical therapy

Various drugs can be used to reduce acidity, stimulate the oesophageal peristalsis, and preserve the oesophageal mucosa[37]:

(1) Anti-acid drugs: these can neutralise gastric acid, relieve the heart-burn feeling, and reduce the secretion of gastrin from pylorus, through which the oesophageal mucosa is well-preserved, and LOS pressure is increased.

(2) H_2 receptor antagonists and proton pump inhibitors can inhibit gastric acid secretion, and reduce the sensitivity of the oesophageal mucosa to acid, through which the symptoms of GERD and reflux oesophagitis can be relieved.

(3) Prokinetic agents such as domperidone can promote the peristalsis of smooth muscle in oesophagus and increase the LOS pressure. Thus gastric content reflux is prevented and gastric emptying is enhanced.

Regarding GERD patients with severe symptoms, comprehensive and frequent drug review is needed. If the symptoms continue after maximal medical therapy, surgical management should be adopted.[38]

Surgical intervention of gastroesophageal reflux disease in children

The aim of surgery is to construct a competent LOS by creating a valve between the lower oesophagus and the stomach and to correct any abnormal anatomy, such as hiatus hernia.[39] The indications for surgery include (1) poor response to medical therapy; (2) GERD associated with oesophagitis or severe oesophageal stricture[40,41]; (3) GERD associated with hiatus hernia; and (4) GERD associated with failure to thrive and persistent emesis.

Various surgical techniques for fundoplication (referred to as wrap) have been described. These include Nissen (total wrap), Thal (partial anterior wrap) and Toupet (partial posterior wrap) procedures. Regarding the surgical approach, laparoscopic fundoplication has been preferred to the traditional open approach.[42,43] This was due to the minimally invasive nature of the procedure which results in significantly less surgical trauma to patients. The underlying surgical principles remain the same: to repair the hiatal defect and perform anti-reflux wrap. Indeed, many studies found that the laparoscopic approach surpassed open anti-reflux surgery as the gold standard of surgical GERD management.[44-50] Hui et al[51] found that laparoscopic fundoplication was effective in eliminating nausea associated with GERD. Thatch et al[52] also compared laparoscopic and open fundoplication efficacy, by targeting patients in the neonatal intensive care unit. This study indicated that laparoscopic fundoplication with gastrostomy was safe and comparable to the open technique.[52] Furthermore, Rothenberg and Bratton[53] showed that laparoscopic fundoplication helped enhance pulmonary function in GERD children with severe asthma. Iwanaka et al[54] also reviewed anti-reflux surgery for infants and children in Japan, and felt that laparoscopic fundoplication had become a standard procedure, even for children with neurological impairment. The potential advantages were many, and included providing a clearer, magnified view of the anatomy, minimising surgical trauma, enabling more rapid patient recovery, and better cosmetic outcomes.

Laparoscopic Nissen fundoplication is the most popular. Although performing a total wrap may give rise to postoperative dysphagia, this is rarely encountered if done by experienced surgeons. The main difference between Nissen and Thal/Toupet procedures lies in the way that fundoplication is fashioned. Regarding Nissen fundoplication, a 360° floppy wrap is created using sutures (fundus to fundus) [Fig 3a]. While for the Thal fundoplication, the fundus is sutured anteriorly to the oesophagus in an inverted U-pattern, using sutures to create a 270° anterior wrap (Fig 3b). The Toupet procedure is performed by fashioning a posterior 270° wrap (Fig 3c). Usually the right side of wrap is first fixed to the right crura with two to three sutures. Then the right side of the wrap is fixed to the oesophagus using two to three sutures. The left part of wrap is sutured to the anterior side of oesophagus that further fixes the upper side of the wrap to the upper edge of the left crura. All three procedures have been shown to be extremely effective for the treatment of GERD; the choice is usually based on the surgeon's preference.

For children with neurological impairment, indications for anti-reflux surgery are: (1) presence of apnoeic episodes, bradycardia, recurrent pneumonia or life-threatening apnoea[55-57]; (2) Barrett's oesophagus; (3) prophylaxis in a patient with a feeding tube placement. A significant relationship between pulmonary disease and the severity of GERD has been reported, whilst silent aspiration can be sufficient to aggravate lung disease and its symptoms.[58,59]

In terms of postoperative complications, they can be divided into those related to surgery in general, those related specifically to fundoplication, and those related to the laparoscopic technique. Those related to surgery include bleeding, infection, adhesions, and relapse. Gas bloating, dumping, dysphagia, and vagus nerve palsy are the potential complications of fundoplication. Those related to the laparoscopic technique vary, and include pneumoperitoneum, increased intra-abdominal pressure, and increased systemic absorption of carbon dioxide. All of these

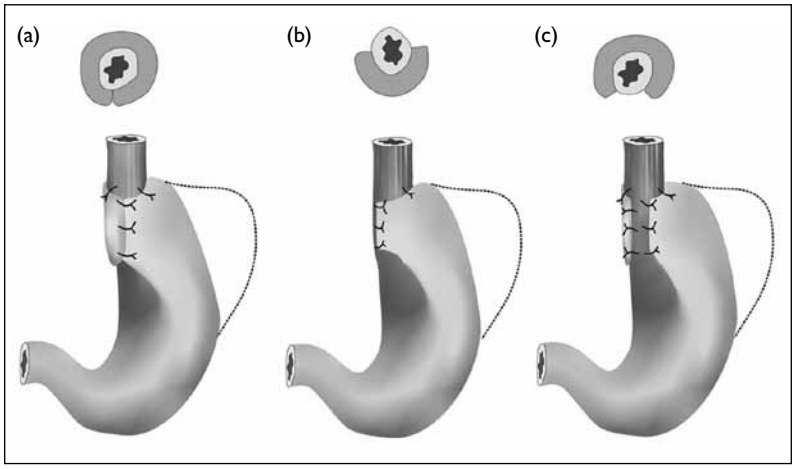

FIG 3. Diagrammatic drawings for three surgical techniques of fundoplication
(a) Nissen (total wrap); (b) Thal (partial anterior wrap); (c) Toupet (partial posterior wrap)

may compromise both the respiratory and cardiac status of the patient.

Regarding the outcome of these patients after laparoscopic Nissen's procedure, Turnage et al[60] targeted 46 infants and children with GER symptoms (57% had significant neurological impairment, and 80% had at least one serious additional medical problem) with a follow-up of at least 5 years later. They concluded that in their study, mortality was related primarily to associated diseases rather than to GER. Nissen's procedure provided efficacious, long-term treatment in infants and children, with acceptable morbidity.[60] Inge et al[61] also reviewed the outcomes of 62 consecutive Nissen's procedure–treated children retrospectively, using intra-operative manometry to standardise the tightness of wrap to prevent complications such as dysphagia, and recurrent post-surgery emesis. Long-term outcomes using this technique were deemed very good based on caregivers' responses.[61] Furthermore, through long-term follow-up, Goessler et al[62] concluded that GER symptoms improved significantly after fundoplication in mentally retarded children. The frequency of recurrent reflux was not related to the type of surgery, and late complications as well as recurrent reflux were significantly associated with preoperative dystrophy.[62]

Regarding the choice of different laparoscopic techniques, reports are sparse. Steyaert et al[63] compared the long-term efficacy between the Nissen and Toupet procedures in normal and neurological impaired children. Their study revealed that long-term results were comparable with either technique and with open surgery; there was no difference in terms of wrap failure in neurologically impaired and normal children.[63] Capito et al[64] also evaluated the long-term efficacy of this procedure in 127 children with primary GERD, 73 of whom were neurologically impaired and 54 were neurologically normal. They concluded that laparoscopic Nissen fundoplication was efficient in the long term for children with primary GERD. For the neurologically impaired children, the results were good; more than 85% were symptom-free after 5 years, although repeated evaluations were required to diagnose late recurrences related to evolving dysmotility disorders.[64] The (unpublished) data from our own series of over 100 laparoscopic fundoplications also support its efficacy.

Conclusion

Gastroesophageal reflux disease in children can cause failure to thrive and other significant symptoms. Clinicians treating children should be aware of the possibility of GERD and refer them for further evaluation early. A combined approach by paediatric gastroenterologists and paediatric surgeons can improve outcomes for both normal children with GERD, and those who are also neurologically impaired.

References

1. Pacilli M, Chowdhury MM, Pierro A. The surgical treatment of gastro-esophageal reflux in neonates and infants. Semin Pediatr Surg 2005;14:34-41.
2. Newell SJ, Booth IW, Morgan ME, Durbin GM, McNeish AS. Gastro-oesophageal reflux in preterm infants. Arch Dis Child 1989;64:780-6.
3. El-Mouzan MI, Abdullah AM, Al-Sanie AM, Al-Khalifah SI. Pattern of gastroesophageal reflux in children. Saudi Med J 2001;22:419-22.
4. Bagucka B, De Schepper J, Peelman M, Van de Maele K, Vandenplas Y. Acid gastro-esophageal reflux in the 10 degrees-reversed-Trendelenburg-position in supine sleeping infants. Acta Paediatr Taiwan 1999;40:298-301.
5. Steiner SJ, Croffie JM, Gupta SK, Pfefferkorn MD, Fitzgerald JF. Circadian variation of gastroesophageal reflux in children. Dig Dis Sci 2003;48:1818-22.
6. Fonkalsrud EW, Ashcraft KW, Coran AG, et al. Surgical treatment of gastroesophageal reflux in children: a combined hospital study of 7467 patients. Pediatrics 1998;101:419-22.
7. Velepic M, Rozmanic V, Velepic M, Bonifacic M. Gastroesophageal reflux, allergy and chronic tubotympanal disorders in children. Int J Pediatr Otorhinolaryngol 2000;55:187-90.
8. Beaumont H, Bennink RJ, de Jong J, Boeckxstaens GE. The position of the acid pocket as a major risk factor for acidic reflux in healthy subjects and patients with GORD. Gut 2010;59:441-51.
9. Mazzadi SA, García AO, Salis GB, Chiocca JC. Peptic esophageal stricture: a report from Argentina. Dis Esophagus 2004;17:63-6.
10. Triadafilopoulos G. Clinical experience with the Stretta procedure. Gastrointest Endosc Clin N Am 2003;13:147-55.
11. Paterson WG. The normal antireflux mechanism. Chest Surg Clin N Am 2001;11:473-83.
12. Jozkow P, Wasko-Czopnik D, Medras M, Paradowski L. Gastroesophageal reflux disease and physical activity. Sports Med 2006;36:385-91.
13. Galmiche JP, Janssens J. The pathophysiology of gastro-oesophageal reflux disease: an overview. Scand J Gastroenterol Suppl 1995;211:7-18.
14. Davidson G. The role of lower esophageal sphincter function and dysmotility in gastroesophageal reflux in premature infants and in the first year of life. J Pediatr Gastroenterol Nutr 2003;37 Suppl 1:S17-22.
15. Stein HJ, Kauer WK, Feussner H, Siewert JR. Bile reflux in benign and malignant Barrett's esophagus: effect of medical acid suppression and nissen fundoplication. J Gastrointest Surg 1998;2:333-41.

16. Wenzl TG, Moroder C, Trachterna M, et al. Esophageal pH monitoring and impedance measurement: a comparison of two diagnostic tests for gastroesophageal reflux. J Pediatr Gastroenterol Nutr 2002;34:519-23.
17. Karamanolis G, Sifrim D. Developments in pathogenesis and diagnosis of gastroesophageal reflux disease. Curr Opin Gastroenterol 2007;23:428-33.
18. Parkman HP, Harris AD, Krevsky B, Urbain JL, Maurer AH, Fisher RS. Gastroduodenal motility and dysmotility: an update on techniques available for evaluation. Am J Gastroenterol 1995;90:869-92.
19. Liakos AM, Bradley NK, Magram G, Muszynski C. Hydrocephalus and the reproductive health of women: the medical implications of maternal shunt dependency in 70 women and 138 pregnancies. Neurol Res 2000;22:69-88.
20. Orenstein SR. Management of supraesophageal complications of gastroesophageal reflux disease in infants and children. Am J Med 2000;108 Suppl 4a:139S-143S.
21. Rudolph CD. Supraesophageal complications of gastroesophageal reflux in children: challenges in diagnosis and treatment. Am J Med 2003;115 Suppl 3A:150S-156S.
22. Orenstein SR. Tests to assess symptoms of gastroesophageal reflux in infants and children. J Pediatr Gastroenterol Nutr 2003;37 Suppl:S29-32.
23. Smith GS, Isaacson JR, Draganic BD, Baladas HG, Falk GL. Symptomatic and radiological follow-up after para-esophageal hernia repair. Dis Esophagus 2004;17:279-84.
24. Liu J, Wang Q, Li W. Estimation of surgical results of achalasia by gastro-esophageal scintiscan [in Chinese]. Zhonghua Wai Ke Za Zhi 1995;33:67-8.
25. Yaghoobi M, Farrokhyar F, Yuan Y, Hunt RH. Is there an increased risk of GERD after *Helicobacter pylori* eradication?: a meta-analysis. Am J Gastroenterol 2010;105:1007-13; quiz 1006, 1014.
26. Pan JJ, Levine MS, Redfern RO, Rubesin SE, Laufer I, Katzka DA. Gastroesophageal reflux: comparison of barium studies with 24-h pH monitoring. Eur J Radiol 2003;47:149-53.
27. Emmerson AJ, Chant T, May J, Vales P. Assessment of three methods of pH probe positioning in preterm infants. J Pediatr Gastroenterol Nutr 2002;35:69-72.
28. Kahrilas PJ, Quigley EM. Clinical esophageal pH recording: a technical review for practice guideline development. Gastroenterology 1996;110:1982-96.
29. Charbel S, Khandwala F, Vaezi MF. The role of esophageal pH monitoring in symptomatic patients on PPI therapy. Am J Gastroenterol 2005;100:283-9.
30. Mackalski BA, Ilnyckyj A. Esophageal pH testing in patients refractory to proton pump inhibitor therapy. Can J Gastroenterol 2008;22:249-52.
31. van Wijk MP, Benninga MA, Omari TI. Role of the multichannel intraluminal impedance technique in infants and children. J Pediatr Gastroenterol Nutr 2009;48:2-12.
32. Mousa HM, Rosen R, Woodley FW, et al. Esophageal impedance monitoring for gastroesophageal reflux. J Pediatr Gastroenterol Nutr 2011;52:129-39.
33. Wenzl TG, Silny J, Schenke S, Peschgens T, Heimann G, Skopnik H. Gastroesophageal reflux and respiratory phenomena in infants: status of the intraluminal impedance technique. J Pediatr Gastroentrol Nutr 1999;28:423-8.
34. Rosen R, Nurko S. The importance of multichannel intraluminal impedance in the evaluation of children with persistent respiratory symptoms. Am J Gastroenterol 2004;99:2452-8.
35. Rosen R, Lord C, Nurko S. The sensitivity of multichannel intraluminal impedance and the pH probe in the evaluation of gastroesophageal reflux in children. Clin Gastroenterol Hepatol 2006;4:167-72.
36. Salvatore S, Arrigo S, Luini C, Vandenplas Y. Esophageal impedance in children: symptom-based results. J Pediatr 2010;157:949-54.e1-2.
37. Yellon RF, Goldberg H. Update on gastroesophageal reflux disease in pediatric airway disorders. Am J Med 2001;111 Suppl 8A:78S-84S.
38. Lobe TE. The current role of laparoscopic surgery for gastroesophageal reflux disease in infants and children. Surg Endosc 2007;21:167-74.
39. Di Lorenzo C, Orenstein S. Fundoplication: friend or foe? J Pediatr Gastroenterol Nutr 2002;34:117-24.
40. Randolph J. Experience with the Nissen fundoplication for correction of gastroesophageal reflux in infants. Ann Surg 1983;198:579-84.
41. Shub MD, Ulshen MH, Hargrove CB, Siegal GP, Groben PA, Askin FB. Esophagitis: a frequent consequence of gastroesophageal reflux in infancy. J Pediatr 1985;107:881-4.
42. Zitsman JL. Pediatric minimal-access surgery: update 2006. Pediatrics 2006;118:304-8.
43. Meehan JJ, Georgeson KE. Laparoscopic fundoplication in infants and children. Surg Endosc 1996;10:1154-7.
44. Humphrey GM, Najmaldin AS. Laparoscopic Nissen fundoplication in disabled infants and children. J Pediatr Surg 1996;31:596-9.
45. Thompson WR, Hicks BA, Guzzetta PC Jr. Laparoscopic Nissen fundoplication in the infant. J Laparoendosc Surg 1996;6 Suppl 1:S5-7.
46. Zamir O, Udassin R, Seror D, Vromen A, Freund HR. Laparoscopic Nissen fundoplication in children under 2 years of age. Surg Endosc 1997;11:1202-5.
47. Rothenberg SS. Experience with 220 consecutive laparoscopic Nissen fundoplications in infants and children. J Pediatr Surg 1998;33:274-8.
48. Esposito C, Montupet P, Reinberg O. Laparoscopic surgery for gastroesophageal reflux disease during the first year of life. J Pediatr Surg 2001;36:715-7.
49. Somme S, Rodriguez JA, Kirsch DG, Liu DC. Laparoscopic versus open fundoplication in infants. Surg Endosc 2002;16:54-6.
50. Saedon M, Gourgiotis S, Germanos S. Is there a changing trend in surgical management of gastroesophageal reflux disease in children? World J Gastroenterol 2007;13:4417-22.
51. Hui TT, Fass SM, Giurgiu DI, Iida A, Takagi S, Phillips EH. Gastroesophageal disease and nausea: does fundoplication help or hurt? Arch Surg 2000;135:545-9.
52. Thatch KA, Yoo EY, Arthur LG 3rd, et al. A comparison of laparoscopic and open Nissen fundoplication and gastrostomy placement in the neonatal intensive care unit population. J Pediatr Surg 2010;45:346-9.
53. Rothenberg SS, Bratton D. The effects of laparoscopic Nissen fundoplication to enhance pulmonary function in the treatment of a patient with severe asthma and gastroesophageal reflux disease. J Allergy Clin Immunol 2008;121:1069-70.
54. Iwanaka T, Kanamori Y, Sugiyama M, et al. Laparoscopic fundoplication for gastroesophageal reflux disease in infants and children. Surg Today 2010;40:393-7.
55. Herbst JJ, Minton SD, Book LS. Gastroesophageal reflux causing respiratory distress and apnea in newborn infants. J Pediatr 1979;95:763-8.
56. Spitzer AR, Boyle JT, Tuchman DN, Fox WW. Awake apnea

associated with gastroesophageal reflux: a specific clinical syndrome. J Pediatr 1984;104:200-5.
57. Walsh JK, Farrell MK, Keenan WJ, Lucas M, Kramer M. Gastroesophageal reflux in infants: relation to apnea. J Pediatr 1981;99:197-201.
58. Hoyoux C, Forget P, Lambrechts L, Geubelle F. Chronic bronchopulmonary disease and gastroesophageal reflux in children. Pediatr Pulmonol 1985;1:149-53.
59. Sindel BD, Maisels MJ, Ballantine TV. Gastroesophageal reflux to the proximal esophagus in infants with bronchopulmonary dysplasia. Am J Dis Child 1989;143:1103-6.
60. Turnage RH, Oldham KT, Coran AG, Blane CE. Late results of fundoplication for gastroesophageal reflux in infants and children. Surgery 1989;105:457-64.
61. Inge TH, Carmeci C, Ohara LJ, Berquist WB, Cahill JL. Outcome of Nissen fundoplication using intraoperative manometry in children. J Pediatr Surg 1998;33:1614-7.
62. Goessler A, Huber-Zeyringer A, Hoellwarth ME. Recurrent gastroesophageal reflux in neurologically impaired patients after fundoplication. Acta Paediatri 2007;96:87-93.
63. Steyaert H, Al Mohaidly M, Lembo MA, Carfagna L, Tursini S, Valla JS. Long-term outcome of laparoscopic Nissen and Toupet fundoplication in normal and neurologically impaired children. Surg Endosc 2003;17:543-6.
64. Capito C, Leclair MD, Piloquet H, Plattner V, Heloury Y, Podevin G. Long-term outcome of laparoscopic Nissen-Rossetti fundoplication for neurologically impaired and normal children. Surg Endosc 2008;22:875-80.