20 Esophageal Motor Disorders: Achalasia, Diffuse Esophageal Spasm, Nonspecific Motor Disorders, Eosinophilic Esophagitis

Hayat Mousa and Ann Aspirot

General Background Physiology

The esophagus is a collapsible organ in the digestive tract with the main function of transporting contents from the mouth to the stomach. The muscle layer is composed of circular, longitudinal, striated, and smooth muscle to assist peristalsis. Its three primary parts are the upper esophageal sphincter (UES), esophageal body (EB), and lower esophageal sphincter (LES). The UES is made of three muscles and cricoid cartilage which prevent inspired air from entering the digestive tract as well as esophageal contents from refluxing into the hypopharynx [1, 2]. Anterior to the EB are the larynx and trachea; the EB descends along the front of the vertebral column [3]. During swallows it collapses, distending to the anterior–posterior 2 cm and laterally to 3 cm. Primary peristalsis is initiated by either wet or dry swallows and facilitates esophageal clearance [4]. Secondary peristalsis occurs in response to refluxed materials or esophageal distention and contributes to the esophageal clearance [5]. Central and neural circuitry must coordinate in order for peristalsis to continue through the esophagus. The LES, comprising the gastroesophageal junction, works to prevent gastroesophageal reflux (GER) episodes, though allowing gaseous reflux contents.

Manometry is the primary assessment method for esophageal motor activity, specifically contractions [6]. It measures UES and LES pressures, esophageal body contraction amplitude, and peristaltic sequences [7, 8]. Manometry is a diagnostic tool recommended for use only after endoscopy and fluoroscopy have ruled out organic pathology [9]. Typically a manometry catheter is inserted from the pharynx to the stomach. The catheter has sensors which detect pressure and muscle contractions as the patient swallows, although it can be difficult to perform in the presence of pharyngeal or upper esophageal obstructions, severe coagulopathy cardiac conditions causing intolerance to vagal stimulation, and patient noncompliance [6, 7, 10]. Accurate diagnosis is obtained with proper instrumentation, standard technique and evaluation. Interpretation of the manometric tracings can be altered by the patient activity, body position, age, and gender [8, 11, 12]. More

H. Mousa, M.D. (✉)
Division of Gastroenterology, Nationwide Children Hospital, J West 1985, Columbus, OH, 43205, USA
e-mail: hayat.mousa@nationwidechildrens.org

A. Aspirot, M.D.
Pediatric Surgery Division, Department of Surgery, Sainte-Justine University Health Center, University of Montreal, Montreal, QC, Canada

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details about the different methods used to measure esophageal manometry are addressed in chapter 8.

Evaluation of Esophageal Bolus Transit and Clearance

There are several options to evaluate bolus transit and clearance:

Cineradiography

Cineradiology or video fluorography (VFG), is a method examining different phases of swallowing to identify motor abnormalities [13]. In this test, the patient digests, or is injected with, various concentrations of barium while altering body position to evaluate esophageal mucosa, motility, and structures [14–16]. The swallows are followed by several radiographs which detect esophageal clearance. Abnormal peristalsis identified in at least two swallows defines abnormal motility [15]. VFG is generally used as a screening tool with high sensitivity, though affected by number of swallows and body positions [16, 17].

Esophageal Transit Scintigraphy

Scintigraphy focuses on esophageal emptying, evaluates bolus transit in segments, and identifies reflux episodes [18]. In this test, the patient ingests a radio-labeled bolus and several images are taken to inspect bolus transit and clearance [19]. The study measures the level of radioactivity as it relates to clearance. Use of liquidized bolus is more standardized than semisolid bolus. Also, patients usually usually lie in the supine position to eliminate gravity as a source of error [18]. Scintigraphy is more sensitive than VFG, though the necessary equipment is not as widely available. More details about esophageal transit scintigraphy are addressed in Chap. 14.

Esophageal Impedance and pH Monitoring

Another method involves esophageal impedance and pH monitoring. When combined, these techniques can assess bolus transit, clearance, and chemical content of the bolus or refluxate. Similar to manometry, a catheter with several sensors is utilized for assessment. Several liquid and viscous swallows are required. Impedance demonstrates 97% concordance with fluoroscopy, though only fluoroscopy can study swallows with a solid bolus [20]. Among its many advantages, impedance can be (repeatedly) employed on pregnant women and children because it does not involve radiation; it also relates to esophageal mucosal integrity [21]. However, swallowed air can make brief changes in impedance unrelated to bolus transit.

Esophageal Function Testing

Esophageal function testing (EFT) is a union of manometry and multichannel intraluminal impedance monitoring. EFT gathers information on bolus transit patterns, swallow associated events, nonobstructive dysphagia, chest pain, and general motility disorders [22, 23]. It is also a helpful evaluation tool before antireflux surgery. Again, catheters are used for evaluation and several types are available depending on how many channels, sensors, pressure transducers, are needed [24]. In one exam, EFT provides information previously gathered in separate exams from manometry and fluoroscopy, even though it is typically used after both of those methods produce negative results [22]. By evaluating the transit time, EFT classifies esophageal dysmotility into two categories: either abnormal manometry with abnormal transit or abnormal manometry with normal transit. Abnormal manometry with abnormal transit includes conditions such as achalasia, scleroderma, ineffective esophageal motility, and distal esophageal spasm. Abnormal manometry with normal transit includes conditions such as nutcracker esophagus, hypertensive LES, hypotensive LES, and poor relaxing LES.

Esophageal Dysmotility

Prevalence of Esophageal Dysmotility in Children and Adolescents

As reported previously by Glassman et al., up to 25% of children and adolescents who present with chest pain, dysphagia, and vomiting have abnormal esophageal motility study [25]. The most common patterns of esophageal dysmotility in symptomatic children with dysphagia, chest pain, and vomiting are diffuse esophageal spasm (33%), achalasia (19%), hypotensive lower esophageal sphincter (14%), aperistaltic distal esophagus (14%), nutcracker esophagus (10%), and hypertensive lower esophageal sphincter in (10%) [25].

Clinical Presentation of Esophageal Dysmotility

Dysphagia

Swallowing is an important developmental process for human life. It requires the coordination between the mouth, pharynx, and esophagus for successful completion. Esophageal dysphagia or difficulty swallowing can be the result of behavioral, developmental, neurological, respiratory, GER, and inflammatory diseases [26, 27]. It is observed in 25–45% of developing children and even more in those with developmental disorders [28]. Dysphagia can occur with solid foods and/or liquids. Exclusively experiencing solid food dysphagia is more characteristic of a mechanical rather than a neurological disorder, whereas solid and/or liquid dysphagia is characteristic of neuromuscular disorder [27]. A child may indicate dysphagia by demonstrating little interest in food or eating, displaying straining or extension of muscles during feedings, taking extensive time to complete feeding, spilling food or liquid out of the mouth, emesis, coughing or gagging during feeding, struggling with breathing/stridor when feeding, and failing to thrive [26]. Patients undergo barium esophagogram or upper GI endoscopy to evaluate UES function, or manometry to assess motility when esophageal dysphagia is suspected [26, 27]. In infants, parents may additionally be provided a questionnaire and/or a physician may observe the child while feeding.

Chest Pain

Noncardiac chest pain can be indicative of esophageal dysmotility in infants and children. Because the heart and esophagus have similar neural pain pathways, it can be difficult to determine cardiac and noncardiac chest pain [29]. Compared to other sources to noncardiac chest pain (i.e., musculoskeletal pain and asthma), studies indicate that gastrointestinal diseases represent less than 10–15% of cases [30]. Glassman et al. reviewed the cases of 83 children aged 1–20 years with chest pain and vomiting or dysphagia for prevalence of esophageal motility disorders. Of the 83, 47 had normal esophageal manometry and endoscopy [25]. The remaining 36 patients had evidence of esophageal disease, indicated by either abnormal endoscopy, abnormal manometry, or both. Among the 21 patients with abnormal manometry, diffuse esophageal spasm was the most common diagnosis followed by achalasia, hypotensive LES, aperistalsis, nutcracker esophagus, and hypertensive LES. Most of these patients (16 of 21) were symptomatic of their disease. Berezin et al. performed a similar study of 51 children, aged 8–20 years, of which 27 were found to have idiopathic chest pain [29]. Twenty-one of those patients were diagnosed with esophagitis or diffuse esophageal spasm using manometry and histology; though only five had abnormal motility. Additionally, Glassman et al. found that with treatment chest pain was more easily resolved than esophageal symptoms.

Foreign Body Impaction

Children ingest materials that become impacted in the esophagus, usually in the upper esophagus, and obstruct esophageal transit; by comparison ingested items rarely enter the tracheobronchial tree [31, 32]. Children primarily ingest nonfood items such as coins and small toys, whereas adults tend to have impacted meat and bones [32]. Children with meat impactions should be evaluated for either anatomic esophageal malforma-

tion, motility/functional disorders or eosinophilic esophagitis [31].

Classification: The Chicago Classification 2009

High-resolution esophageal pressure topography (HROPT) is a novel technical development in the study of motility. Traditionally, manometry was used to examine esophageal motility but did not report pressures within the organ; this was a task reserved for pressure topography. HROPT provides the benefits of manometry and pressure topography in one technique. The Chicago Classification is a schema used to categorize results of HROPT used in clinical evaluations. It is based on a study of 400 patients and 75 controls by Kahrilas et al. [33]. In summary, HROPT classifies nonspecific esophageal motility disorders, diffuse esophageal spasm, nutcracker esophagus subtypes, vigorous achalasia, and functional obstruction. Among its advantages, HROPT is easily interpreted and standardized, saves time, provides high-quality data, and allows for more specific diagnoses.

Esophageal Motility Disorders

Esophageal Achalasia

Esophageal achalasia is a primary motor disorder presenting with dysphagia secondary to functional obstruction due to the dysfunction of the body of the esophagus and the lower esophageal sphincter. It is characterized by the absence of peristalsis and incomplete relaxation of the lower esophageal sphincter.

Epidemiology and Incidence

Achalasia is an infrequent adult disease with an incidence of 1.63/100,000 and a prevalence of 10.8/100,000, based on a recent population-based study [34]. Because of the relative rarity of childhood and adolescent achalasia, much of the literature on achalasia is based on the adult population, with information by pediatric gastroenterologists noted only in case series and retrospective studies. An incidence of less than 0.1/100,000 has been found in children in England and Wales [35]. Most of the cases are diagnosed between 7 and 15 years. Infants are rarely affected (6%), but symptoms are described to be present during the first year of life in 18% [36]. Infantile achalasia is reported as case reports in the literature [37]. Diagnosis may not be as rigorous in young children as it is in adults [35], many published cases were not confirmed by esophageal manometry, the gold standard diagnostic tool.

Pathophysiology

Acquired degeneration of the Auerbach's myenteric plexus is the primary mechanism of achalasia. Loss of nitrergic inhibitory enteric neurons occurring prior to loss of cholinergic neurons results in an imbalance between excitatory and inhibitory input leading to ineffective esophageal peristalsis and incomplete lower esophageal sphincter relaxation [38]. Nitric oxide (NO) is the predominant inhibitory neurotransmitter but others have been described such as vasopeptide intestinal peptide (VIP). Studies on resected specimen have demonstrated decreased number of myenteric ganglia, lymphocytic infiltrate, and collagen deposition within ganglia. Some specimens had normal number of myenteric ganglion cells, but myenteric fibrosis was observed. Preservation of cholinergic excitatory neurons could explain the occurrence of vigorous achalasia which has been hypothesized to be an earlier form of the disease [39]. These findings suggest a progressive immune mediated destruction of neuronal cells. The pathologic findings could be different in childhood achalasia where less neuronal inflammation was found [40].

Etiology

Achalasia can be primary (idiopathic) or secondary. The etiology of primary achalasia remains unknown. Numerous hypotheses have been proposed including infection, hereditary, and autoimmunity. Chagas disease is the prototype of secondary achalasia that is caused by the parasite *Trypanosma cruzi*. The disease is common in South and Central America. Whether the disease

is similar to idiopathic achalasia remains controversial [41]. Because of the associated inflammatory infiltration mainly composed of lymphocytes, viruses such as measles, HSV-1, and VZV have been suspected as a cause of idiopathic achalasia. A cause–effect relationship between viruses and achalasia has yet to be identified. Studies have associated achalasia with trisomy 21 [42], Hirschsprung's disease [43], Allgrove's syndrome, and familial dysautonomia, which suggest a genetic link. However, familial history is the exception in achalasic patients even in the pediatric age [36]. Allgrove's or 4 "A" syndrome, which presents with achalasia, alacrima, autonomic disturbance, and corticotrophin (ACTH) insensitivity, is the only condition associated with achalasia that has been linked to a specific chromosomal anomaly which is the AAAS gene on chromosome 12q13 [44–46]. Because of the rarity of achalasia in childhood, it is important to refer younger patients to Genetics and screen for adrenal insufficiency. The third broad hypothesis is autoimmunity that could precipitate an immune reaction directed to the esophageal myenteric ganglia. Studies are contradictory in demonstrating a link between antineuronal antibodies and achalasia [38, 47].

Clinical Presentation

Achalasia presents with progressive dysphagia (first for liquids and eventually for solid food), chest pain, and regurgitation of undigested food, not mixed with gastric secretions [48]. Nurko and Rosen [49] summarized the clinical symptoms in 528 pediatric patients from 23 series. The most common symptoms are vomiting (80%) and dysphagia (75%). Weight loss is reported in 64% and failure to thrive in 31%. Chest pain and odynophagia are sometimes present (45%), but less common in younger children. Diagnosis is often delayed in children because of multiple factors including lower incidence of achalasia, incapacity to verbalize complaints, and unspecific symptoms, such as food refusal and failure to thrive. Parents will sometimes report that their child is a slow eater. Children additionally present nocturnal symptoms such as choking and regurgitated food on the pillow (21%). Respiratory symptoms occur in 44% which is more frequent than in the adult population. In children, regurgitation, respiratory problems, and failure to thrive are frequently attributed to gastroesophageal reflux (GER) which is much more predominant than achalasia in this population. Extraesophageal complications of achalasia include recurrent pulmonary aspirations and tracheal compression by the megaesophagus. Sudden death has also been reported.

Differential Diagnosis

Apart from GER, differential diagnosis includes mechanical obstruction by foreign body, intrinsic esophageal pathology (esophageal stenosis, leiomyomas), and extrinsic compression of the esophagus (foregut duplication, mediastinal tuberculosis). Malignant neoplasms are more frequently seen in the adult population but need to be included in the differential diagnosis even in children. Chagas disease is always a possibility in patients coming from endemic regions. Achalasia has also been mistaken as eating disorders [50], emphasizing the importance of a thorough evaluation of the upper gastrointestinal tract anatomy and function in patients suspected of having primary anorexia nervosa.

Diagnosis

Diagnosis is often delayed because of the poor specificity of symptoms and the overlap with other more frequent pathologies such as gastroesophageal reflux disease. The specific workup includes radiographic studies, upper endoscopy, and esophageal manometry to confirm the diagnosis of achalasia.

Radiography

Plain chest radiograph may show an air-fluid level in the lower chest, a widened mediastinum, and an absent gastric bubble [51]. Contrast esophagogram will demonstrate the stagnation of contrast in the distal esophagus and possibly absent or tertiary peristalsis. The typical dilated esophagus tapering smoothly at its distal end ("bird's beak") is not necessary to make the diagnosis, but is highly suggestive of the disease. Using manometry as the gold standard, Parkman found a positive pre-

dictive value of 96%, a sensitivity of 100% and a specificity of 98% [52]. However, the correlation of severity as assessed by esophagogram and patient's symptoms is poor, which can also lead to a delayed diagnosis [53]. Barium esophagogram is also useful to monitor the success of treatment.

Endoscopy

Upper endoscopy may show retained food in a dilated esophagus. The gastroesophageal junction may appear tight (difficult to distend with air insufflation) but it is usually possible to reach the stomach. The main goal of upper endoscopy is to rule out mechanical obstruction at the gastroesophageal junction (pseudoachalasia) [54]. If pseudoachalasia is suspected, further investigation with ultrasound, endoscopic ultrasonography, and other imaging studies will help to differentiate between the numerous neoplastic and non-neoplastic causes of pseudoachalasia [55].

Manometry

The diagnosis of achalasia is confirmed by esophageal manometry. Absence of peristalsis in the esophageal body is the sine qua non criteria to diagnose esophageal achalasia [48]. Frequently, the lower esophageal sphincter relaxation is incomplete (residual pressure above 8 mmHg) [56, 57]. Hypertensive lower esophageal sphincter (resting pressure above 45 mmHg) is sometimes seen as well as an increased esophagogastric gradient. Recently, high-resolution esophageal manometry has been used more frequently and has permitted a better understanding of the motility abnormalities found in achalasia. Based on topographic plot characteristics, Pandolfino [58] has proposed a classification of achalasia in three subtypes:

- Type I: Classic achalasia: Mean integrated LES relaxation pressure (IRP) ≥15 mmHg, absent peristalsis, no or minimal distal esophageal pressurization.
- Type II: Achalasia with esophageal compression: Mean IRP ≥15 mmHg, absent peristalsis, with panesophageal pressurization to greater than 30 mmHg in ≥20% of swallows (Fig. 20.1.)
- Type III: Spastic achalasia. Mean IRP ≥15 mmHg, absent peristalsis and spasm (contractile front >8 cm^{-1}) in ≥20% of swallows with or without compartmentalized pressurization (Fig. 20.2).

These subtypes have different prognosis implication with type II having the best response to any therapy (pneumatic dilation, Heller myotomy, botulinum toxin) while type III have the worst response to all treatments. This information can be brought in the discussion with the patients and parents and also may guide the clinician in the therapeutic decision.

Treatment

Achalasia affects permanently the esophageal motility. Treatments for achalasia, similar to other esophageal disorders, focus on relieving symptoms [59]. The three primary types of treatment are pharmacologic, endoscopic, and surgical. The therapy of choice in children is still debated [60]. Proper treatment of achalasia is important to prevent progression toward dilated mega-esophagus where esophagectomy may become inevitable. Barium esophagogram can help monitor success of the treatment plan (Table 20.1).

Pharmacologic treatments include nitrates, calcium channel blockers, and phosphodiesterase inhibitors. Although significant decrease of lower esophageal sphincter pressure has been observed by manometry, symptom improvement occurred in 53–87% of patients [61]. In some cases, these medications are used temporarily while determining a more effective means of treatment. Pharmacologic interventions are also the treatment of choice for patients who are not candidates for or do not wish to receive more aggressive therapy. These medications have frequent side effects (headache, hypotension). Experience in children is limited to calcium channel blockers and nitrates and consists mainly of case reports [62–64]. Isosorbide dinitrate patch (long acting nitrate) has been used in an 8-year-old [63] with

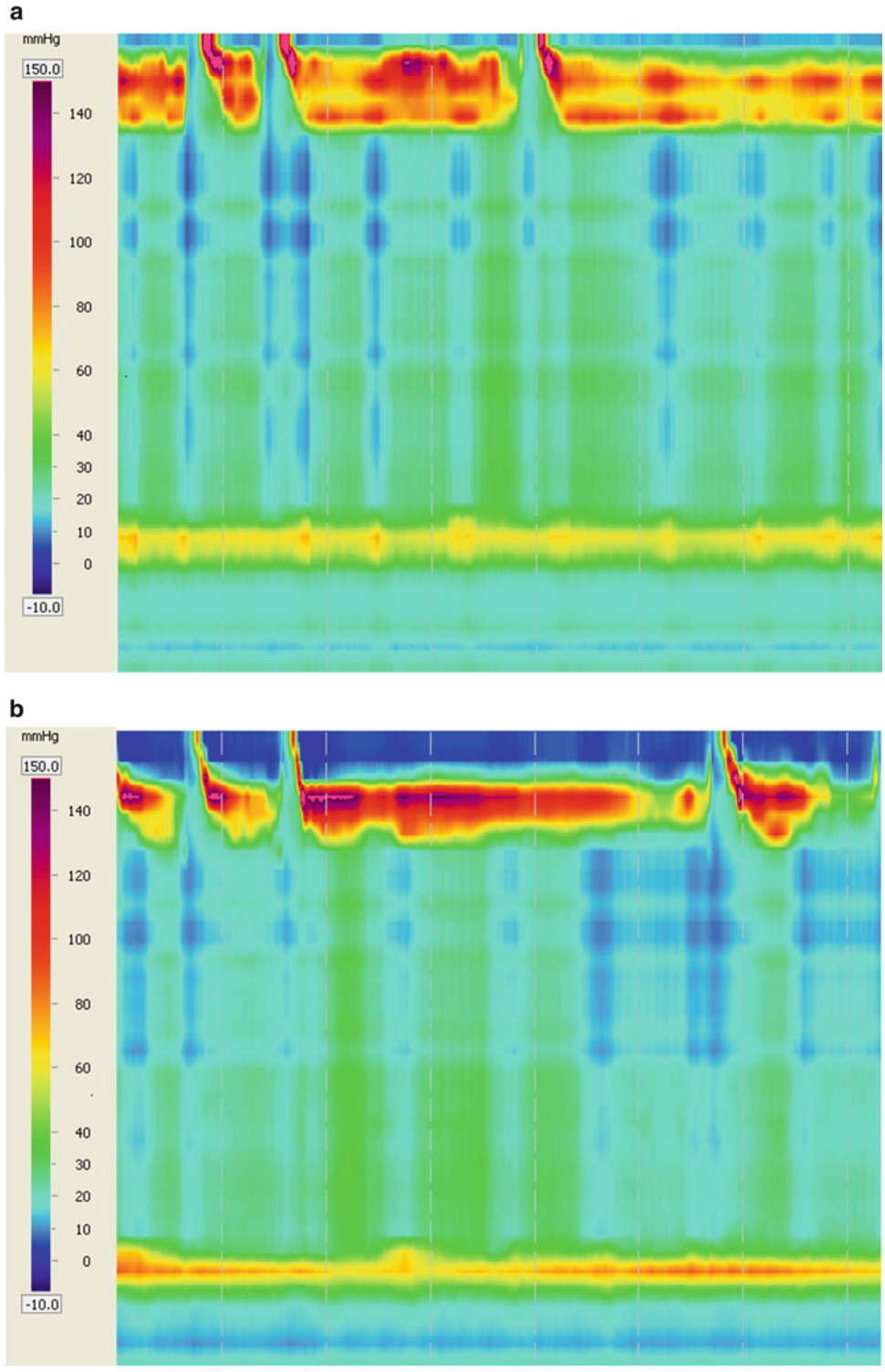

Fig. 20.1 Type II esophageal achalasia (with compression)

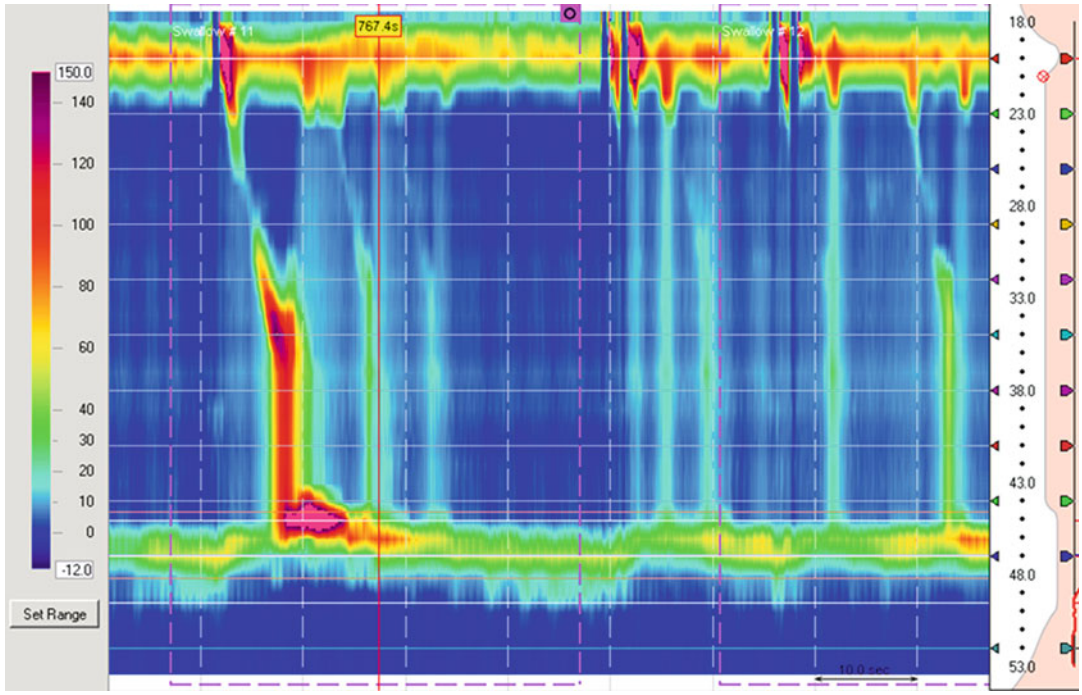

Fig. 20.2 Type III esophageal achalasia (spastic)

good short-term success. Nifedipine (10 mg) before meal was used in four adolescents with good clinical response and a decrease of LES pressure on manometry but there was recurrence of symptoms when the medication was stopped [62]. Long-term pharmacologic therapy is not actually recommended. Short use can be useful while waiting for definitive therapy (establishing weight gain, awaiting school vacation).

Endoscopic therapies include botulinum toxin injection into the LES, pneumatic dilation, and stenting. The use of intrasphincteric botulinum toxin was first reported by Pasricha et al. [65]. This potent neurotoxin blocks the release of acetylcholine at the neuromuscular junction leading to decreased lower esophageal sphincter pressure. A double-blind placebo-controlled trial demonstrated a good initial response in adults [66]. Long-term results showed that it is necessary to repeat the injection and the response decreases with repeated injections [67]. Experience in children is once again limited to retrospective case series [68–71], but shows similar results of good initial clinical response and high rate of recurrence. The data are however insufficient to conclude to the same certitude as in the adult population. Botulinum toxin injection can also be used as a diagnostic tool in patients with early and unclear diagnosis [72]. However, submucosal fibrosis resulting from intrasphincteric injections may complicate the subsequent surgical myotomy [73]. Esophageal dilation is the oldest treatment modality [48]. Balloon dilation is preferred over rigid bougienage because it is thought to permit a controlled tearing of the muscle fibers, even though it was not proven in animal studies [74]. It is less invasive than surgical treatment and is considered the most effective nonsurgical treatment of achalasia in adults [75, 76], and the first-line treatment in some pediatric centers [60]. The main complication is esophageal perforation which was reported in 1.6% of patients [75, 76]. Long-term efficacy of pneumatic dilation ranges from 40 to 60% [77–79]. Pediatric results are variable and difficult to compare because of the nonstandardization of the technique [49]. Pneumatic dilation can also serves as a rescue therapy after an incomplete

Table 20.1 Analysis of selected esophageal motility disorder treatment methods

Method of treatment	Associated disorders	Advantages	Disadvantages	Success
Acid suppression	DES, NE, NEMDs, SSc	Relieves GERD symptoms	May only treat GERD symptoms	Low success in children
Antibiotics	Caustic ingestion, CIIP, SSc			
Botox injection	Achalasia	Suitable for long-term use	May contribute to fibrosis at injection site	
Elemental diet	Caustic ingestion, EoE, DES, NE, SSc	Quick resolution of symptoms	Formulas not palatable Lower quality of life Cost/insurance coverage	Compliance difficult for children
Elimination diet	EoE, CIIP	Still allows for some food intake by mouth	Requires careful review of all food choices for allergens Does not always indicate specific food allergen at fault	Must continue elimination for long-term resolution
Esophageal dilation	Achalasia, caustic ingestion, DES, EoE, NE	Highly effective when strictures are also present	Chest pain Esophageal perforations	Common treatment in adults
Other surgical procedures	Achalasia, caustic ingestion, DES, HD, NE		Complications may further complicate disease	Usually successful with rare complications
Systemic or topical corticosteroids	EoE, SSc	Direct administration to eosinophilia (topical) Variety of administration (swallowed or inhaled)	Low bioavailability May not fully penetrate eosinophilia (topical)	Satisfactory symptom resolution High rate of symptom relapse upon discontinuation

myotomy [51]. Temporary self-expanding metallic stent is a new therapeutic option that has been used in patients as young as 12 years old but more studies and long-term experience is needed before recommending it [80].

Surgical treatment usually consists of a longitudinal division of the muscle fibers of the lower esophageal sphincter and proximal stomach coupled or not with an antireflux procedure. The name of Heller myotomy comes from the first description of this procedure by Ernest Heller in 1913 [59]. Laparoscopic Heller myotomy is now the most commonly performed surgical treatment of achalasia because it reduces the morbidity compared to the open approach. It has been shown to be as effective as open approaches [81] and superior to thoracoscopic approach [82, 83]. Clinical response after myotomy ranges from 83 to 100% [84] and the benefits persists in 67 to 85% in long-term (more than 10 years) studies [85, 86]. Randomized controlled trials compared favorably laparoscopic Heller myotomy to pneumatic dilation [87, 88]. Clinical deterioration over time has been associated with GER [89] which has led to randomized controlled studies comparing Heller myotomy with and without fundoplication [90]. Recently, it has been suggested that a more aggressive balloon dilatation results in comparable results to myotomy [91, 92]. Based on long-term success rates of 47–82% at 10 years, laparoscopic Heller myotomy with partial fundoplication is considered by many the surgical procedure of choice [75, 93, 94]. However, a study has reported that up to 30% of myotomized patients will require re-treatment within the first 12 years [95]. Pandolfino has reported different response to therapy according to the type of achalasia. According to his classification, type I (classic) achalasia responds best to Heller myotomy, type II (with compression) responds to any therapy, and type III (spastic) has a poor response to any therapy [58].

Laparoscopic Heller myotomy has also been found safe and effective in children [96]. Rates of good to excellent results of 90.9% have been reported [97–99]. As in the adult literature [100], the same surgical controversies exist which include extension of the myotomy [101], addition of fundoplication [102], and type of fundoplication if performed. Complications after Heller myotomy include esophageal perforation, phrenic nerve paralysis, hemorrhage, herniation of stomach. Long-term complications are persistent dysphagia and GER. The intra-operative use of endoscopy [103] and esophageal manometry [104] have been suggested to decrease the rate of incomplete myotomy. It is important to emphasize that while myotomy should improve the bolus transit by reducing the LES pressure, ineffective peristalsis can still remain an issue (Fig. 20.3) [105].

An approach to the child with persistent dysphagia after myotomy has been proposed since it is a frequent and debilitating problem [106]. Differential diagnosis of this problem include esophageal dysmotility, incomplete myotomy, fibrosis at the distal end of the myotomy, obstructive fundoplication, esophageal stricture and preoperative error in diagnosis [107–109]. A thorough evaluation is the basis of management, starting with a good clinical history. Contrast esophagogram and esophageal manometry complete the initial work up. Depending on the findings, endoscopy with pneumatic dilation may be indicated as the first therapeutic step. Surgical treatment is reserved for persistent significant obstruction of the distal esophagus [106].

Outcome

Regardless of the elected therapy, patients must continue with regular follow-up to prevent progression toward a more serious disease. A rare, yet critical complication of achalasia is squamous cell carcinoma in the esophagus. It is thought to result from stasis and uncontrolled bacterial growth [110]. Based on a review of the literature, Dunaway has reported a mean prevalence of 3% which represents of 50-fold increased risk over the general population [111]. Chronic gastroesophageal reflux resulting from the successful treatment of achalasia is also a risk factor for the development of adenocarcinoma [112, 113]. More recently, a prospective cohort study of 448 achalasia patients reported esophageal cancer in 3.3% with an annual incidence of 0.34 and, despite structured endoscopic surveillance, most

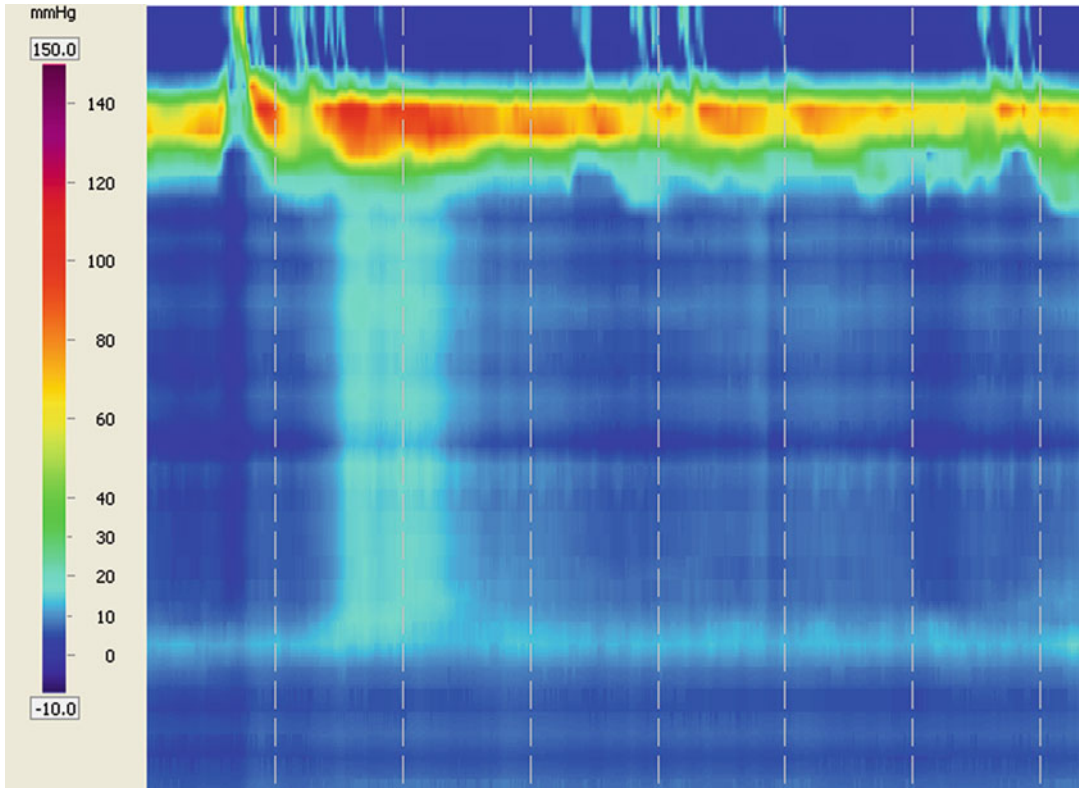

Fig. 20.3 Postoperative esophageal manometry after Heller myotomy

neoplastic lesions were detected at an advanced stage [114]. However, the overall life expectancy of patients with achalasia does not appear to be significantly decreased [115] and up to now, no cases of esophageal carcinoma have been reported in patients who had achalasia diagnosed as children [49]. Routine diagnostic tests are not recommended but patients developing recurrence or development of new symptoms should be investigated thoroughly.

Diffuse Esophageal Spasm and Nutcracker Esophagus

The incidence in children is not known and the literature is scarce, limited to case reports and small case series [25, 116]. In a retrospective study of 83 children with chest pain investigated by esophageal manometry and endoscopy, Glassman identified 4 patients with DES.

Diffuse esophageal spasm (DES) and nutcracker esophagus (NE), also known as hypertensive peristalsis, are benign and very rare, representing less than 10% of abnormal adult manometry diagnoses [117–119]. The etiology and pathogenesis of both conditions remain unknown [117]. Both DES and NE share symptoms of intermittent dysphagia and chest pain, with or without swallowing [16, 117, 120, 121]. Symptoms are usually experienced while eating or drinking [117, 120]. DES tends to present comorbidly in infants and children [122]. Infants may additionally present with apnea and brachycardia and younger children with aspiration pneumonia; symptoms of older children most resemble those observed in adults [123]. Because symptoms are intermittent, it is easy to distinguish these two conditions from more progressive diseases (i.e., achalasia and esophageal cancer) [120].

There is controversy regarding the diagnosis and treatment of DES and NE. Both can be diagnosed using manometry; however, only clinical symptoms are helpful to diagnose DES [120, 121]. pH monitoring can determine whether gastroesophageal reflux disease (GERD) is present which identifies need for anti-GERD therapies in treatment [124]. Barium esophagograms are often normal in DES and NE patients [120]. Possible treatment options for DES and NE include pharmaceutical interventions, surgery, and anti-GERD therapies [120]. Nitrates, calcium channel blockers, and botulinum toxin, all decrease LES pressure; though esophageal function is further complicated when the LES becomes too relaxed due to medications [124–126]. Anxiolytics may be used in DES patients diagnosed with anxiety or depression [120, 121]. The use of visceral analgesics (tricyclic antidepressants, serotonin reuptake inhibitors (SSRIs)) improved global symptoms scores in individuals with esophageal contraction abnormalities and DES. There is no evidence on the effect of visceral analgesics on NE. *Medical and surgical* approaches are intended to alleviate pain and decrease severity of symptoms [120]. Patients may undergo pneumatic dilation to relieve symptoms but the procedure is not consistently effective because the balloon can be difficult to place. Surgery is usually reserved for those patients with dysphagia and hypertensive sphincter. Selecting a treatment option should be used based on bolus transit and manometry findings [9].

Eosinophilic Esophagitis

Eosinophilic Esophagitis (EoE) is a condition in which the esophagus becomes inflamed due to infiltration by eosinophils. Detection of ≥15–21 eosinophils/HPF in squamous epithelium is postulated as qualifying criterion for EoE diagnosis though some controversy remains [127–131]. Eosinophilic infiltration is common in the GI tract in cases of eosinophilic gastroenteritis, allergic colitis, IBD, and GER [132, 133]. EoE is now appreciated as a condition separate from GERD and reflux esophagitis [128]. The exact incidence and prevalence of EoE remains unknown. Dohil et al. suggest a prevalence of 30 in 100,000 people [134]. It is postulated that 10% of children with GER, unresponsive to acid suppression therapies have EoE [128]. Overall, prevalence tends to be higher in individuals with a history of dysphagia and pre-diagnosed/existing cases of GERD, reflux esophagitis, and food impaction [130].

Etiopathogenesis of EoE remains unknown, though researchers suggest infiltration is related to food allergen hypersensitivity in non-idiopathic cases of EoE [128]. GERD, aperistalsis, dysphagia, and poor esophageal clearance are described as complications of EoE [128, 133, 135].

Mechanisms responsible for esophageal dysmotility associated with EoE are somewhat uncertain. Eosinophils contain substances that cause inflammation and may damage surrounding tissue when released [136]. A suggested trigger of inflammation in epithelial cells of the esophagus is eotaxin-3, an eosinophil chemoattractant [133]. This inflammation subsequently penetrates other cell layers. For instance, it may lead to inflammation of the epithelium which furthers dysmotility [130, 133]. Axonal necrosis is thought to result from eosinophilic degranulation creating damaged nerve tissue and consequently weak esophageal contractions. Increased eosinophil cationic protein (ECP) is shown to result from the co-culture of eosinophils and fibroblasts; ECP encourages abnormal fibroblast contractions [133, 136].

The following are symptoms of EoE in adults: dysphagia, food impaction and retrosternal pain with or without swallowing [129, 132, 133, 137]. Pediatric patients may additionally experience vomiting, abdominal pain, failure to thrive, food aversion, feeding difficulties, and other symptoms imitating GERD [128, 137, 138]. Normal frequency of reflux episodes, an allergic history, and poor response to acid suppression are also characteristic of EoE patients [128]. Due to symptom overlap between EoE and GERD, diagnosis must be confirmed by endoscopy [139, 140].

The diverse array of EoE symptoms speak to the variety of treatment options available to EoE patients: diet management, fluticasone inhalants,

Table 20.2 Summary of EoE treatment methods

Method of treatment	Advantages	Disadvantages	Success
Elimination diet	Still allows for some food intake by mouth	Requires careful review of all food choices for allergens	Must continue elimination for long-term resolution
		Does not always indicate specific food allergen at fault	
Elemental diet	Quick resolution of symptoms	Formulas not palatable	Compliance difficult for children
		Lower quality of life	
		Cost/insurance coverage	
Acid suppression	Can distinguish between EoE and GERD	May only treat GERD symptoms	Low success in children
Topical corticosteroids	Direct administration to areas with eosinophilia	May not fully penetrate eosinophilia	High rate of symptom relapse
Systemic corticosteroids	Variety of administration (swallowed or inhaled)	Low bioavailability	Satisfactory symptom resolution
Esophageal dilation	Highly effective when strictures are also present	Chest pain	Common treatment in adults
		Esophageal perforations	

acid suppression, topical and systemic corticosteroids, and esophageal dilation [138]. Esophageal dilation is a surgical treatment option more common in adults with strictures, but is also used for pediatric EoE [138, 141]. The primary, yet rare risks associated with esophageal dilation are wall disruption and perforation [138]. Patients may prefer this method of treatment after seeing no improvement with dietary or other medical intervention (Table 20.2).

Collagen Vascular Disorders

Among collagen vascular disorders, scleroderma is the most severe and commonly manifests in the gastrointestinal tract. Other collagen vascular disorders with esophageal manifestations are systemic lupus erythematosus (SLE), mixed connective tissue diseases (MCTDs), Sjörgen syndrome, and rheumatoid arthritis. Scleroderma consists of the hardening of tissues resulting from an autoimmune response. Systemic scleroderma (SSc) is characterized by collagen deposition in body tissue, especially the esophagus. SSc affects esophageal tissue and motility in 75–90% of adult cases [142, 143]; pediatric studies indicate lower prevalence [144, 145]. In a multi-center study, Foeldvari et al. reported 65% (88/135) of pediatric SSc patients presented GI tract involvement [146]. Of those 135 cases, under 50% ($n=63$) involved the esophagus [146].

A study of SSc revealed that childhood-onset is sometimes preceded by trauma in the area of deposition; a unique phenomenon compared to adult cases of scleroderma [145]. In the presence of SSc, esophageal manometry reveals an incompetent LES and low-amplitude smooth muscle contractions of the esophagus [142]. The retrograde movement of gastric contents, related to low LES pressure, exposes the esophagus to acidity, which can further compromise peristalsis. Frequent contact between acidic gastric contents and esophageal mucosa degrades tissue quality; esophagitis, bleeding, and strictures are other known complications. However, studies have noted that many who experience esophageal dysmotility secondary to SSc are sometimes asymptomatic [142, 147]. Aside from manometry, barium esophagram, 24-h ambulatory pH, and endoscopy are also used to diagnose the extent of esophageal disturbance secondary to SSc [142]. Autoimmune markers such as the anti-endonuclear antigens anti-ScL-70 and anti-centromere antibodies may be present.

Common symptoms of SSc with esophageal involvement are dysphagia, chest pain, weight loss, food impaction, and early satiety [142, 148]. Weber et al. reported reflux events in over 60% of pediatric patients with SSc [147]. Overall mortal-

ity for SSc with esophageal involvement is very rare; death is usually a consequence of multisystem involvement [145, 146]. Treatment of SSc primarily involves immunosuppressants (prednisone, methotrexate, mycophenolate mofetil, tumor necrosis factor-alpha, cyclophosphamide) [145, 149]. However, there is no specific treatment for SSc esophageal involvement. Gunawardena and McHugh suggest proton pump inhibitors, bulking agents, nutritional supplements, and antibiotics as additional treatment options [148, 150].

Chronic Idiopathic Intestinal Pseudo-Obstruction

Chronic idiopathic intestinal pseudo-obstruction (CIIP) is a rare primary disorder that involves the entire gastrointestinal tract. Esophageal involvement is very common [151, 152]. Non-idiopathic intestinal pseudo-obstruction is usually secondary to systemic, metabolic, genetic or mitochondrial etiologies. CIIP is often diagnosed during infancy and childhood and symptoms are usually both severe and frequent at onset. Patients with esophageal involvement present clinical symptoms of GER, dysphagia, nausea and vomiting, and weight loss [153]. Dysphagia, however, is usually a chief complaint when CIIP is secondary to another disorder.

Abnormal manometry findings include uncoordinated or low-amplitude contractions with swallowing [152, 154]; these findings are more common than aperistalsis. Decreased LES pressure is also a common finding. Pharmacologic treatment of CIIP is similar to that of other esophageal motility disorders, involving antiemetics, prokinetics, and antispasmodics.

Hirschsprung's Disease

Lack or poor formation of the enteric nervous system defines Hirschsprung's Disease (HD). Though primarily a disease of the small and large bowel, HD is occasionally associated with abnormal esophageal motility indicated by poor peristaltic wave propagation [155, 156]. Staiano et al. examined esophageal involvement in children with HD, in comparison to those with idiopathic megacolon and healthy controls with no esophageal or colonic diseases. Abnormalities in the amplitude and frequency of distal esophageal body contractions were significantly higher in HD patients than other groups [157]. The severity of HD in this group was unrelated to esophageal involvement.

Caustic Ingestion

Caustic ingestion of harmful substances is a common accident among young children, especially in developing countries. Common signs and symptoms include salivation, oropharyngeal burns, vomiting, bleeding, epigastric and retrosternal pain, and malignant transformation [158, 159]. A recent study examined the extent of esophageal damage in 94 toddlers (mean age 38 months) who experienced caustic ingestion [159]. Over 80% of cases had second to third degree esophageal burns which were highly associated with the development of esophageal strictures. Strictures occurred in 46 cases overall (49%) and were associated with development of dysphagia, contributing to poor nutrient intake, and dysmotility.

Esophageal manometry has revealed hypoperistalsis, usually with normal UES and LES function, in cases of caustic ingestion [160, 161].

Ineffective Esophageal Motility

Spechler and Castell defined ineffective esophageal motility (IEM) as having low or normal esophageal sphincter pressure, normal LES relaxation, and greater than 30% low-amplitude waves characterized by the following: wave amplitude <30 mmHg, peristalsis that does not travel the length of the esophagus, simultaneous contractions <30 mmHg, or aperistalsis [162]. Currently there is little data regarding IEM in the pediatric population. Literature suggests IEM as a predictor for GERD in adults, though the nature of the association is controversial. It has not yet been determined whether IEM is a rare primary disorder or merely secondary to increased acid exposure. IEM

hypocontractions and incomplete peristalsis of the esophagus may be diagnosed using manometry and/or high-frequency intraluminal ultrasound (HFIUS). Pioneered by Mittal [163], HFIUS provides real-time images of esophageal function which has proven especially beneficial during manometry. Using HFIUS, Kim et al. sought to examine esophageal muscle thickness in patients diagnosed with IEM [164]. Of 283 eligible patients, 46 (16%) had IEM, with just over half of those cases associated with GERD ($n=26$). The non-GERD IEM group had greater LES muscle thickness than the GERD group, supporting an association, but not causal relationship between the two. HFIUS, coupled with manometry, will likely become an increasingly utilized examination and diagnostic tool for gastroenterologists as more data is collected on IEM [162, 165].

Nonspecific Esophageal Motility Disorders

Nonspecific esophageal motility disorders (NEMDs) capture those cases with abnormal manometry, but without characteristics of an established disorder [118, 120, 166]. Criteria for NEMDs are ≥30% of wet swallows with nontransmitted or low-amplitude contractions or at least one of the following contraction abnormalities: triple-peaked contraction, retrograde contraction, prolonged duration peristaltic waves (>6 s), or isolated incomplete LES relaxation (>8 mmHg) [166]. Low-amplitude contractions are thought to be the most common manometric finding [167]. NEMDs differ from achalasia in that with swallows there are intermittent normal and abnormal peristaltic waves; while complete lack of peristalsis is characteristic of achalasia. Additionally, NEMDs involve low-amplitude waves, whereas DES typically involves high-amplitude pressure waves. Despite these notably distinct symptoms, it is suggested that NEMDs may be an early disease state of achalasia and DES [167]. Naftali et al. reported a minority of patients who progressed from NEMD to achalasia or DES diagnosed during a repeat manometry test.

Common symptoms are dysphagia, vomiting, chest and epigastric pain, and food impactions [118, 120, 124]. NEMDs are rarer than other primary esophageal motility disorders, such as achalasia and DES. In a cohort of 154 children with upper GI symptoms, 30 were not diagnosed with GER. Of those 30 patients, 43% ($n=13/30$) were found to have NEMDs, representing 8% of the entire cohort [168]. In addition to normal esophageal pH, many of those diagnosed demonstrated normal endoscopic appearance and esophageal histology; thus clinical findings (i.e., food impaction) are of great significance with regard to NEMDs [168]. Palliative treatment interventions for NEMDs usually involve antispasmodic agents, prokinetics, antacids (when GER is present), and/or PPIs [118, 120]. Improvement with these methods is variable; some patients may even improve without pharmacologic intervention [168].

References

1. Kahrilas PJ, et al. Upper esophageal spincter function during deglutition. Gastroenterology. 1988;95(1):52–62.
2. Sivarao DV, Goyal RK. Functional anatomy and physiology of the upper esophageal sphincter. Am J Med. 2000;108(Suppl 4a):27S–37.
3. Kuo B, Urma D. Esophagus—anatomy and development. In: Goyal RK, Shaker R, editors. Goyal and Shaker's GI Motility Online. New York: Nature Publishing Group; 2006.
4. Miller MJ, Kiatchoosakun P. Relationship between respiratory control and feeding in the developing infant. Semin Neonatol. 2004;9(3):221–7.
5. Holloway RH. Esophageal body motor response to reflux events: secondary peristalsis. Am J Med. 2000;108(Suppl 4a):20S–6.
6. Passaretti S, et al. Standards for oseophageal manometry. A position statement from the gruppo italinao di studio motilita apparato digerente (gismad). Dig Liver Dis. 2000;32(1):46–56.
7. Katz P, Menin R, Gideon R. Utility and standards in esophageal manometry. J Clin Gastroenterol. 2008;42(5):620–6.
8. Chitkara DK, Fortunado C, Nurko S. Prolonged monitoring of esophageal motor function in healthy children. J Pediatr Gastroenterol Nutr. 2004;38(2):192–7.
9. Tutuian R, et al. Symptom and function heterogenicity among patients with distal esophageal spam: studies using combined impedance-manometry. Am J Gastroenterol. 2006;101:464–9.
10. Gideon R. Manometry: technical issues. Gastrointest Endosc Clin N Am. 2005;15(2):243–55.
11. Bremner RM, et al. Normal esophageal body function: a study using ambulatory esophageal monometry. Am J Gastroenterol. 1998;93:183–7.

12. Pursnani K, et al. Comparison of lower oesophageal sphincter pressure measurement using circumferential vs unidirectional transducers. Neurogastroenterol Motil. 1997;9(3):177–80.
13. Russo S, et al. Videofluorography swallow study of patients with systemic sclerosis. Gastrointest Radiol. 2009;114:948–59.
14. Fordham LA. Imaging of the esophagus in children. Radiol Clin North Am. 2005;43(2):283–302.
15. Levine MS, Rubesine SE, Laufer I. Barium esophagography: a study for all seasons. Clin Gastroenterol Hepatol. 2008;6(1):11–25.
16. Summerton SL. Radiographic evaluation of esophageal function. Gastrointest Endosc Clin N Am. 2005;15(2):231–42.
17. Schima W, et al. Esophageal motor disorders: videofluoroscopic and manometric evaluation-prospective study in 88 symptomatic patients. Radiology. 1992;185:487–91.
18. Mariani G, et al. Radionucleotide gastroesophageal motor studies. J Nucl Med. 2004;15(2):231–42.
19. Iascone C, et al. Use of radiographic esophageal transit in the assessment of patients with symptoms of reflux and non-specific esophageal motor disorders. Dis Esophagus. 2004;17(3):218–22.
20. Imam H, et al. Bolus transit patterns in healthy subjects: a study using simultaneous impedance monitoring, videoesophagram, and esophageal manometry. Am J Physiol Gastrointest Liver Physiol. 2005;288(5):G1000–6.
21. Brednoord AJ, et al. Technology review: esophageal impedance monitoring. Am J Gastroenterol. 2007;102(1):187–94.
22. Bredneoord AJ, Smout AJ. Esophageal motility testing: impedance-based transit measurement and high-resolution manomotry. Gastroenterol Clin North Am. 2008;37(4):775–91.
23. Tutuian R, Castell DO. Esophageal function testing: role of combined multichannel intraluminal impedance and manometry. Gastrointest Endosc Clin N Am. 2005;4:265–75.
24. Savarino E, Tutuian R. Combined multichannel intraluminal impedance and manometry testing. Dig Liver Dis. 2008;40(3):167–73.
25. Glassman MS, et al. Spectrum of esophageal disorders in children with chest pain. Dig Dis Sci. 1992;37(5):663–6.
26. Prasse JE, Kikano GE. An overview of pediatric dysphagia. Clin Pediatr. 2009;48(3):247–51.
27. Lawal A, Shaker R. Esophageal dysphagia. Phys Med Rehabil Clin N Am. 2008;19:729–45.
28. Lefton-Greif MA. Pediatric dysphagia. Phys Med Rehabil Clin N Am. 2008;19(4):837–51.
29. Berezin S, et al. Chest pain of gastrointestinal origin. Arch Dis Child. 1988;63:1457–60.
30. Eslick GD. Classification, natural history, epidemiology, and risk factors of noncardiac chest pain. Dis Mon. 2008;54(9):593–603.
31. Webb WA. Management of foreign bodies of the upper gastrointestinal tract: update. Gastrointest Endosc. 1995;41(1):39–51.
32. Macpherson RI, et al. Esophageal foreign bodies in children: diagnosis, treatment, and complications. Am J Roentgenol. 1996;166:919–24.
33. Ghosh SK, et al. Oesophageal peristaltic transition zone defects: real but few and far between. Neurogastroenterol Motil. 2008;20(12):1283–90.
34. Sadowski DC, et al. Achalasia: incidence, prevalence and survival. A population-based study. Neurogastroenterol Motil. 2010;22(9):256–61.
35. Mayberry JF, Mayell MJ. Epidemiological study of achalasia in children. Gut. 1988;29(1):90–3.
36. Myers NA, Jolley SG, Taylor R. Achalasia of the cardia in children: a worldwide survey. J Pediatr Surg. 1994;29(10):1375–9.
37. Asch MJ, et al. Esophageal achalasia: diagnosis and cardiomyotomy in a newborn infant. J Pediatr Surg. 1974;9(6):911–2.
38. Kraichely RE, Farrugia G. Achalasia: physiology and etiopathogenesis. Dis Esophagus. 2006;19(4):213–23.
39. Goldblum JR, Rice TW, Richter JE. Histopathologic features in esophagomyotomy specimens from patients with achalasia. Gastroenterology. 1996;111(3):648–54.
40. Bohl J, et al. Childhood achalasia: a separate entity? Z Gastroenterol. 2007;45(12):1273–80.
41. Herbella FA, Oliveira DR, Del Grande JC. Are idiopathic and Chagasic achalasia two different diseases? Dig Dis Sci. 2004;49(3):353–60.
42. Wallace RA. Clinical audit of gastrointestinal conditions occurring among adults with Down syndrome attending a specialist clinic. J Intellect Dev Disabil. 2007;32(1):45–50.
43. Kelly JL, et al. Coexistent Hirschsprung's disease and esophageal achalasia in male siblings. J Pediatr Surg. 1997;32(12):1809–11.
44. Kimber J, et al. Allgrove or 4 "A" syndrome: an autosomal recessive syndrome causing multisystem neurological disease. J Neurol Neurosurg Psychiatry. 2003;74(5):654–7.
45. Brooks AS, et al. Homozygous nonsense mutations in KIAA1279 are associated with malformations of the central and enteric nervous systems. Am J Hum Genet. 2005;77(1):120–6.
46. Khelif K, et al. Achalasia of the cardia in Allgrove's (triple A) syndrome: histopathologic study of 10 cases. Am J Surg Pathol. 2003;27(5):667–72.
47. Moses PL, et al. Antineuronal antibodies in idiopathic achalasia and gastro-oesophageal reflux disease. Gut. 2003;52(5):629–36.
48. Pohl D, Tutuian R. Achalasia: an overview of diagnosis and treatment. J Gastrointestin Liver Dis. 2007;16(3):297–303.
49. Rosen R, Nurko S. Other motor disorders. In: Walker WA, editor. Pediatric gastrointestinal disease. Hamilton: BC Decker Inc; 2004. p. 424–62.
50. Dabritz J, et al. Achalasia mistaken as eating disorders: report of two children and review of the literature. Eur J Gastroenterol Hepatol. 2010;22(7):775–8.

51. Berquist WE, et al. Achalasia: diagnosis, management, and clinical course in 16 children. Pediatrics. 1983;71(5):798–805.
52. Parkman HP, et al. Optimal evaluation of patients with nonobstructive esophageal dysphagia. Manometry, scintigraphy, or videoesophagography? Dig Dis Sci. 1996;41(7):1355–68.
53. Blam ME, et al. Achalasia: a disease of varied and subtle symptoms that do not correlate with radiographic findings. Am J Gastroenterol. 2002;97(8):1916–23.
54. Eckardt AJ, Eckardt VF. Current clinical approach to achalasia. World J Gastroenterol. 2009;15(32):3969–75.
55. Liu W, et al. The pathogenesis of pseudoachalasia: a clinicopathologic study of 13 cases of a rare entity. Am J Surg Pathol. 2002;26(6):784–8.
56. Castell JA, Gideon MR, Castell DO. Esophageal manometry. In: Schuster MM, editor. Atlas of gastrointestinal motilily in health and disease. Hamilton: BC Decker; 2002. p. 69–85.
57. Pandolfino JE, Kahrilas PJ. AGA technical review on the clinical use of esophageal manometry. Gastroenterology. 2005;128(1):209–24.
58. Pandolfino JE, Kwiatek MA, Nealis T. Achalasia: a new clinically relevant classification by high resolution manometry. Gastroenterology. 2008;135:1526–33.
59. Williams VA, Peters JH. Achalasia of the esophagus: a surgical disease. J Am Coll Surg. 2009;208(1):151–62.
60. Jung C, et al. Treatments for pediatric achalasia: Heller myotomy or pneumatic dilatation? Gastroenterol Clin Biol. 2010;34(3):202–8.
61. Vaezi MF, Richter JE. Current therapies for achalasia: comparison and efficacy. J Clin Gastroenterol. 1998;27(1):21–35.
62. Maksimak M, Perlmutter DH, Winter HS. The use of nifedipine for the treatment of achalasia in children. J Pediatr Gastroenterol Nutr. 1986;5(6):883–6.
63. Efrati Y, et al. Radionuclide esophageal emptying and long-acting nitrates (Nitroderm) in childhood achalasia. J Pediatr Gastroenterol Nutr. 1996;23(3):312–5.
64. Smith H, et al. The use of nifedipine for treatment of achalasia in children. J Pediatr Gastroenterol Nutr. 1988;7(1):146.
65. Pasricha PJ, et al. Treatment of achalasia with intrasphincteric injection of botulinum toxin. A pilot trial. Ann Intern Med. 1994;121(8):590–1.
66. Pasricha PJ, et al. Intrasphincteric botulinum toxin for the treatment of achalasia. N Engl J Med. 1995;332(12):774–8.
67. Pasricha PJ, et al. Botulinum toxin for achalasia: long-term outcome and predictors of response. Gastroenterology. 1996;110(5):1410–5.
68. Khoshoo V, LaGarde DC, Udall Jr JN. Intrasphincteric injection of Botulinum toxin for treating achalasia in children. J Pediatr Gastroenterol Nutr. 1997;24(4):439–41.
69. Walton JM, Tougas G. Botulinum toxin use in pediatric esophageal achalasia: a case report. J Pediatr Surg. 1997;32(6):916–7.
70. Hurwitz M, et al. Evaluation of the use of botulinum toxin in children with achalasia. J Pediatr Gastroenterol Nutr. 2000;30(5):509–14.
71. Ip KS, et al. Botulinum toxin for achalasia in children. J Gastroenterol Hepatol. 2000;15(10):1100–4.
72. Katzka DA, Castell DO. Use of botulinum toxin as a diagnostic/therapeutic trial to help clarify an indication for definitive therapy in patients with achalasia. Am J Gastroenterol. 1999;94(3):637–42.
73. Smith CD, et al. Endoscopic therapy for achalasia before Heller myotomy results in worse outcomes than Heller myotomy alone. Ann Surg. 2006;243(5):579–84. discussion 584–6.
74. Vantrappen G, Janssens J. To dilate or to operate? That is the question. Gut. 1983;24(11):1013–9.
75. Campos GM, et al. Endoscopic and surgical treatments for achalasia: a systematic review and meta-analysis. Ann Surg. 2009;249(1):45–57.
76. Kadakia SC, Wong RK. Pneumatic balloon dilation for esophageal achalasia. Gastrointest Endosc Clin N Am. 2001;11(2):325–46. vii.
77. West RL, et al. Long term results of pneumatic dilation in achalasia followed for more than 5 years. Am J Gastroenterol. 2002;97(6):1346–51.
78. Chan KC, et al. Short-term and long-term results of endoscopic balloon dilation for achalasia: 12 years' experience. Endoscopy. 2004;36(8):690–4.
79. Karamanolis G, et al. Long-term outcome of pneumatic dilation in the treatment of achalasia. Am J Gastroenterol. 2005;100(2):270–4.
80. Zhao JG, et al. Long-term safety and outcome of a temporary self-expanding metallic stent for achalasia: a prospective study with a 13-year single-center experience. Eur Radiol. 2009;19(8):1973–80.
81. Ali A, Pellegrini CA. Laparoscopic myotomy: technique and efficacy in treating achalasia. Gastrointest Endosc Clin N Am. 2001;11(2):347–58. vii.
82. Patti MG, et al. Comparison of thoracoscopic and laparoscopic Heller myotomy for achalasia. J Gastrointest Surg. 1998;2(6):561–6.
83. Stewart KC, et al. Thoracoscopic versus laparoscopic modified Heller Myotomy for achalasia: efficacy and safety in 87 patients. J Am Coll Surg. 1999;189(2):164–9. discussion 169–70.
84. Spechler SJ. AGA technical review on treatment of patients with dysphagia caused by benign disorders of the distal esophagus. Gastroenterology. 1999;117(1):233–54.
85. Malthaner RA, et al. Long-term results in surgically managed esophageal achalasia. Ann Thorac Surg. 1994;58(5):1343–6. discussion 1346–7.
86. Jara FM, et al. Long-term results of esophagomyotomy for achalasia of esophagus. Arch Surg. 1979;114(8):935–6.
87. Csendes A, et al. Late results of a prospective randomised study comparing forceful dilatation and oesophagomyotomy in patients with achalasia. Gut. 1989;30(3):299–304.
88. Kostic S, et al. Pneumatic dilatation or laparoscopic cardiomyotomy in the management of newly diag-

nosed idiopathic achalasia. Results of a randomized controlled trial. World J Surg. 2007;31(3):470–8.
89. Csendes A, et al. Very late results of esophagomyotomy for patients with achalasia: clinical, endoscopic, histologic, manometric, and acid reflux studies in 67 patients for a mean follow-up of 190 months. Ann Surg. 2006;243(2):196–203.
90. Richards WO, et al. Heller myotomy versus Heller myotomy with Dor fundoplication for achalasia: a prospective randomized double-blind clinical trial. Ann Surg. 2004;240(3):405–12. discussion 412–5.
91. Zerbib F, et al. Repeated pneumatic dilations as long-term maintenance therapy for esophageal achalasia. Am J Gastroenterol. 2006;101(4):692–7.
92. Vela MF, et al. The long-term efficacy of pneumatic dilatation and Heller myotomy for the treatment of achalasia. Clin Gastroenterol Hepatol. 2006;4(5):580–7.
93. Zaninotto G, et al. Four hundred laparoscopic myotomies for esophageal achalasia: a single centre experience. Ann Surg. 2008;248(6):986–93.
94. Jeansonne LO, et al. Ten-year follow-up of laparoscopic Heller myotomy for achalasia shows durability. Surg Endosc. 2007;21(9):1498–502.
95. Lopushinsky SR, Urbach DR. Pneumatic dilatation and surgical myotomy for achalasia. JAMA. 2006;296(18):2227–33.
96. Askegard-Giesmann JR, et al. Minimally invasive Heller's myotomy in children: safe and effective. J Pediatr Surg. 2009;44(5):909–11.
97. Mehra M, et al. Laparoscopic and thoracoscopic esophagomyotomy for children with achalasia. J Pediatr Gastroenterol Nutr. 2001;33(4):466–71.
98. Rothenberg SS, et al. Evaluation of minimally invasive approaches to achalasia in children. J Pediatr Surg. 2001;36(5):808–10.
99. Patti MG, et al. Laparoscopic Heller myotomy and Dor fundoplication for esophageal achalasia in children. J Pediatr Surg. 2001;36(8):1248–51.
100. Litle VR. Laparoscopic Heller myotomy for achalasia: a review of the controversies. Ann Thorac Surg. 2008;85(2):S743–6.
101. Tannuri AC, et al. Laparoscopic extended cardiomyotomy in children: an effective procedure for the treatment of esophageal achalasia. J Pediatr Surg. 2010;45(7):1463–6.
102. Corda L, et al. Laparoscopic oesophageal cardiomyotomy without fundoplication in children with achalasia: a 10-year experience: a retrospective review of the results of laparoscopic oesophageal cardiomyotomy without an anti-reflux procedure in children with achalasia. Surg Endosc. 2010;24(1):40–4.
103. Adikibi BT, et al. Intraoperative upper GI endoscopy ensures an adequate laparoscopic Heller's myotomy. J Laparoendosc Adv Surg Tech A. 2009;19(5):687–9.
104. Jafri M, et al. Intraoperative manometry during laparoscopic Heller myotomy improves outcome in pediatric achalasia. J Pediatr Surg. 2008;43(1):66–70. discussion 70.
105. Tovar JA, et al. Esophageal function in achalasia: preoperative and postoperative manometric studies. J Pediatr Surg. 1998;33(6):834–8.
106. Pensabene L, Nurko S. Approach to the child who has persistent dysphagia after surgical treatment for esophageal achalasia. J Pediatr Gastroenterol Nutr. 2008;47(1):92–7.
107. Zaninotto G, et al. Etiology, diagnosis, and treatment of failures after laparoscopic Heller myotomy for achalasia. Ann Surg. 2002;235(2):186–92.
108. Zaninotto G, et al. Treatment of esophageal achalasia with laparoscopic Heller myotomy and Dor partial anterior fundoplication: prospective evaluation of 100 consecutive patients. J Gastrointest Surg. 2000;4(3):282–9.
109. Zaninotto G, et al. Minimally invasive surgery for esophageal achalasia. J Laparoendosc Adv Surg Tech A. 2001;11(6):351–9.
110. Sandler RS, et al. The risk of esophageal cancer in patients with achalasia. A population-based study. JAMA. 1995;274(17):1359–62.
111. Dunaway PM, Wong RK. Risk and surveillance intervals for squamous cell carcinoma in achalasia. Gastrointest Endosc Clin N Am. 2001;11(2):425–34. ix.
112. Zendehdel K, et al. Risk of esophageal adenocarcinoma in achalasia patients, a retrospective cohort study in Sweden. Am J Gastroenterol. 2011;106(1):57–61.
113. Brucher BL, et al. Achalasia and esophageal cancer: incidence, prevalence, and prognosis. World J Surg. 2001;25(6):745–9.
114. Leeuwenburgh I, et al. Long-term esophageal cancer risk in patients with primary achalasia: a prospective study. Am J Gastroenterol. 2010;105(10):2144–9.
115. Eckardt VF, Hoischen T, Bernhard G. Life expectancy, complications, and causes of death in patients with achalasia: results of a 33-year follow-up investigation. Eur J Gastroenterol Hepatol. 2008;20(10):956–60.
116. Fontan JP, et al. Esophageal spasm associated with apnea and bradycardia in an infant. Pediatrics. 1984;73(1):52–5.
117. Sperandio M, et al. Diffuse esophageal spasm: not diffuse but distal esophageal spasm (des). Dig Dis Sci. 2003;48(7):1380–4.
118. Smout AJ. Advances in esophageal motor disorder. Curr Opin Gastroenterol. 2008;24:285–9.
119. Tutuian R, Castell DO. Review article: oesophageal spasm-diagnosis and management. Aliment Pharmacol Ther. 2006;23(10):1393–402.
120. Adler DG, Romero Y. Primary esophageal motility disorders. Mayo Clin Proc. 2001;76(2):195–200.
121. Grubel C, et al. Diffuse esophageal spasm. Am J Gastroenterol. 2008;103:450–7.
122. Rosen J, et al. Diffuse esophageal spasm in children (abstract). J Pediatr Gastroenterol Nutr. 2005;41(4):561.
123. Hussain SZ, Di Lorenzo C. Motility disorders. Diagnosis and treatment for the pediatric patient. Pediatr Clin North Am. 2002;49(1):27–51.

124. Herbella FAM, et al. Primary versus secondary esophageal motility disorders: diagnosis and implications for treatment. J Laparoendosc Adv Surg Tech A. 2009;19(2):195–8.
125. Allen ML, DiMarino AJ. Manometric diagnosis of diffuse esophageal spasm. Dig Dis Sci. 1996;41(7):1346–9.
126. Lacy BE, Weiser K. Esophageal motility disorders: medical therapy. J Clin Gastroenterol. 2008;2(5):652–8.
127. Putnam PE. Eosinophilic esophagitis in children: clinical manifestations. Gastroenterol Clin North Am. 2008;37:369–81.
128. Markowitz JE, Liacouras CA. Eosinophilic esophagitis. Gastroenterol Clin North Am. 2003;32(2003):949–66.
129. Nurko S, Rosen R, Furuta GT. Esophageal dysmotility in children with esoinophilic esophagitis: a study using prolonged esophageal manometery. Am J Gastroenterol. 2009;104:3050–7.
130. Rothenberg ME. Biology and treatment of eosinophilic esophagitis. Gastroenterology. 2009;137:1238–49.
131. Orenstein SR, et al. The spectrum of pediatric eosinophilic esophagitis beyond infancy: a clinical series of 30 children. Am J Gastroenterol. 2000;95:1422–30.
132. Xu X, et al. Mast cells and eosinophils have a potential profibrogenic role in Crohn Disease. Scand J Gastroenterol. 2004;39:440–7.
133. Nurko S, Rosen R. Esophageal dysmotility in patients who have eosinophilic esophagitis. Gastrointest Endosc Clin N Am. 2008;18(1):73–89. ix.
134. Dohil R, et al. Oral viscuous budesonide is effective in children with eosinophilic esophagits in a randomized, placedbo-controlled trail. Gastroenterology. 2010;139:418–29.
135. Hejazi RA, et al. Disturbances of esophageal motility in esoinophilic esophagitis: a case series. Dysphagia. 2010;25:231–7.
136. Zagai U, et al. The effect of eosinophils on collagen gel contraction and implications for tissue remodeling. Clin Exp Immunol. 2004;135:427–33.
137. Straumann A. The natural history and complications fo esoinophilic esophagits. Gastrointest Endosc Clin N Am. 2008;18(1):99–118.
138. Shah A, Hirano I. Treatment of esosinophilic esophagitis: drugs, diet, or dilation? Curr Gastroenterol Rep. 2007;9(3):181–8.
139. Putnam PE. Evaluation of the child who has eosinophilic esophagitis. Immunol Allergy Clin North Am. 2009;29:1–10.
140. Liacouras CA. Eosinophilic esophagitis. Curr Opin Pediatr. 2004;16(5):560–6.
141. Aceves SS, Furuta GT, Spechler SJ. Integrated approach to treatment of children and adults with eosinophilic esophagitis. Gastrointest Endosc Clin N Am. 2008;18:195–217.
142. Ntoumazios SK, et al. Esophageal involvement in scleroderma: gastroesophageal reflux, the common problem. Semin Arthritis Rheum. 2006;36:173–81.
143. Duraj V, et al. Esophageal damages in systemic scleroderma (abstract). Med Arch. 2007;61(1):47–8.
144. Vancheeswaran R, et al. Childhood-onset secleroderma: is it different from adult-onset disease? Arthritis Rheum. 1996;39(6):1041–9.
145. Denton CP, Derrett-Smith EC. Juvenile-onset systemic sclerosis: children are not small adults. Rheumatology. 2008;48:96–7.
146. Foeldvari I, et al. Favourable outcome in 135 children with juvenile systemic sclerosis: results of a multinational survey. Rheumatology. 2000;39:556–9.
147. Weber P, et al. Twenty-four hour intraesophageal pH monitoring in children and adolescents with scleroderma and mixed connective tissue disease (abstract). J Rheumatol. 2000;27(11):2692–5.
148. Gunawardena H, McHugh N. Features and recommended treatment of systemic sclerosis. Prescriber. 2008;19(18):56–65.
149. Hedrich CM, et al. Presentations and treatment of childhood scleroderma: Localized scleroderma, eosinophilic fasciitis, systemic sclerosis, and graft-versus-host disease. Clin Pediatr (Phila). 2011;50(7):604–14.
150. Domsic R, Fasanella K, Bielefeldt K. Gastrointestinal manifestations of systemic sclerosis. Dig Dis Sci. 2008;53:1163–74.
151. Antonucci A, et al. Chronic intestinal pseudo-obstruction. World J Gastroenterol. 2008;14(19):2953–61.
152. Boige N, et al. Manometrical evaluation in visceral neuropathies in children. J Pediatr Gastroenterol Nutr. 1994;19(1):71–7.
153. Panganamamula KV, Parkman HP. Chronic pseudo-obstruction. Curr Treat Options Gastroenterol. 2005;8:3–11.
154. Byrne WJ, et al. Chronic idiopathic intestinal pseudo-obstruction syndrome in children—clinical characteristics and prognosis. J Pediatr. 1977;90(4):585–9.
155. de Lorijn F, Boechxstaens GE, Benninga MA. Symptomatology, pathophysiology, diagnostic work-up, and treatment of Hirschsprung disease in infancy and childhood. Curr Gastroenterol Rep. 2007;9:245–53.
156. Faure C, et al. Duodenal and esophageal manometry in total colonic aganglionosis. J Pediatr Gastroenterol Nutr. 1994;18(2):193–9.
157. Staiano A, et al. Esophageal motility in children with Hirschsprung's disease. Am J Dis Child. 1991;145(3):310–3.
158. Karagiozoglou-Lampoudi T, et al. Conservative management of caustic substance ingestion in a pediatric department setting, short-term and long-term outcome. Dis Esophagus. 2010;2(42):86–91.
159. Sanchez-Ramirez CA, et al. Caustic ingestion and oesophageal damage in children: clinical spectrum and feeding practices. J Pediatr Child Health. 2011;47(6):378–80.

160. Dantas RO, Mamede RC. Esophageal motility in patients with esophageal caustic injury. Am J Gastroenterol. 1996;91(6):1157–61.
161. Genc A, Mutaf O. Esophageal motility changes in acute and late periods of caustic esophageal burns and their relation to prognosis in children. J Pediatr Surg. 2002;37(11):1526–8.
162. Spechler SJ, Castell D. Classification of oesophageal motility abnormalities. Gut. 2001;49:145–51.
163. Mittal KR. Motor and sensory function of the esophagus: revelations through ultrasound imaging. J Clin Gastroenterol. 2005;39 Suppl 2:S42–8.
164. Kim JH, et al. Is all ineffective esophageal motility the same? A clinical and high-frequency intraluminal US study. Gastrointest Endosc. 2008;68:422–31.
165. Botoman VA. How effective are we at understanding ineffective esophageal motility? Gastrointest Endosc. 2008;68(3):432–3.
166. Leite LP, et al. Ineffective esophageal motility (IEM): the primary finding in patients with nonspecific esophageal motility disorder. Dig Dis Sci. 1997;42(9):1859–65.
167. Naftali T, et al. Nonspecific esophageal motility disorders may be an early stage of a specific disorder, particularly achalasia. Dis Esophagus. 2009;22:611–5.
168. Rosario JA, et al. Nonspecific esophageal motility disorders in children without gastroesophageal reflux. J Pediatr Gastroenterol Nutr. 1999;28(5):480–5.