



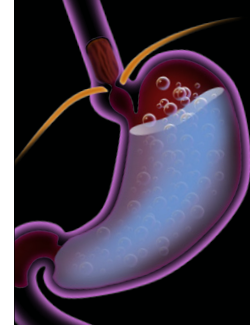
A GLOBAL, EVIDENCE-BASED CONSENSUS ON THE DEFINITION OF GASTROESOPHAGEAL REFLUX DISEASE IN THE PEDIATRIC POPULATION

A variety of health care providers frequently encounter gastroesophageal reflux disease (GERD) in the pediatric age group, which includes infants, children, and adolescents. Yet, the variety of definitions of GERD and inconsistent nomenclature contributes to wide variations in patient management, as well as confusion in interpreting clinical trial literature and employing the available diagnostic tests.

GERD CONSENSUS DEFINITION SUMMARY FACULTY:

Benjamin D. Gold, MD and Philip Sherman, MD

SCIENCE WRITER: Paul Sinclair (INSINC Consulting Inc. Guelph, Ontario, Canada)



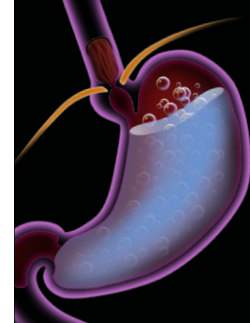
This summary of the Evidence-Based Consensus on the Definition of Gastroesophageal Reflux Disease in the Pediatric Population – based on the Montreal Definition of GERD¹ (i.e., in adults) and the process used to develop it – was developed to provide pediatric health care providers, general pediatricians and subspecialists with a uniform definition of GERD that could be employed in these age groups. These consensus statements are intended to be used for the development of future clinical practice guidelines and as a basis for clinical trials. This document is different from the revised GERD clinical practice guidelines² which provide management recommendations.

GENERAL CONCEPTS

A patient-centered definition – based on symptoms becoming sufficiently troublesome so as to have a measurable impact on the quality of life of the patient – was used with certain caveats. These important caveats make the Global Consensus Definition quite distinct from the adult-based Montreal Definition of GERD.

Although the verbal child can communicate pain, descriptions of the intensity, location, and severity may be unreliable until at least eight years of age, and in some children even later. Younger children are generally more suggestible; so queries from parents or clinicians regarding a specific symptom may be biased toward affirmative responses. Thus, in younger patients, reliance on a parent or caregiver is generally necessary, although symptom reporting by these surrogates may decrease the validity of diagnosis. Validated symptom questionnaires related to specific age groups are needed for achieving reliability in the child at any age, as well as for diagnostic and evaluative validity related to symptom reporting in pediatrics.

Gastroesophageal reflux (GER) refers to the passage of gastric contents into the esophagus or oropharynx; with or without vomiting. GER can be a daily, normal physiological occurrence in infants, children and adolescents. Most episodes of GER in healthy individuals last <3 minutes, occur in the postprandial period, and cause few or no troublesome symptoms. Regurgitation or spitting up is the most obviously visible symptom to caregivers and pediatricians, particularly in the very young child, occurring daily in about 50% of infants <3 months of age. Regurgitation resolves spontaneously in most healthy infants by 12-14 months of age^{3,4,5}. Gastroesophageal reflux disease (GERD) refers to the symptoms and complications that may develop secondary to persistent GER. Differentiating GER from GERD is critical for the clinician in order to avoid unnecessary diagnostic testing and exposure to medications.



DEFINITIONS RELATED TO GERD IN PEDIATRICS

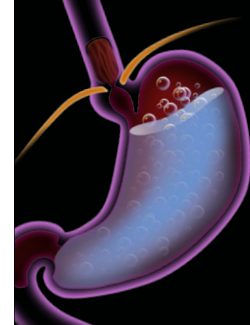
GERD:	Reflux of gastric contents causes troublesome symptoms and/or complications
Troublesome symptoms:	When GER symptoms have an adverse effect on the well-being of the pediatric patient
Troublesome dysphagia:	When older children and adolescents need to alter eating patterns or report food impaction
Regurgitation:	The passage of refluxed contents into the pharynx, mouth, or from the mouth
Heartburn:	In older children and adolescents, a burning sensation in the retrosternal area
Non-erosive reflux disease:	The presence of troublesome symptoms caused by the reflux of gastric contents and by the absence of mucosal breaks during endoscopy
Reflux esophagitis:	Endoscopically visible breaks of the distal esophageal mucosa
Reflux stricture:	A persistent luminal narrowing of the esophagus caused by GERD
Endoscopically Suspected Esophageal Metaplasia (ESEM):	Endoscopic findings consistent with Barrett's esophagus that await histological confirmation

SYMPTOMS

- **Symptoms of GERD Vary by Age**

In infants, there is uncertainty as to whether regurgitation, food refusal, and crying represent acid reflux, presenting a problem in symptom-based diagnosis. For 1 to 11 year olds, there are relatively few data on presenting symptoms. Toddlers and young children (1–6 years) tend to present with food refusal, regurgitation, and abdominal pain. In contrast, the predominant symptoms in children 6–17 years are regurgitation or vomiting, cough and epigastric pain, or heartburn. The older the child, the more heartburn and regurgitation become predominant presenting symptoms, as in adults.

- **Pediatric population-based studies of reflux symptoms are insufficient and are a priority for further research.**



Troublesome Symptoms

To be defined as GERD, reflux symptoms must be troublesome to the infant, child, or adolescent, and not simply be troublesome to the caregiver. In addition, patients may be asymptomatic or unable to report “troublesome” symptoms (e.g., infants or neurologically impaired children), but still have complications of reflux and thereby meet the criteria for the definition of GERD.

- **Otherwise healthy newborns (age: 1 – 30 days) and infants (age: >30 days to < 1 year) with reflux symptoms that are not troublesome and are without complications should not be diagnosed with GERD.**
- Up to 70 % of completely healthy newborns and infants have regurgitation that is physiologic, resolving without intervention in 95 % of the individuals by 12–14 months of age. Crying is also common in infants; the issue of unexplained crying is complicated and must also incorporate patterns and characteristics of crying and parental responses to crying. Consequently, in infants, normal regurgitation and normal crying, or abnormal crying due to a cause other than GERD, may be mistaken for GERD.
- **Reflux symptoms that are not troublesome**
 - in toddlers and children (age: 1–10 years), or
 - in adolescents (age: 11–17 years)**should not be diagnosed as GERD.**
- **In clinical practice, adolescents are generally able to describe specific GERD symptoms and to determine whether those symptoms are troublesome.**

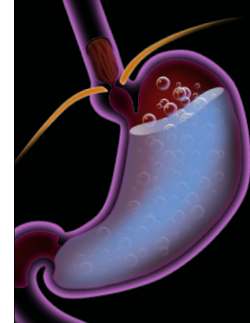
Heartburn

- GER (i.e. reflux) in older children and adolescents is the most common cause of heartburn.
- Heartburn in older children and adolescents can have a number of non-reflux-related causes.

Regurgitation vs. Rumination and Vomiting

- **Regurgitation is a characteristic symptom of reflux in infants, but is neither necessary nor sufficient for a diagnosis of GERD, because it is not sensitive or specific.**

The specificity of regurgitation for diagnosing GERD is hampered by the frequency of its occurrence in normal infants, and by difficulties in distinguishing it from vomiting as well as a myriad of conditions that cause vomiting in infants.



- **When assessing GERD, rumination should be distinguished from regurgitation.**

Rumination refers to the effortless regurgitation of recently ingested food into the mouth with subsequent mastication and re-swallowing of food. Rumination is common in infants and children with neurological impairment, but it can also occur in subjects without obvious neurologic deficits. Rumination is increasingly recognized among older children, especially adolescent females, and is considered by some to lie within the spectrum of eating disorders.

- **Bilious vomiting should not be diagnosed as GERD**

Bilious vomiting is an alarm signal that warrants further investigations to rule out anatomic abnormalities, such as intestinal malrotation, or acute illnesses causing intestinal obstruction.

“Typical Reflux Syndrome”

- **The Typical Reflux Syndrome is characterized by heartburn with or without regurgitation.**
- **“Typical Reflux Syndrome” cannot be diagnosed in infants and children who lack the cognitive ability to reliably report symptoms.**
- **Heartburn and regurgitation in older children and adolescents, with cognitive development sufficient to reliably report symptoms, are characteristic.**
- **In neurologically intact adolescents, the Typical Reflux Syndrome can be diagnosed on the basis of the characteristic symptoms, without additional diagnostic testing.**

Other Symptoms

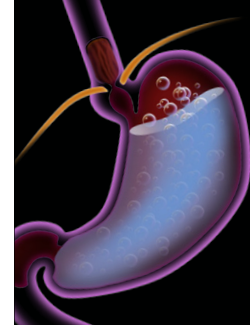
- **GERD may be associated with sleep disturbances in newborns and infants, toddlers and children, and adolescents.**

Although GERD may be associated with sleep disturbance, a cause-and-effect relationship and the direction of any causality remain to be proved.

- **Symptoms of GERD, particularly in infants, may be indistinguishable from those of food allergy.**

In infants, GERD and milk protein (cow or soy) allergy may both manifest as regurgitation or as vomiting; crying, fussing, or irritability related to food intake; or as failure to thrive. Distinguishing the two on clinical presentations alone is difficult, thus, instituting a protein hydrolysate diet may resolve symptoms that are suggestive of GERD.

- **Epigastric pain in older children and adolescents can be a major symptom of GERD.**
- **Physical exercise in toddlers and children, and in adolescents, may induce troublesome symptoms of GERD in individuals who have no or minimal symptoms at other times (exercise-induced reflux).**



Exercise-induced GERD is well recognized in adults, and may be related to strain-induced reflux that is caused by increases in intra-abdominal pressure. Evidence for the existence of exercise-induced GERD in children is sparse and primarily anecdotal.

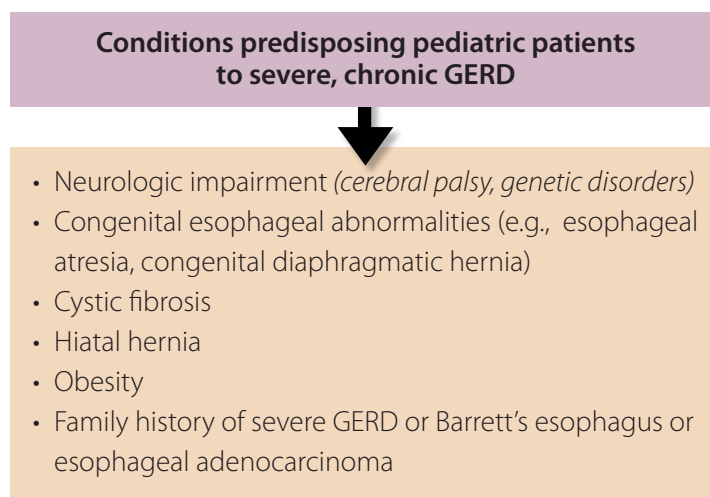


FIGURE 1: *Conditions predisposing to severe, chronic GERD.*
Adapted from Sherman, et al'.

SYNDROMES WITH ESOPHAGEAL INJURY

- **In pediatric patients, esophageal complications of GERD are reflux esophagitis, hemorrhage, stricture, Barrett's esophagus, and, rarely, adenocarcinoma.**

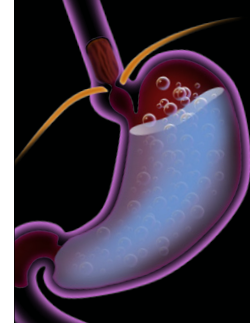
Erosive esophagitis is more prevalent and severe in pediatric-age patients with underlying GERD-promoting disorders, such as neurologic impairment or esophageal atresia. In addition, stricture, Barrett's esophagus, and adenocarcinoma are also more common in this group of patients with GERD-promoting disorders.

- **Insufficient data exist for recommending histology as a tool to diagnose or to exclude GERD in children.**
- **A primary role for esophageal histology is to rule out other conditions in the differential diagnosis.**

The main role for esophageal histology in clinical practice is to either diagnose or rule out other causes of esophagitis that have specific histologic findings, including: eosinophilic esophagitis, Barrett's esophagus, Crohn's disease, infection, and graft-versus-host disease.

- **When reflux-related erosions are present during endoscopy, the grade should be described according to one of the recognized classifications of erosive esophagitis.**

The presence and severity of reflux esophagitis determined at diagnostic upper endoscopy supports clinical management decision-making and assessment of treatment outcomes. The endoscopic classification of Hetzel and Dent and the Los Angeles classification have been the commonly used ones in pediatric studies.



- In otherwise healthy pediatric patients, reflux esophagitis may not be chronic or recurrent after treatment.
- Reflux esophagitis in pediatric patients with chronic neurologic impairment, repaired esophageal atresia, hiatal hernia, or chronic respiratory diseases is usually chronic and recurrent.
- The characteristic symptom of a stricture in pediatric patients is persistent troublesome dysphagia.
- Dysphagia in older children and adolescents is a perceived impairment of the passage of food from the mouth into the stomach.

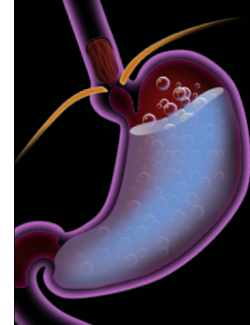
In a minority of pediatric patients, GERD leads to the narrowing of the esophageal lumen causing persistent dysphagia. Persistent, progressive, or troublesome dysphagia is a warning symptom for esophageal stricture warranting additional investigation. Endoscopy with esophageal biopsies is indicated to distinguish it from the other causes of esophageal narrowing, particularly eosinophilic esophagitis which also presents with dysphagia.

- In the pediatric age group, Barrett's esophagus mainly occurs in individuals with hiatal hernia, and in those with certain underlying disorders that predispose to severe GERD.
- Documentation of esophogastric landmarks together with multiple biopsies are necessary to characterize Endoscopically Suspected Esophageal Metaplasia (ESEM).
- When biopsies from Endoscopically Suspected Esophageal Metaplasia (ESEM) show columnar epithelium, it should be called Barrett's esophagus and the presence or absence of the intestinal metaplasia specified.

The term "endoscopically suspected esophageal metaplasia" acknowledges that the endoscopic appearance may not be diagnostic and requires histologic confirmation. Even a rigorous biopsy protocol for the detection of intestinal-type metaplasia has imperfect sensitivity, and additionally, there is now some doubt whether only mucosa containing goblet cell metaplasia is premalignant.

EXTRAESOPHAGEAL SYNDROMES

- Sandifer's syndrome (torticollis) is a specific manifestation of GERD in pediatric patients.
- There is insufficient evidence that GERD causes or exacerbates sinusitis, pulmonary fibrosis, pharyngitis, and serous otitis media in the pediatric population.



- **Chronic cough, chronic laryngitis, hoarseness, and asthma may be associated with GERD.**
- **In the absence of heartburn or regurgitation, unexplained asthma is less likely to be related to GERD.**
- **Chronic cough, chronic laryngitis, hoarseness, and asthma are multifactorial disease processes and acid reflux can be an aggravating cofactor.**
- **GERD may cause dental erosions in pediatric patients.**
- **At present, no single diagnostic test can prove or exclude extraesophageal presentations of GERD in pediatrics.**

Clinicians employ laryngoscopy, bronchoscopy and alveolar lavage, endoscopy, esophageal and laryngeal biopsies, pH monitoring in the hypopharynx, and multi-channel intraluminal impedance monitoring to diagnose GERD in pediatric patients presenting with extraesophageal symptoms. However, none of these tools independently establishes the diagnosis of GERD with extraesophageal symptoms.

Neonates and Infants

- **There is an association between GERD and bronchopulmonary dysplasia in neonates and infants, but the cause-and-effect relationship is uncertain.**

As most studies have been cross sectional or case – control in design, it remains to be determined whether GERD is, in fact, a causal factor predisposing infants to the development of bronchopulmonary dysplasia (BPD), propagates the condition, or BPD in fact causes GERD. For this reason, the above statement is located under “possible associations” in the Figure 2.

- **In premature infants, a relationship between GER (i.e. reflux) and pathologic apnea and/or bradycardia has not been established.**

Despite a lack of convincing evidence, if pathological apnea occurs in the face of pre-existing reflux, then the following two statements are the most common features:

- **Although reflux causes physiologic apnea, it causes pathologic apneic episodes in only a very small number of newborns and infants.**
- **When reflux causes pathological apnea, the infant is more likely to be awake and the apnea is more likely to be obstructive in nature.**
- **A diagnosis of an acute life-threatening event (ALTE) warrants consideration of causes other than GER (i.e. reflux).**

Reflux of gastric acid seems to be related to ALTEs (episodes of combinations of apnea, color change, change in muscle tone, choking, and gagging) in < 5 % of infants with ALTE.

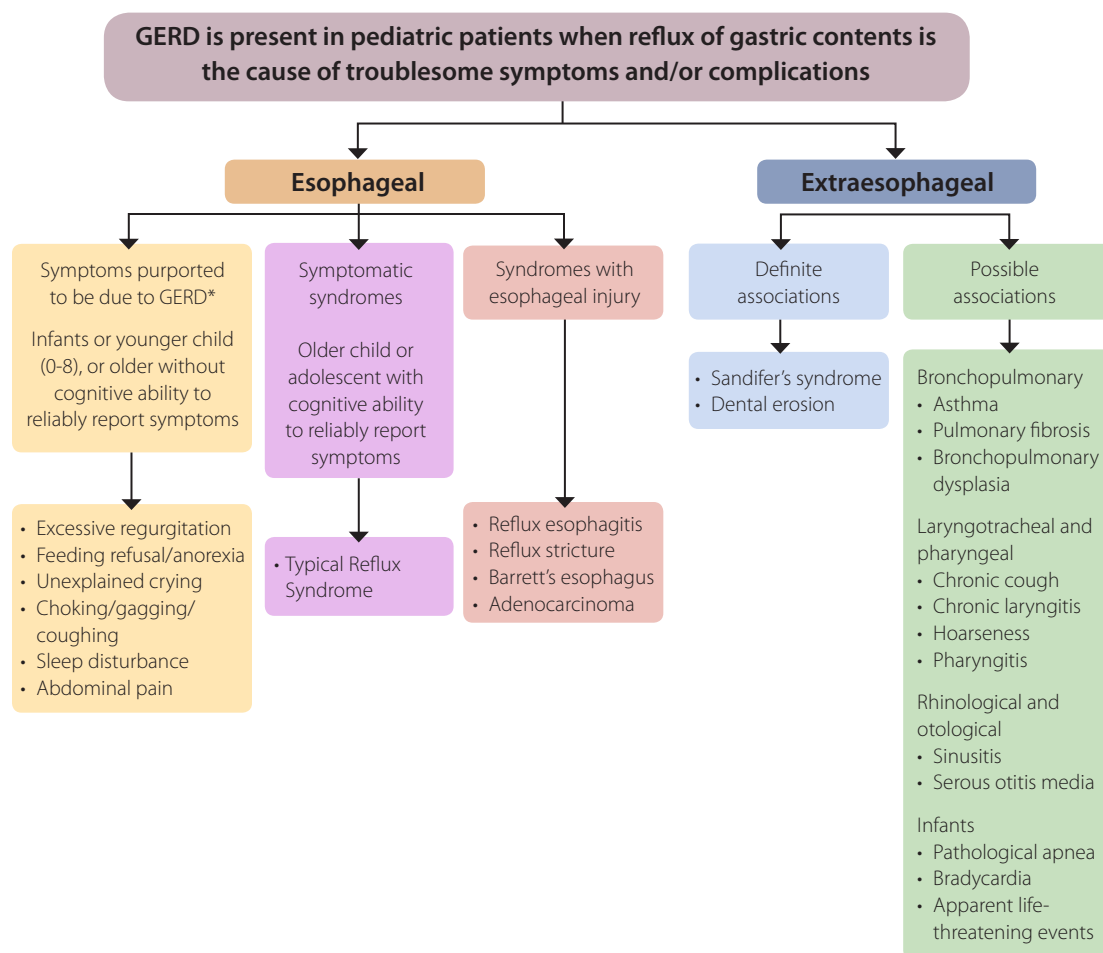
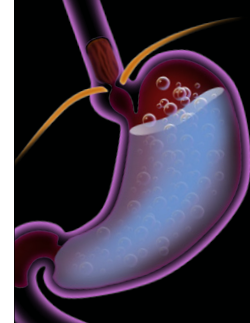
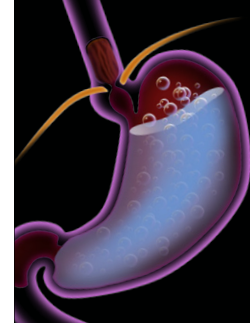


FIGURE 2: Global definition of GERD in the pediatric population¹.

- 1 Sherman PM, Hassall E, Fagundes-Neto U, Gold BD, Kato S, Koletzko S et al. A global, evidence-based consensus on the definition of gastroesophageal reflux disease in the pediatric population. *Am J Gastroenterol* 2009;104:1278-95.
- 2 Vandenas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L et al. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2009;49:498-547.
- 3 Nelson SP, Chen EH, Syniar GM, Christoffel KK. Prevalence of symptoms of gastroesophageal reflux during infancy. A pediatric practice-based survey. Pediatric Practice Research Group. *Arch Pediatr Adolesc Med* 1997;151(6): 569-572.
- 4 Martin AJ, Pratt N, Kennedy JD, Ryan P, Ruffin RE, Miles H, et al. Natural history and familial relationships of infant spilling to 9 years of age. *Pediatrics* 2002;109(6): 1061-1067.
- 5 Rudolph CD, Mazur LJ, Liptak GS, Baker RD, Boyle JT, Colletti RB, et al. Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: recommendations of the North American Society for Pediatric Gastroenterology and Nutrition. *J Pediatr Gastroenterol Nutr* 2001;32(Suppl 2): S1-S31.

Support: Support for this Summary of the Global Definition was provided by AstraZeneca L.P. and Takeda North America Pharmaceuticals Inc. This work was sponsored by CDHNF.



Newborn (1-30 days) / Infant (>30 days-1 yr)	Toddlers/Children (1-10 yr)	Adolescents (11-17 yr)
Reflux symptoms that are not troublesome and are without complications should not be diagnosed as GERD	Reflux symptoms that are not troublesome should not be diagnosed as GERD	Reflux symptoms that are not troublesome should not be diagnosed as GERD
Regurgitation is characteristic of reflux but not necessary/sufficient to diagnose GERD	Heartburn is defined as a burning sensation in the retrosternal area (older children)	Heartburn is defined as a burning sensation in the retrosternal area
GERD symptoms may be indistinguishable from those of food allergy		Generally able to describe specific GERD symptoms and to determine whether those symptoms are troublesome
Typical Reflux Syndrome cannot be diagnosed if the cognitive ability to reliably report symptoms is lacking	Typical Reflux Syndrome cannot be diagnosed if the cognitive ability to reliably report symptoms is lacking	Typical Reflux Syndrome can be diagnosed on the basis of the characteristic symptoms, without additional diagnostic testing (neurologically intact adolescents)
An association between GERD and bronchopulmonary dysplasia exists but cause-and-effect is uncertain	Heartburn and regurgitation are characteristic if cognitive development is sufficient to reliably report symptoms	Heartburn and regurgitation are characteristic if cognitive development is sufficient to reliably report symptoms
GERD may be associated with sleep disturbances	GERD may be associated with sleep disturbances	GERD may be associated with sleep disturbances
In premature infants, a relationship between GER (i.e. reflux) and pathologic apnea and/or bradycardia has not been established	GER (i.e. reflux) in older children is the most common cause of heartburn	GER (i.e. reflux) is the most common cause of heartburn
Although reflux causes physiologic apnea, it causes pathologic apneic episodes in only a very small number	Heartburn can have a number of non-reflux-related causes (older children)	Heartburn can have a number of non-reflux-related causes
When reflux causes pathological apnea, the infant is more likely to be awake and the apnea is more likely to be obstructive	Epigastric pain can be a major symptom of GERD (older children)	Epigastric pain can be a major symptom of GERD
	Physical exercise may induce troublesome symptoms of GERD in individuals who have no or minimal symptoms at other times	Physical exercise may induce troublesome symptoms of GERD in individuals who have no or minimal symptoms at other times
	Dysphagia is a perceived impairment of the passage of food from the mouth into the stomach (older children)	Dysphagia is a perceived impairment of the passage of food from the mouth into the stomach.
	Troublesome dysphagia is present when older children need to alter eating patterns or report food impaction	Troublesome dysphagia is present when adolescents need to alter eating patterns or report food impaction