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Clinical Perspectives on Esophageal Disorders in Infants

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Abstract

Esophageal pathologies are complex and lend themselves to multivariable analysis before a definitive diagnosis can be considered. It is imperative that the clinician establish a methodology for selecting the appropriate technological assessment within scientific testing parameters to establish optimal clinicopathological presentation and determine best practice for patient care.

Introduction

The prevalence of feeding problems in neonates and infants is high, owing to higher survival rates and shifts in morbidities. Furthermore, recent advances in technology and available methods are able to clarify inherent disease and pathophysiological mechanisms of feeding problems; as a result, better therapies and monitoring strategies are possible. Coordinated multidisciplinary feeding management strategies are essential as the problems pertinent to the esophageal domain are managed by several disciplines, such as nutrition, speech-language pathology, occupational therapy, neonatology and general pediatrics, pediatric gastroenterology, pediatric surgery, oto-rhino-laryngology, radiology, pediatric pulmonology, and primary care.

The complexity and causes of feeding problems in infants are numerous, and the list can be exhaustive; furthermore, the aerodigestive symptoms can be heterogeneous and nonspecific to airway or digestive pathologies. The approach to evaluation of such feeding problems is dependent on primary and secondary symptoms, feeding and growth patterns, identifying the systems or target organs of dysfunction, and clinico-pathological correlation. This approach forms the basis for individualized therapies.

Often, the esophagus is considered the source of the problem, whether it is due to dysphagia or gastroesophageal reflux disease (GERD). Empiric therapies are often considered based on clinical observation of heterogeneous and nonspecific symptoms. The purpose of this article is to discuss our clinical perspectives on esophageal disorders in infants. Specifically, we will discuss the (a) definition and significance of esophageal disorders in infants, (b) functions of the esophagus, (c) investigative approach to evaluate esophageal pathologies, (d) methods to evaluate esophageal disorders, and (e) approach to diagnosis and management of esophageal problems in neonates and infants.

Definition and Significance

It is a common perception that the esophagus is merely a conduit tube between the oropharynx and stomach; this perception contrasts its complex physiology and pathophysiology. The functions of safe oral feeding, safe swallowing, airway protection, and respiration intersect at the proximal aerodigestive tract. Thus, esophageal disorders may conveniently be categorized under feeding and swallowing problems, in addition to problems with airway protection. Furthermore, frequent symptoms related to esophageal origin are swallowing problems, choking and aspiration, throat clearing symptoms, irritability and arching, grimace and pain, as well as regurgitation and reflux. Some esophageal disorders are associated with airway symptoms, such as apnea, stridor, wheezing, and chronic lung disease. The exact prevalence of such symptoms related to esophageal pathologies is not known.

In addition, the exact prevalence of esophageal disorders in neonates, infants, or children is not known. The significance of this problem can be gleaned from the following reports:

- About 48% (range, 10%–90%) of premature neonates are being discharged on acid suppressive medications from the nursery (Malcolm et al., 2008).
- Healthy premature infants typically achieve full oral feeding skills by 36–38 weeks postmenstrual age, and co-morbidities are important confounders to the acquisition of timely feeding milestones (Dodrill, Donovan, Cleghorn, McMahon, & Davies, 2008; Jadcherla, Wang, Vijayapal, & Leuthner, 2010).
- A large survey of children with GERD (N = 1,980; aged 2–18 yr) showed that they were associated with a several-fold increase in the risk of sinusitis, laryngitis, asthma, pneumonia, and bronchiectasis compared to control children (N = 7,920; El-Serag, Gilger, Kuebler, & Rabeneck, 2001).
- The incidence rate for esophageal adenocarcinoma in adulthood was found to be increased more than 7-fold in a large cohort (N = 3,364, prematurity at birth), and an 11-fold risk was found if the birth weight was less than 2,000 g (Kaijser, Akre, Cnattingius, & Ekblom, 2005).
- After discharge, a prospective study in the United Kingdom and the Republic of Ireland found that 33% of extremely premature infants (N = 283, 20–26 week gestational age at birth) continued to demonstrate feeding difficulties beyond discharge (Wood et al., 2003).
- Feeding difficulties have been noted to occur in 30%–40% of children with cerebral palsy (Andrew, Parr, & Sullivan, 2012).

Functions of Neonatal Esophagus

The above facts attest to the relevance of controlling and coordinating neuromotor and neurosensory factors involved in feeding and safe bolus propagation from oral phase to pharynx, esophagus, and finally to the stomach while preventing the occurrence of aspiration and gastroesophageal reflux (GER). Thus, the most important function of the esophagus is to transport boluses of food and liquid to the downstream digestive and absorptive organs of the gastrointestinal tract. In fact, this function evolves during fetal life as the primitive esophagus transports swallowed amniotic fluid into the stomach. This is called the *peristaltic reflex*, generated by coordination with the pharyngeal phase of swallowing and the appropriate sequential relaxation of the upper esophageal sphincter (UES). Later, there is restoration of UES tone, ordered sequential esophageal body peristalsis, and coordinated relaxation of the lower esophageal sphincter (LES), followed by

restoration of LES tone (Jadcherla, Duong, Hofmann, Hoffmann, & Shaker, 2005; Mittal & Balaban, 1997; Pena et al., 2010; Ritcher & Castell, 2004).

Esophageal peristalsis can be classified into primary and secondary peristalsis. Primary peristalsis or deglutitive response is triggered in the pharyngeal phase of swallow and propagates distally into the stomach. This sequence is normally associated with a respiratory pause called *deglutitive apnea*. Secondary peristalsis is a swallow-independent sequence and is triggered by esophageal provocation. This reflex occurs due to esophageal distension, chemosensitive stimulation, or osmosensitive stimulation of the esophagus (Gupta et al., 2009; Jadcherla, Duong, Hoffmann, & Shaker, 2003; Jadcherla, Hoffmann, & Shaker, 2006). Combined, these esophageal peristaltic functions participate in the propulsion of the bolus presented during feeding and swallowing, and also during GER events.

An equally important supportive function of the esophagus is aerodigestive protective function. This function is responsible for vigilance, coordination, and anti-reflux defenses. The refluxed material during GER events can be injurious to the esophagus and the aerodigestive tract. The properties of the refluxate or of its presence in the esophagus contribute to the injury potential; this property can be related to acidity or alkalinity, enzymatic content, infective nature, or the physical composition of the refluxate. Often, the acidity is balanced by the esophageal mucosal protective mechanisms, also called the *mucosal defenses*. Mucosal HCO_3^- , which neutralizes the acidic reflux, is a key element in preventing epithelial damage (Flemström & Isenberg, 2001). Additionally, GER events increase the production of saliva. The increased secretion of saliva leads to peristalsis, which further aids in the clearance of the acidic gastric refluxate back into the stomach. The alkaline saliva neutralizes the small amount of acidic refluxate that may still adhere to the esophageal mucosa after the bolus is cleared.

Aerodigestive protection is ensured by several reflexes either separately or collectively. Esophageal peristalsis can be classified into primary and secondary peristalsis. The esophagus and airway share similar innervation by the vagus, and the interaction of afferent and efferent neuronal pathways modulates sensory-motor function, ensuring safe swallowing and airway protection (Goyal, Padmanabhan, & Sang, 2001). We have recognized the following esophageal reflexes to be of interest in ensuring aerodigestive protection in infants: esophago-deglutition reflex, secondary peristaltic reflex, UES contractile reflex, LES relaxation reflex, and pharyngeal reflexive swallows, in addition to airway-protective pharyngo-glottal closure reflex and esophago-glottal closure reflex (Gupta et al., 2009; Jadcherla et al., 2003; Pena et al., 2010). Collectively, these reflexes prevent the ascending spread of the bolus, favor descending propulsion to ensure esophageal clearance, and enhance aerodigestive vigilance. As part of aerodigestive protective function, prevention of pulmonary aspiration is an important function of the esophagus. Pulmonary aspiration is a potential cause of mortality and/or morbidity in high-risk infants. Laryngeal adduction in response to pharyngeal or esophageal stimulation results in closure of the glottis and protects against airway aspiration; these reflexes are called *pharyngo-glottal closure reflex* and *esophago-glottal closure reflex* (Gupta et al., 2009; Jadcherla, Gupta, Coley, Fernandez, & Shaker, 2007). These vigilant reflexes are usually associated with pharyngeal reflexive swallows and deglutition response or secondary peristalsis. Glottal closure accentuates the aspiration preventing barrier, while esophageal peristalsis clears the bolus or stimulus.

Investigative Approach To Evaluate Esophageal Pathologies

First, a clinical assessment must be made to define predisposing risk factors and anatomical defects in the infant and to recognize alternate diagnoses for feeding problems before attributing problems to esophageal pathologies. Predisposing risk factors and alternate

diagnoses must be excluded (Rudolph et al., 2001). Risk factors for feeding problems, dysphagia, or GERD include anatomic malformations and congenital foregut anomalies, such as craniofacial birth defects, pharyngeal clefts and webs, esophageal atresia or tracheoesophageal fistula, omphalocele, gastroschisis, duodenal atresia or web, hiatus hernia, diaphragmatic hernia, intestinal malrotation, and hypertrophic pyloric stenosis. Feeding problems of esophageal origin persist despite restoration or modification of primary structural abnormality. Reasons for swallowing or esophageal problems may include mechanical or functional obstruction, dysmotility, stasis and delayed peristalsis, or GERD.

In addition, non-structural causes and non-esophageal causes of dysfunction need to be considered. External compression on the esophagus due to pressure from the trachea or left bronchus, left atrial enlargement, or post-cardiothoracic surgery consequences need to be considered on a case-by-case basis. In addition, sepsis, metabolic diseases (disorders of amino acid metabolism, urea cycle defects, galactosemia, congenital adrenal hyperplasia), and structural abnormalities of the brain also need to be ruled out in cases of persistent feeding problems of esophageal origin. Of importance, eosinophilic esophagitis is increasingly recognized in older infants and children (Hommel et al., 2012).

Methodologies To Evaluate Esophageal Functions in Infants

Esophageal disorders require diverse approaches and strategies in diagnosing and correcting the problems. Multichannel intraluminal impedance and pH esophageal testing (MII-pH) monitoring, manometry, upper gastrointestinal fluoroscopy, and videofluoroscopic swallow studies can be helpful in objectively characterizing the structural and functional esophageal pathologies. The advantages, limitations, and clinical relevance of these techniques are summarized and referenced in Table 1.

Reflux Monitoring Tests

The 24-hour standard pH monitoring was considered the gold standard to detect acid GER and evaluate atypical symptoms such as cough or apnea; however, esophageal pH studies alone are losing popularity (Orenstein & Hassall, 2007; Putnam, 2010). This is because nearly 60%–90% of GER episodes in infants were nonacid (milk buffering gastric content; Jadcherla & Rudolph, 2005). The limitations of detecting clinically significant nonacid reflux ($\text{pH} > 4.0$) was resolved by the new technology, MII-pH. The MII-pH testing evaluates bolus transit through the esophagus and detects acid and nonacid GER events without time delay (Peter, Sprodowski, Bohnhorst, Silny, & Poets, 2002; Wenzl, 2002; Wenzl et al., 2001). This technique is recognized as the most sensitive tool in quantifying reflux (Sifrim, Castell, Dent, & Kahrilas, 2004). In addition, the reflux assessment is reproducible (Bredenoord, Weusten, Timmer, & Smout, 2005). When combined with concurrent symptom documentation and statistical correlation with reflux indices of various types, one can decide the clinico-pathological significance of GERD contributing to the patient's feeding problems (Jadcherla, Chan, et al., 2011; Jadcherla et al., 2008; Jadcherla, Peng, et al., 2011).

Nevertheless, there are some limitations to MII-pH monitoring. For patients with achalasia, the assessment of esophageal bolus transit is difficult because of a low impedance baseline in the distal esophagus (Nguyen et al., 2004). Furthermore, analysis requires experience and is more laborious compared to the standard pH tracings, which makes clinical application of MII-pH monitoring unrealistic in most settings.

Esophageal Motility Tests

Conventional esophageal basal and adaptive manometry studies permit evaluation of esophageal pressures and peristalsis, velocity of propagation, and sphincter responses to

swallow and reflux events in neonates (Jadcherla, 2003; Jadcherla et al., 2003; Jadcherla et al., 2005; Jadcherla, Gupta, Stoner, Fernandez, & Shaker, 2007; Jadcherla et al., 2006). Combined multichannel intraluminal impedance and esophageal manometry provides simultaneous information regarding bolus transit and motility. Recent introduction of high-resolution manometry allows enhanced spatial and temporal resolution across the body of the esophagus because of the closely spaced and increased number of sensors compared to conventional manometry (Kahrilas, Ghosh, & Pandolfino, 2008).

All the instrumental diagnostic approaches mentioned require highly skilled and experienced personnel who are familiar with the tedious procedures, subject safety, symptom correlation, interpretation, and analysis.

Tests To Assess Esophageal Anatomy

The upper gastrointestinal fluoroscopy uses X-rays to diagnose problems in the esophagus, stomach, and duodenum. It is best utilized to identify anatomic abnormalities and structural defects—such as hiatal hernias, pyloric stenosis, malrotation, esophageal, and antral webs—or even more distal lesions, such as intestinal atresia and stenosis (Hillemeier, 1996). This study lacks adequate sensitivity and specificity to screen for either esophageal dysphagia or GERD (Tsou & Bishop, 1998).

The videofluoroscopic swallow study defines the anatomy of the oropharynx, detects physiological swallowing dysfunctions, and determines the physiologic mechanism for habilitation of the problem. The application of videofluoroscopic swallow methods in the evaluation of neonatal dysphagia is well known and the most widely available technology to determine feeding safety. Dysphagic abnormalities are most commonly described by the presence of aspiration, laryngeal penetration, nasopharyngeal reflux, delayed swallow, or pharyngeal pooling. With all evaluations, there are limitations; the videofluoroscopic swallow study alone may result in delayed initiation and presentation of appropriate oromotor sensory stimuli, which may lead to behavioral feeding disorders (Linscheid, Budd, & Rasnake, 2003). Also, an abnormal videofluoroscopic swallow study can heighten the fear of the impact of aspiration and limit the recommendation for attempts to orally feed the infant or child (Byars et al., 2003; Gleeson, Egli, & Maxwell, 1997).

Summary and Conclusions

It is important to understand that there is no single symptom or sign that is specific to esophageal pathologies, and there is no single test to provide a definitive diagnosis of esophageal dysfunction. Therefore, clinicians need to cautiously weigh the benefits and weaknesses of different technologies and methods, scientific appropriateness of the testing conditions, and clinico-pathological correlation. While evaluating esophageal functions, it is important to assess structural, functional, and protective functions. Practice consensus guidelines on GERD may be helpful (Tsou & Bishop, 1998; Vandenplas et al., 2009).

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age or less. Archives of Disease in Childhood–Fetal and Neonatal Edition. 2003; 88(6):F492–F500. [PubMed: 14602697]

Table 1**Studies to Evaluate Esophageal Functions**

Test	Advantages	Disadvantages
Videofluoroscopic swallow study, upper gastrointestinal fluoroscopy study	Evaluates anatomical abnormalities in the upper gastrointestinal tract, a test for detecting aspiration	Inadequate screen for GER events Involves radiation exposure
Distal esophageal pH monitoring	Smaller probe size, ambulatory, automated analysis available, user-friendly	Feeds alter pH; non-acid GER and total GER are not measured Cannot detect most proximal extent
Multichannel intraluminal impedance-pH	Ambulatory, detects liquid-, mixed-, gas-GER Detects acid- and non-acid GER Clinical research indication with reliable symptom documentation Detects frequency, height, duration of reflux events regardless of pH	No quantitative data regarding volume or pressure or mechanisms Analysis cumbersome, semi-automated and labor intensive Stiffer probes and malfunctions
Basal and adaptive esophageal manometry	Provides mechanistic sensory-motor evaluation of esophageal peristaltic reflexes in response to provocation	Not commonly available Clinical correlation is needed Lacks sensitivity/specificity