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Pathophysiology of Aerodigestive Pulmonary Disorders in the Neonate

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Introduction to Aerodigestive Pulmonary Disorders

Technological advances in perinatal and neonatal care, respiratory management, and nutritional support have contributed to the increasing survival of high-risk neonates. Concomitantly, the prevalence of aerodigestive pathologies in survivors is also increasing. The exact prevalence of aerodigestive pulmonary disorders in the neonate is unknown. This fact may be related to increased survival of premature infants, changing definitions, and the heterogeneous nature of aerodigestive symptoms impeding accurate diagnosis. An estimate can be gleaned from the observations that 30% of preterm infants with birth weights less than 1000 g develop bronchopulmonary dysplasia (BPD),^{1,2} and the estimated prevalence of swallowing problems in infants with BPD is 26%.³

Chronic lung disease of infancy (CLDI), a heterogeneous group of disorders, is associated with positive pressure mechanical ventilation and prolonged respiratory support requiring supplemental oxygen. The pathophysiology and management of BPD and CLDI are discussed elsewhere in this issue. Chronic aspiration, gastroesophageal reflux disease (GERD), reactive airway disease, and dysphagia may complicate or contribute to CLDI. An important therapeutic target directed at minimizing neonatal lung disease is management of feeding problems and aerodigestive symptoms. This article highlights the complexity and causes of aerodigestive symptoms and feeding problems (Table 1). Management of feeding problems in persistent CLDI requires further understanding of aerodigestive pathologies,

which may aggravate and complicate recovery. The specific purposes of this article are to discuss

- Anatomy and physiology of the aerodigestive tract
- Maturation of basal and adaptive aerodigestive reflex mechanisms
- Gastroesophageal reflux (GER) and its implications
- Approaches to the evaluation of aerodigestive pathologies

Over the last decade, major advances in this field have led to clarification of aerodigestive pathophysiology, improved understanding of the symptoms, and development of newer multimodal, multidisciplinary clinical and translational approaches in the human neonate. It is anticipated that improved understanding of aerodigestive pathophysiology will result in appropriate evaluation and clarification, timely testing, and improved management of infants with CLDI.

Anatomy of Aerodigestive Tract

The complexities of the aerodigestive apparatus and functions confirm that it is much more than a conduit between the proximal airway, lungs and foregut. This section discusses the definition, developmental anatomy, and neuromuscular components of the aerodigestive apparatus.

Definition of the Aerodigestive Apparatus

For simplicity and clarity, the aerodigestive apparatus can be defined as the common pathway that facilitates safe breathing and safe swallowing. Broadly, this common pathway includes: nasopharynx, oropharynx, hypopharynx, esophagus, and stomach, in addition to supraglottic, glottic, and subglottic tubular airways (Fig. 1).

Developmental Anatomy and Embryology of the Aerodigestive Tract

The intricate relationship between the airway and foregut begins in embryonic life, and excellent articles pertinent to this section are available.⁴⁻⁹ The aerodigestive organs are developed from adjacent segments of the primitive foregut.⁶⁻⁹ The airway and the lung buds, the pharynx, the esophagus, the stomach, and the diaphragm are all derived from the primitive foregut and/or its mesenchyme, and share similar control systems.⁶⁻⁹ By 4 weeks of embryologic life, the tracheobronchial diverticulum appears at the ventral wall of the foregut, with left vagus being anterior and right vagus posterior in position. At this stage of development, the stomach is a fusiform tube with the dorsal side growth rate greater than the ventral side, creating greater and lesser curvatures. At 7 weeks of embryonic life, the stomach also rotates 90° clockwise, and the greater curvature is now displaced to the left. The left vagus innervates the stomach anteriorly, and the right vagus innervates the posterior aspect of the stomach. At 10 weeks, the esophagus and the stomach are in the proper position, with the circular and longitudinal muscle layers and the ganglion cells in place. The true vocal cords begin as glottal folds. By the 6th or 7th week of gestation, a structure superior to the true vocal cords evolves to protect the vocal cords and lower airway. This superior structure consists of epiglottis, aryepiglottic folds, false vocal cords, and the laryngeal ventricles. The epiglottis starts as a hypobranchial eminence behind the future tongue. By 7 weeks, the epiglottis is separated from the tongue. At the same time, 2 lateral folds connect to the base of the epiglottis, at the distal end of which develops the arytenoids cartilages. The larynx begins as a groove in the primitive foregut, which folds upon itself to become the laryngotracheal bud, the subsequent divisions of which form the bronchopulmonary segments. From this phase, 20 generations of conducting airways form. The first 8 generations constitute bronchi and acquire cartilaginous walls. The next 9 to 20

generations comprise the nonrespiratory bronchioles that are not cartilaginous, and contain smooth muscle; the subsequent divisions form the bronchopulmonary segments.⁹

Neuromuscular Components of the Aerodigestive Apparatus

Structurally, the pharynx is made of striated muscle, whereas the esophagus is a hollow tubular organ comprised of inner circular and outer longitudinal muscle layers with myenteric plexus in between. The proximal esophagus has striated muscle, whereas the distal esophagus has smooth muscle. The upper esophageal sphincter (UES), a constriction between the pharynx and the proximal esophagus, is characterized by a high-pressure zone generated by the cricopharyngeus (the principal muscle), proximal cervical esophagus, and inferior pharyngeal constrictor.⁵ In contrast, the lower esophageal sphincter (LES) is an autonomous sphincter comprised chiefly of circular smooth muscle; the gastroesophageal junction integrity is further augmented by diaphragmatic crural fibers, intra-abdominal parts of the esophagus, and sling fibers of the stomach. The UES is innervated by: the vagus via the pharyngoesophageal, superior laryngeal, and recurrent laryngeal branches; the glossopharyngeal nerve; and the sympathetics via the cranial cervical ganglion. The distal end of the esophagus consists of the specialized smooth muscle, the LES, and an autonomous contractile apparatus that is tonically active and relaxes periodically to facilitate bolus transit. Although the LES is considered an important functional segment in preventing GER, other neighboring structures, including oblique sling fibers of stomach, musculofacial diaphragmatic sling, and the intra-abdominal esophagus, also contribute to this function.⁴

The musculature of the larynx is derived from the mesenchyme of the 4th and 6th pharyngeal arches. All laryngeal muscles are innervated by branches of the Xth cranial nerve. The superior laryngeal nerve innervates derivatives of the 4th pharyngeal arch (cricothyroid, levator palatini, and constrictors of pharynx), and the recurrent laryngeal nerve innervates derivatives of the 6th pharyngeal arch (intrinsic muscles of the larynx).

The airways and esophagus share common innervations.^{4,5,10} Foregut afferents are derived from both vagal and dorsal root ganglions with cell bodies in the nodose ganglion. This afferent apparatus conveys signals to the neurons in the nucleus tractus solitarius, located in the dorsomedial medulla oblongata. These signals are integrated in a specific terminal site of the nucleus tractus solitarius, the subnucleus centralis, which is the sole point of termination of esophageal afferents. After sensory integration in the nucleus tractus solitarius, the signals in turn activate airway motor neurons in the nucleus ambiguus and the dorsal motor nucleus of the vagus, producing an efferent parasympathetic response and/or nonadrenergic noncholinergic response.

Thus, the sensory-motor components of aerodigestive tract innervations are as follows: (1) supraglottal mucosal areas from the 9th and 10th nerves, (2) supra-glottal muscular areas from the 10th nerve, (3) infraglottal mucosal and muscular areas from the 10th nerve; and (4) pharynx and esophagus from the 9th and 10th nerves (Tables 2 and 3).

Physiology and Functions of the Aerodigestive Tract

The various organs within the aerodigestive tract have many functions; however, safe breathing and safe swallowing dominate regardless of age. The most important and highly relevant functions of the upper airway are

- Facilitating ventilation
- Phonation
- Lower airway protection

The significant functions of the pharyngoesophageal segment are

- Facilitating safe deglutition and esophageal transport of nutrients
- Volume clearance as in swallowing or emesis
- Airway protection

Glottal and esophageal functions vary depending on the stage of life.^{1,5,11} For example, in fetal life, glottal and pharyngoesophageal transport functions in series, with lung fluid transported out of the primitive airway to the amniotic fluid pool, where it is swallowed by the fetal pharynx by 11 weeks of embryonic life. Primitive swallowing ability develops by 11 weeks; by 18 to 20 weeks, sucking movements appear, and by full-term gestation, the fetus can swallow and circulate nearly 500 mL of amniotic fluid in a day. Aspiration of amniotic fluid (comprised of fetal lung fluid, fetal urine, debris from skin cells, and particulate matter) can occur in utero, under conditions of fetal distress or asphyxia. Therefore, it is conceivable that the fetal larynx prevents aspiration under normal fetal conditions.

With the first breath at birth, the glottal airway and pharyngoesophageal segment functions in parallel and assume different roles. Immediately after birth, pharyngoesophageal functions continue as swallowing, whereas glottal opening and closure regulate the entry of air into and out of the lungs. Complete glottal adduction can occur as in the complex laryngeal chemoreflex, during which variable components of laryngeal adduction, apnea, repetitive swallowing, startle, hypertension and bradycardia, and hypoxia can be noted.¹¹ In fetal and neonatal life, laryngeal chemoreflex and glottal closure protect the airway from the potential hazard of aspiration, and repetitive swallowing clears the pharyngeal airway of any material. In premature and full term neonates, apnea contributes in part to the important airway protection mechanism. However, the consequences of exaggerated apnea and laryngospasm can be deleterious, during which there is an absence of airflow and lack of ventilation, thereby resulting in hypoxia. Subsequently, during infancy through adulthood, prolonged exhalations against partially closed glottis occur in the form of a cough reflex so as to steer irritants away from the airway.

Conditions that point toward malfunction or maladaptation of glottal reflexes across the age spectrum include: choking, anterograde and retrograde aspiration, life-threatening events or sudden deaths, dysphagia syndromes, GERD, intractable chronic lung disease, ventilator-associated pneumonias, and vocal cord paralysis. The underlying mechanisms of malfunction or maladaptation among these conditions are not well understood.

Maturation of Basal and Adaptive Aerodigestive Reflex Mechanisms

Pharyngeal swallowing and esophageal peristalsis constitute the principal methods used to drive the bolus away from the aerodigestive tract to the downstream digestive and absorptive organs of the gastrointestinal tract. This is called the peristaltic reflex, generated by coordination with the pharyngeal phase of swallowing, followed in sequence by relaxation of the UES, restoration of UES tone, ordered esophageal body peristalsis, coordinated relaxation of the LES, and restoration of LES tone.^{12–15}

Peristaltic Reflexes

Pharyngeal swallowing is triggered by bolus movement from the oral cavity or by pharyngeal or esophageal stimulation. Esophageal peristalsis can be classified into primary and secondary peristalsis. Primary peristalsis or the deglutition response triggers the pharyngeal phase of swallowing followed by sequential reflexes that propagate distally into the stomach. This sequence is normally associated with a respiratory pause called deglutition

apnea (Fig. 2). Secondary peristalsis is a swallow-independent sequence and is triggered by esophageal provocation. This reflex can occur due to esophageal distention, chemosensitive stimulation, or osmosensitive stimulation of the esophagus (Fig. 3).^{16–18} Pharyngeal reflexive swallow is another important reflex evoked upon direct pharyngeal stimulation that facilitates pharyngeal clearance and bolus propagation distally (Fig. 4). Prolonged repetitive swallowing is associated with prolonged deglutition apnea and shallow breathing. Combined, these esophageal peristaltic functions participate in propulsion of a bolus presented during feeding and swallowing, and also during esophageal provocation caused by GER events.

Sphincteric Reflexes

Aerodigestive protection is also ensured by the UES and LES. UES and LES maintain a resting tone regardless of age or activity states, thus preventing any foregut luminal contents from reaching the airway. Furthermore, the UES contractile tone is triggered in response to esophageal provocation, the esophago-UES contractile reflex. During this occurrence, the proximal bolus movement of the bolus orad is halted by the vigilant esophago-UES contractile reflex (see Fig. 3). The UES contractile reflex is also triggered upon pharyngeal stimulation, pharyngo-UES contractile reflex. Often, the pharyngo-UES contractile reflex is accompanied by a pharyngeal reflexive swallow (see Fig. 4), thus the combination of these 2 reflexes results in robust swallowing, as is usually the case in adults.

Relaxation of the LES is equally important in facilitating bolus clearance distally. Esophageal provocation results in esophago-LES relaxation reflex (see Fig. 3), whereas pharyngeal provocation results in pharyngo-LES relaxation reflex (see Fig. 4).

Glottal Closure Reflexes

Adduction of the glottis via the laryngeal adductors shuts the glottis and protects any form of potential aspiration. Glottal adduction can occur upon pharyngeal stimulation, the pharyngoglottal closure reflex, or upon esophageal stimulation, the esophagoglottal closure reflex.^{14,16–18} Prolonged glottal closure has physiologic consequences, however, and is associated with bradycardia and desaturation. Generally, either pharyngoglottal closure reflex or esophagoglottal closure reflex is associated with pharyngoesophageal peristalsis. Collectively, these reflexes prevent the ascending spread of the bolus, favor descending propulsion to ensure esophageal clearance, and enhance aerodigestive vigilance.

Laryngeal Chemo Reflex

A constellation of responses within the proximal aerodigestive tract is associated with laryngospasm, cessation of ventilation or airflow, repetitive pharyngeal contraction, and cardiorespiratory changes.¹¹ This reflex is also associated with stiffening of limbs and increased neuromuscular drive. This reflex is considered a brain stem arousal response.

Electrocortical Arousals

Electrocortical arousal, as an effect of visceral provocation or of its temporal relationships with aerodigestive reflexes in infants, is an important hypervigilant or protective state.^{19,20} Sleep problems in aerodigestive pulmonary disorders alter the quality of life in infants. The author described the effects of esophageal provocation on esophageal reflex responses and electrocortical arousals during sleep, and found that electrocortical arousals are dependent on the frequency characteristics of esophageal neuromotor responses. Remarkably, swallow sequences were associated with arousals and sleep state changes, and arousals were associated with incomplete peristalsis, response delays to LES relaxation, and prolonged esophageal volume clearance. GER events (73.5%) provoked arousals. Arousals were

associated with response delays to peristaltic reflexes or volume clearance, sleep state modification, and prolonged respiratory arousal. Midesophageal stimuli provoked arousals and were associated with increased frequency, prolonged latency, and prolonged response duration of peristaltic reflexes and UES contractile reflex, and increased frequency of sleep state changes and respiratory arousals. Electrocardiac arousals add to the highest level of vigilance in response to an aerodigestive threat. Aerodigestive homeostasis is defended by multiple tiers of aerodigestive safety mechanisms, and when esophageal reflexes are delayed, cortical hypervigilance occurs.

Antireflux Mucosal Defenses

The refluxed material during GER events can be injurious to the esophagus and the aerodigestive tract. The properties of the refluxate or 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^- that neutralizes acidic reflux is a key element in preventing epithelial damage.²¹ Additionally, GER events also 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 also neutralizes the small amount of acidic refluxate that may still adhere to the esophageal mucosa after the bolus is cleared.

In summary (see Fig. 1), several tiers of aerodigestive protection exist in infants; there may be many other defensive reflexes that have not yet been discovered. Collectively, all these reflexes facilitate luminal clearance and maintain the respective functions of the airway and digestive tract.

Gastroesophageal Reflexes that Cause and Protect Against GER

Excellent recent articles are available pertinent to GERD and its management in neonates and infants, including a recent position statement from North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition.^{22–28} However, there is no focused guideline to help diagnose and manage GERD in the neonatal intensive care unit.

Symptomatology

Aerodigestive symptoms (see Table 1) provide clues to GER, and persistence of troublesome symptoms in the presence of chronic GER constitutes GERD. Dysphagia or abnormalities of swallowing in its various phases (oral, pharyngeal, esophageal, or gastric phase) can be related to esophageal pathology. GER or GERD are commonly suspected to be causes of swallowing problems. These entities range from simple regurgitation or physiologic reflux in asymptomatic thriving infants to troublesome symptoms seen in the pathologic form of GERD. GERD symptoms and its complications commonly include arching, irritability, throat clearing, autonomic signs such as facial flushing, tearing and cardiorespiratory changes, hoarse cry, choking, coughing and stridor, airway and respiratory compromise, retrograde aspiration, and bronchospasm. The symptoms in GERD syndrome can be due to abnormalities of refluxate clearance or abnormalities of aerodigestive protective functions.

Pathophysiological Basis for Symptoms in GERD

The pathophysiological basis for aerodigestive symptoms lie in sensory–motor modifications of the reflexes evoked in response to esophageal provocation from gastroesophageal refluxate. Owing to the variable composition of refluxed material,

symptoms can vary and depend on the spatial and temporal characteristics of its spread and clearance.^{23–25} For example, the refluxate may vary according to its:

- Physical characteristics: gas, liquid, mixed, or semisolid.
- Chemical characteristics: acid, weakly acid, nonacid or alkaline.
- Content: milk, partially digested milk, enzymes, bacteria, saliva, oral contents.
- Most proximal extent: distal esophagus, midesophagus, proximal esophagus, pharynx, nasopharynx, oropharynx.

Thus, the symptoms that occur from GER are the result of activation of afferent and efferent nerves subserving the route of spread of the refluxate. For example, when the most proximal extent is the pharynx, there is predominance of respiratory symptoms, in contrast to sensory symptoms when the most proximal extent is the distal esophagus.^{24,25}

Furthermore, posture has an important bearing on GER and therefore with the symptoms associated with the events. This is because: (1) the angle at the gastroesophageal junction (angle of His) is obtuse (contrasting with an acute angle in adults), and is altered in different postures; (2) the relationship of the fundus to the esophageal body is modified; and (3) protective mechanisms can be recruited differently.^{23,29–33} The effects of posture are summarized:

- Supine posture is recommended by the American Academy of Pediatrics to prevent sudden infant death syndrome (SIDS). However, GER is more frequent in this position, because the angle of His at the gastroesophageal junction becomes more obtuse. Importantly, airway protection mechanisms are also more favorable in supine position.^{34–37}
- Prone posture is associated with more acute angulation at the gastroesophageal junction, thus preventing GER. However, aerodigestive clearance and protection mechanisms are impaired under these conditions. In extreme cases of GERD, this position is permissible under monitored, in-patient conditions.^{29,38–40}
- Left lateral posture is associated with less GER.^{27,29}
- Right lateral posture is associated with better gastric emptying, but more GER, implying that GER and gastric emptying may be unrelated.³¹

Causal Mechanisms of GER

GER is more frequent in neonates and young infants than at any other age owing to the following mechanisms

- Transient LES relaxation (TLESR): GER occurs most commonly due to transient LES relaxation in response to esophageal, gastric, or fundic distention.⁴¹ This is a reflex mediated by the vagus nerve. The neurotransmitters implicated in increased TLESR include vasoactive intestinal peptide, nitric oxide, cholecystokinin, and acetylcholine. In contrast, gamma aminobutyric acid (GABA-B) receptors and opioids inhibit TLESR.^{42–44} In addition, inflammation increases TLESR and decreases resting LES tone.
- Shorter esophageal length and intra-abdominal LES: LES length is shorter in premature infants. In addition, the intra-abdominal part of the LES develops in the postnatal period.⁴⁵
- Smaller capacity of stomach: Premature infants have relatively small stomach capacity relative to the required volumes of feeding for optimal growth. This

increases the predisposition to GER. Given the shorter esophageal length, the most proximal extent of GER also is higher.

- **Role of diaphragm:** The diaphragm and the phrenoesophageal ligaments or crural elements help to maintain the anatomic integrity of the gastroesophageal junction. With each inspiration there is an augmentation of LES resting tone. With TLESR, the crural diaphragm is inhibited concurrent with LES relaxation by the vagus nerve-mediated reflex, and thus the antireflux barrier is weakened.^{13,46}

Approach to Evaluation of Aerodigestive Pathologies

Clinical Assessment

In a personalized program, detailed clinical assessment is a necessity before embarking on diagnostic testing.⁴⁷ Clinical aerodigestive assessment must include: predisposing risk factors, nutrition and growth details, review of anatomic defects, duration of illness, details of aerodigestive symptoms (see Table 1), feeding methods and symptom diary, as well as medication history. History of airway and digestive supportive therapies such as duration of respiratory support and feeding supportive methods can be helpful. Predisposing risk factors and alternate diagnoses must be excluded.⁴⁸

Risk factors for aerodigestive problems, dysphagia, or GERD include: mechanical or functional obstruction; foregut dysmotility; anatomic malformations and congenital foregut anomalies, such as craniofacial birth defects, pharyngeal clefts, and webs; laryngeal clefts; postoperative esophageal strictures (following esophageal atresia or trachea–esophageal fistula repair), hiatus hernia, postoperative diaphragmatic hernia, intestinal malrotation, and hypertrophic pyloric stenosis. External compression of the esophagus due to pressure from trachea or left bronchus, left atrial enlargement, or postcardiothoracic surgery consequences should be considered on a case-by-case basis. Of importance, eosinophilic esophagitis is increasingly recognized in older infants and children.^{49–52} In most of the previously mentioned circumstances, airway and digestive pathologies coexist.

Investigative Methods

Aerodigestive disorders require diverse approaches and strategies in diagnosing and correcting the problem. Esophageal pH-multichannel intraluminal impedance (pH-MII) monitoring, manometry, upper gastrointestinal fluoroscopy, and video–fluoroscopic swallow studies can be helpful in characterizing the esophageal structural and functional pathologies objectively. The advantages, limitations, and clinical relevance of these techniques are summarized in Table 4.

Summary

There is no single symptom or sign that is specific to aerodigestive pathologies, nor can a single test provide a definitive diagnosis for aerodigestive interactions. Therefore, clinicians need to cautiously weigh the benefits and weaknesses of different technologies and methods, scientific appropriateness of the testing conditions, clinico–pathologic correlation, and pharmacologic approaches. GERD symptoms and airway symptoms and disease can coexist, and cannot be distinguished without specific tests and direct observations. Important aerodigestive disorders include dysphagia, GERD, and aggravation of airway injury due to malfunctions of the swallowing or airway protection mechanisms. Application of consensus guidelines on GERD can be helpful in some circumstances.²⁸ In the evaluation of aerodigestive pathologies, assessment of structural, functional, and protective functions is important. Objective evaluation of aerodigestive reflexes and symptom correlation may provide support for evidence-based management of feeding and airway protection strategies.

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Key Points

- Embryologic origins and development, innervation, and functions of airway and pharyngoesophageal segment (which together constitute the aerodigestive tract) are closely interrelated, and have codependent functions.
- The most important functions of the upper airway are facilitating ventilation, phonation, and lower airway protection; these functions are enabled by brain stem-mediated vagal reflexes that participate at multi-tier levels.
- The significant functions of the pharyngoesophageal segment include facilitating safe deglutition and esophageal transport of nutrients, volume clearance as in swallowing or emesis, and esophageal and airway protection.
- Aerodigestive symptoms and signs are not specific and can coexist.
- Nonpharmacologic approaches to manage gastroesophageal reflux disease are based on the physiology of esophago-gastric functions.
- Investigative methods to assess the aerodigestive tract have test-specific strengths and limitations.

Fig. 1.
Schematic representation of aerodigestive reflexes.

Fig. 2.

An example of secondary peristaltic reflex along with esophago-UES contractile reflex, anterograde propagation (*long arrow*), and LES relaxation reflex (*arrow head*) evoked upon midesophageal stimulation (*shaded box*).

Fig. 3.

An example of secondary peristaltic reflex along with esophago-UES contractile reflex, anterograde propagation (*long arrow*), and LES relaxation reflex (*arrow head*) evoked upon midesophageal stimulation (*shaded box*).

Fig. 4.

An example of pharyngeal reflexive swallow evoked upon pharyngeal infusion (*shaded box*). Note the pharyngeal contraction (peak), UES relaxation, anterograde propagation (*long arrow*), LES relaxation, and deglutition apnea associated with this event.

Table 1
Aerodigestive symptoms and related clinical mechanisms in neonates

Aerodigestive Symptoms	Related Clinical Mechanisms
Irritability and arching	Oromotor inertia, delayed swallowing, Dystonic neck muscles
Throat clearing and grunting	Poor pharyngeal clearance, nasopharyngeal reflux
Cough, stridor and wheeze, CLDI	Laryngeal penetration and airway microaspiration, airway Inflammation, macroaspiration
Regurgitation, reflux, and emesis	Gastroesophageal reflux, gastroesophageal reflux disease, gastroparesis, intestinal
Tachypnea, apnea and hyperpnoea, increased work of breathing, bradycardia and desaturations, apparent life-threatening events	Exaggerated airway protective and compensatory mechanisms, failed airway protective mechanisms, endurance and fatigue problems, lack of electrocortical arousal response

Table 2
Neuromuscular apparatus of the aerodigestive tract

Cranial Nerve (CN)	Location	Muscles Innervated
CN V (trigeminal)	Pons	Temporalis, masseter, medial pterygoid, lateral pterygoid, mylohyoid, digastric, tensor veli palatini
CN VII (facial)	Pons	Orbicularis oris, buccinators, stylohyoid, digastric
CN IX (glossopharyngeal)	Medulla	Stylopharyngeus, pharyngeal muscles
CN X (vagus)	Medulla	Thyroarytenoid, arytenoid, cricoarytenoid, aryepiglottic, thyroepiglottic, esophageal and stomach muscles
CN X and CN XI (accessory)	Medulla	Levator veli palatini, palatoglossus, uvular, palatopharyngeus, salpingopharyngeus, pharyngeal constrictors
CN XII (hypoglossal)	Medulla, C1	Intrinsic and extrinsic tongue muscles, geniohyoid
Ansa cervicalis/CN XII	C1, C2	Omohyoid, sternohyoid, thyrohyoid, sternothyroid

Table 3
Hierarchy of aerodigestive protection mechanisms in neonates

Organ	Reflexes	Physiologic Implications
Brain	<ul style="list-style-type: none"> • Arousals • Hypervigilant awake state 	<ul style="list-style-type: none"> • Poor sleep patterns • Life-threatening events
Airway	<ul style="list-style-type: none"> • Glottal Closure • Bronchial muscle spasm • Reactive airway disease • Increase secretion in airway • Cough 	<ul style="list-style-type: none"> • Obstructive apnea, desaturation, and bradycardia • Restrictive airway disease • Cough • Airway clearance
Pharynx	<ul style="list-style-type: none"> • Pharyngeal reflexive swallow • Pharyngoglottal closure reflex • Deglutition apnea 	<ul style="list-style-type: none"> • Pharyngeal clearance • Airway clearance and pharyngeal clearance • Airway protection
Esophageal	<ul style="list-style-type: none"> • Deglutition reflex • Secondary peristalsis • Upper esophageal sphincter contractile reflex • Lower esophageal sphincter relaxation reflex 	<ul style="list-style-type: none"> • Swallowing esophageal clearance • Airway protection esophageal clearance

Table 4
Methods to investigate aerodigestive pathologies

Method	Advantages	Disadvantages
Upper gastrointestinal fluoroscopy ^{53,54}	Evaluates structural anatomy	Involves radiation exposure and transport
Video–fluoroscopic Swallow Study ^{55,56}	Clarifies oral bolus transit and anatomic abnormalities in the proximal aerodigestive tract	Involves radiation exposure, testing methods and conditions can contribute to variability in interpretation
Distal esophageal pH monitoring ^{57,58}	Smaller probe size, ambulatory, automated analysis available, user friendly	Feeds alter pH; nonacid GER and total GER are not measured; Cannot detect most proximal extent
pH-multichannel intraluminal impedance ^{23–25,59–64}	Ambulatory, detects liquid-, mixed-, gas- GER; detects acid and nonacid GER; reliable symptom documentation and analysis can increase objectivity; detects frequency, height, duration of reflux	Analysis cumbersome, semiautomated and labor-intensive, stiffer probes and malfunctions are frequent
Basal and adaptive esophageal manometry ^{12,16,17,45,65,66}	Provides mechanistic sensory–motor evaluation of esophageal peristaltic reflexes in response to provocation	Not commonly available; clinical correlation with direct observation is needed; analysis cumbersome and requires advanced training