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ADVANCES WITH NEONATAL AERODIGESTIVE SCIENCE IN THE PURSUIT OF SAFE SWALLOWING IN INFANTS: INVITED REVIEW

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Abstract

Feeding, swallowing and airway protection are three distinct entities. Feeding involves a process of sequential, neurosensory and neuromotor interactions of reflexes and behaviors facilitating ingestion. Swallowing involves anterograde bolus movement during oral-, pharyngeal- and esophageal phases of peristalsis into stomach. During these events, coordination with airway protection is vital for homeostasis in clearing any material away from airway vicinity. Neurological-airway-digestive inter-relationships are critical to the continuum of successful feeding patterns during infancy, either in health or disease. Neonatal feeding difficulties encompass a heterogeneous group of neurological, pulmonary and aerodigestive disorders that present with multiple signs posing as clinical conundrums. Significant research breakthroughs permitted understanding of vagal neural pathways and functional aerodigestive connectivity involved in regulating swallowing and aerodigestive functions either directly or indirectly by influencing the supra-nuclear regulatory centers and peripheral effector organs. These neurosensory and neuromotor pathways are influenced by pathologies during perinatal events, prematurity, inflammatory states and coexisting medical and surgical conditions. Approaches to clarify pathophysiologic mapping of aerodigestive interactions, as well as translating these discoveries into the development of personalized and simplified feeding strategies to advance child health are discussed in this review article.

1. INTRODUCTION

Technological advances with biomedical sciences have permitted applications to improve survival among vulnerable neonates; however, there is significant shift in aerodigestive and neurodevelopmental morbidity towards an unacceptable societal and economic burden.^{1,2} Neonates at high risk of aerodigestive and or oral feeding difficulties include infants born prematurely or with low birth weight, CLDI, congenital anomalies, perinatal asphyxia, post-surgical or sepsis states. Generally, such infants require supplemental prolonged parenteral nutrition or nasogastric tube feeding and or supplemental oxygen. Symptom presentation

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with neonatal aerodigestive or feeding difficulties include poor nipple skills, arching and irritability, regurgitation or emesis, aspiration during oral feeding or during gastroesophageal reflux (GER) events, apnea, cough and or gagging, exacerbations with chronic lung disease of infancy (CLDI), pharyngo-nasal reflux or behavioral feeding disorders or feeding aversion.^{3,4}

A) Prevalence of Neonatal Aerodigestive Problems

The exact prevalence of neonatal aerodigestive disorders is not known. The prevalence of feeding difficulties among infants born before 37 wks gestation is about 10.5%, and increases to about 24.5% among those born less than 1500 grams birth weight.⁵ On the other hand, among infants born at less than 28 weeks gestation, oral feeding is significantly delayed and the length of hospitalization is prolonged in comparison to infants greater than 28 weeks of gestational age; however, in this study, a large majority of healthy premature infants do indeed achieve oral feeding skills by 36–38 weeks of postmenstrual age.⁶ Neurodevelopmental problems are increasing among surviving neonates, and overall 20–80% of such infants have feeding difficulties during infancy.^{3,7} About 26% of preterm infants demonstrated swallowing abnormalities and or aspiration syndromes. In about 31% of those with persistent feeding difficulties under 1 year age, the underlying primary condition was bronchopulmonary dysplasia (BPD).⁸

B) Goals of this review article

The underpinnings of neonatal aerodigestive difficulties involve the central and enteric reflexes, neuromuscular apparatus involved with feeding, swallowing and airway protection, as well as cardiorespiratory rhythm patterns. Three major systems are at play in the genesis of such symptoms: a) developing central and enteric nervous system, b) airway and pulmonary systems, c) oropharyngeal and esophago-gastric systems. Thus, multiple macro-physiological organ systems are operational. In this review we discuss, 1) pertinent focused integrated physiology of aerodigestive responses and functions, as well as symptom triggers; and 2) increased understanding of pathophysiology of neonatal aerodigestive system will translate pathways for objective evidence based diagnosis and management. This will then form the basis for personalized precision medicine among infants vulnerable to aerodigestive compromise.

2) PATHOPHYSIOLOGY OF AERODIGESTIVE SYSTEMS

A) Neurophysiological Regulatory Systems

Pharynx, upper esophageal sphincter (UES) and proximal esophagus are made up of striated muscle. The UES high pressure zone is a constriction between the pharynx and the proximal esophagus generated by the cricopharyngeus (the principal muscle), proximal cervical esophagus, and inferior pharyngeal constrictor.⁹ The distal esophagus and the lower esophageal sphincter (LES) comprises of smooth muscle with inner layer consisting of circular muscle cells and outer layer comprising of longitudinal muscle cells with myenteric plexus in between. LES is an autonomous sphincter comprised chiefly of circular smooth muscle, and the gastroesophageal junction integrity is further augmented by a)

diaphragmatic crural fibers, b) intra-abdominal part of esophagus, and sling fibers of the stomach.¹⁰

The musculature of larynx is innervated by branches of the X nerve. The superior laryngeal nerve innervates the cricothyroid, levator palatini, and constrictors of pharynx, whereas the recurrent laryngeal nerve innervates the intrinsic muscles of the larynx.

The UES is innervated by 1) the Vagus via the pharyngo-esophageal, superior laryngeal and recurrent laryngeal branches; 2) the glossopharyngeal nerve; and 3) the sympathetics via the cranial cervical ganglion. The LES is an autonomous contractile apparatus that is tonically active and relaxes periodically to favor bolus peristalsis; in addition, along with the oblique sling fibers of stomach, musculo-fascial diaphragmatic sling, and intra-abdominal esophagus helps to prevent GER.¹¹

The airways and esophagus share common innervations.^{9,11,12} Foregut afferents are derived from both Vagal and dorsal root ganglions with cell bodies in the nodose ganglion. The sensory signals are conveyed 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 non-adrenergic non cholinergic response mediated via vasoactive intestinal polypeptide or nitric oxide.^{13–15}

B) Physiology of Peristaltic and Aerodigestive Protective Reflexes

Evidences for swallowing reflex and esophageal peristalsis are noted as the fetal esophagus transports swallowed amniotic fluid into the stomach. This reflex matures during development in the prematurely born neonate with regards to its sensory-motor characteristics. This peristaltic activity is generated by coordination with pharyngeal phase of swallowing; appropriate sequential relaxation of UES followed by sequential esophageal peristalsis, and coordinated relaxation of the LES. At the end of this sequence, the integrity of UES and LES are maintained with adequate resting tone.^{10,16–18} The normal neonatal swallowing mechanism is characterized by 3 phases, the oral, pharyngeal, and esophageal phase.¹⁹ While pharyngeal and esophageal phases are evident earlier during fetal development, the oral phase is more complex and evolves with further maturation by 32–34 weeks gestation.

The oral phase continues to advance during infancy. The oral phase includes extraction of the bolus involving sucking-expression bursts^{20–26}, lingual-palatal coordination and airway protection via the epiglottis. The pharyngeal phase is characterized by propulsion of the bolus and airway protection, whereas the main feature of a normal esophageal phase is peristalsis and airway protection. Esophageal peristalsis can be of two types: a) *Primary peristalsis* is triggered in the pharyngeal phase of swallow and propagates distally into the stomach, and is associated with a respiratory pause called deglutition apnea. b) *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.^{27–29} Combined, these esophageal peristaltic functions participate in propulsion of bolus presented during feeding and swallowing, and also during GER events. Thus, the regulating neuromotor and neurosensory factors targeting safe bolus transit from oromotor apparatus to stomach, and yet prevent the occurrence of aspiration and GER during the feeding is important. This important aerodigestive protective function is responsible for vigilance, coordination, and anti-reflux defenses. The refluxate can be injurious to the esophagus or to the aerodigestive tract, and may be related to acidity or alkalinity, enzymatic content, infective nature, or the physical composition of the refluxate. Mucosal HCO_3^- that neutralizes the acidic reflux is also a key element in preventing epithelial damage.³⁰

Aerodigestive protection is ensured by several cumulative reflexes as summarized (Figure 1). The esophagus and airways share similar innervation by vagus, and the interaction of afferent and efferent neuronal pathways modulate sensory-motor function to ensure safe swallowing and airway protection.¹² We have discovered the following esophageal reflexes to be of interest in ensuring aerodigestive protection in infants: a) Esophago-Deglutition Reflex, b) Secondary Peristaltic reflexes, c) UES contractile reflex, d) LES relaxation reflex, and e) Pharyngeal Reflexive Swallows, in addition to airway protective f) Pharyngo-Glottal Closure Reflex and g) Esophago-Glottal Closure Reflex.^{17,27–29} We have also characterized the sensory-motor properties of these reflexes during maturation. Notably the characteristics of esophageal-stimulus^{27,28,31} and pharyngeal-stimulus induced reflexes (Figure 2) advance with maturation (Figure 3).^{32,33} The interactions between pharyngeal and esophageal stimulus and airway responses have also been systematically evaluated. Glottal closure and cough reflex responses (Figure 4) are noted, and may reflect hypersensitivity and or heightened airway reactivity^{34–36}. 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 can occur during oro-pharyngeal-esophageal phases of swallowing (anterograde aspiration) or during retrograde GER events (retrograde aspiration), and is a potential cause of mortality and or morbidity in convalescing infants in the NICU. Laryngeal adduction in response to pharyngeal or esophageal bolus stimulation results in closure of glottis and protects against airway aspiration; these reflexes are called Pharyngo- Glottal Closure Reflex and Esophago-Glottal Closure Reflex.^{29,34} Such an entity occurring with peri-laryngeal infusion has been evaluated before, and has been termed laryngeal chemoreflex^{37–40} 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 perceived stimulus. Mapping of this and related neural circuitry can be referenced.³⁵ Thus, abnormalities of structure and or function of aerodigestive and neuromuscular apparatus predispose to the development of feeding difficulties and aerodigestive disorders.

C) Aerodigestive Pathophysiological mechanisms

Sick premature or full term born infants surviving after respiratory or cardiac interventions undergo multifaceted interventions over a prolonged period of time. This may mean

prolonged intubation, positive pressure airway support, dependency on oxygen. Such infants also undergo digestive tract interventions with intragastric feeding strategies. Maturation of the aerodigestive sub-systems under such conditions is often impaired. Since the Vagal and supra-nuclear neural pathways are involved in regulating swallowing and aerodigestive functions, these neurosensory and neuromotor aerodigestive pathways are influenced by pathologies during perinatal events, prematurity, inflammatory states and coexisting medical and surgical conditions (Figure 5).^{10,16,41,42}

Oro-pharyngeal phase of swallowing involves integratory functions of multiple neural circuits (involving multiple cranial nerves, afferent and efferent neurons, excitatory and inhibitory neurons, neural networks, central pattern generator and various neuronal synapses) which are directly involved in coordinating the orofacial and oropharyngeal muscle tissues. Influences of other neural and muscle pathways such as the neuro-endocrine (such as, hunger and satiety, smell and taste and thirst) or inflammatory situations (such as, infection, injury, nociceptive and drug action) contribute to the functional or dysfunctional mechanisms of swallowing.

Pathophysiological considerations during oro-pharyngeal phase of feeding can be due to oromotor inertia and oral pooling, delayed initiation of the pharyngeal phase, cardio-respiratory events, penetration, aspiration, airway symptoms, and oral aversion. These abnormal manifestations lead to neonatal swallowing problems in the oral-pharyngeal phase and or the pharyngeal-esophageal phase. Reasons behind these symptoms include latching problems related to apposition at lips and tongue with the nipple, delay in suck, lack of biological rhythm and lingual propulsive movement, poor extraction of bolus, naso-pharyngeal regurgitation, delayed initiation of pharyngeal swallow, silent aspiration, peristaltic failure, gagging, arching and irritability. The symptoms and signs observed in the pharyngeal-esophageal phase include, pharyngeal pooling, wet gurgly breathing, cough with feeds, stridor, nasopharyngeal regurgitation, delayed pharyngeal phase, pharyngo-upper esophageal sphincter dys-coordination, laryngeal penetration, laryngeal aspiration, apnea, bradycardia and desaturations, and cardio-respiratory events. The symptoms in both these phases could cause overt or silent antero-grade aspiration and airway/lung disease or GERD and retrograde aspiration and airway/lung disease as well as oral aversion and behavioral feeding problems. Understanding the mechanisms for the genesis of symptoms is critical to the development of innovative aerodigestive therapies.

Aspiration occurs when bolus passes through the true vocal folds thus breaching airway protection usually provided by normally functioning true vocal folds. The 3 major types of aspiration are antero-grade (characterized by pre-, intra- and post-deglutitive), retrograde (as in GER events) and silent aspiration (without any symptoms). Incidence of aspiration varies among infants with swallowing dysfunction⁸ and about 85% of children exhibiting deep laryngeal penetration eventually aspirated, and aspiration occurred 15 sec after laryngeal penetration.^{43,44} Infantile swallowing differed from the adult swallowing in terms of epiglottic movement, tongue driving force, amplitude of pharyngeal contraction, and UES pressure. There is however, comparable pharyngeal shortening and pharyngeal wall movement.⁴⁵

Aspiration can occur in small quantities in adults and if it is cleared by the body's defense mechanism then there is low risk for any serious harm. 50% of normal subjects aspirate small volumes (0.01–0.2 ml) during sleep.⁴⁶ About 45% of normal patients had detectable aspiration during sleep and those sleeping more soundly were found to be at a greater risk.⁴⁷ Neurologically normal subjects also aspirate.⁴⁸ However, the amounts aspirated by neonates and infants are unclear, as such there is an absence of reliable and easily testable markers to diagnose aspiration.

Rommel and colleagues focus on swallowing pathophysiology, specifically related to dysphagia and aspiration. These investigators studied children utilizing high resolution esophageal pressure topography, impedance, and videofluoroscopy methods^{3,49–53}. Notable works that may translate to the neonatal population include: 1) assessment of oropharyngeal dysphagia and aspiration utilizing pressure-flow analysis, a method to assess swallowing physiology by detecting motor function, bolus flow and transit, and correlation with symptoms,^{54–58} and 2) development a bolus residue scale to detect pharyngeal retention⁵⁹.

Omari and colleagues focus on swallowing mechanics^{60–63}, and lower aerodigestive tract pathophysiology, specifically esophageal dysphagia related to GERD^{64–67}, across the age spectrum utilizing high resolution impedance manometry. Notable works that may translate to neonatal population include: 1) development of automated impedance manometry for pressure flow analysis^{63,68–70}, 2) effect of GERD therapies in infants and children^{71–77}, and the 3) effect of stimulus characteristics on esophageal function^{78,79}.

3) TRANSLATIONAL IMPLICATIONS

A) Challenges with feeding infants with special needs

Types of aerodigestive and or feeding difficulties can be several during the course of infant's hospitalization. The optimal timing and the need for diversion procedures such as gastrostomy, or airway maintenance procedures such as tracheostomy, or even the proper timing for initiating and maintaining high risk convalescing infants is not clear. Attributable aerodigestive symptoms are related to pre-prandial, intra-prandial, or postprandial periods; thus, the specific diagnosis can be challenging. While safe oral feeding requirement with adequate weight gain is an essential criterion for hospital discharge⁸⁰ these young patients demonstrate feeding problems that include feeding-related bradycardia and desaturation, coughing, gagging, arching and irritability, refusal to feed or aversion, and inadequate nipple feeding ability associated with failure to thrive.^{81,82} Thus, development of discharge feeding strategies can be challenging to both the parents and the providers. Anecdotal experiences and empiric therapies result in changes to feeding plans frequently. Ascertaining the optimal timing for gastrostomy, as well as the development of post-gastrostomy rehabilitation strategies remains unclear. All these concerns will continue to escalate the health care costs.⁸³

B) Our experience with precision medicine in the development of personalized feeding strategies^{4,82,84}

For the patients, parents and providers, 3 major conundrums exist with feeding and breathing safety: a) Feeding and swallowing difficulties involving upper aerodigestive systems, b) GERD and the consequences of disease and or therapies, and c) impaired airway protection. While feedings (nutrients) are fundamental to overall growth and development, the appropriate institution of feedings (strategies) to attain this goal must go hand-in-hand because feeding targets are constantly changing in the context of variations in ontogeny of gut and oromotor development, as well as changing patterns of disease in the NICU infant.

The concepts provided in the prior sections of this manuscript and application of the methodology developed to interrogate the effects of stimulus on aerodigestive sensory-motor patterns has permitted us to develop precision medicine approaches at the point of care. In these endeavors, we are able to recognize the neurosensory and neuromotor patterns and symptom occurrences, reproducibility of symptom-less responses, mapping the peristaltic and sphincteric reflexes, recognizing the airway responses, as well as defining the underlying mechanisms restoring aerodigestive homeostasis. Importantly, these approaches have permitted us to educate parents and providers in clarifying pathophysiology in relation to feeding and breathing safety, as well as develop personalized feeding management strategies.

In 100 infants referred for long term gastrostomy feeding strategies, with the development and institution of such approaches, we were able to avert gastrostomy in 51% of the subjects at discharge; furthermore, 84% of infants were able to achieve independent oral feeding abilities by 1 year age. The savings in health care costs by avoiding the placement of 51 gastrostomy tubes in this cohort was significant with an approximate amount of \$9.1 million saved over 5 years.⁸² Thus, the development of functional swallowing and aerodigestive protection is a process in continuum that is modified over time. The factors that modify these functions involve multiple afferent and efferents and feedback systems including but not limited to the brain, airway and respiratory system, and the foregut.

C) Our experience with disseminating knowledge to feeding therapy teams to standardize feeding-process

In a broad sense, impediments to achieving feeding milestones are due to two factors: a) patient's skills or physiology and b) provider approaches. Targeted continuous provider education was provided by integrating these two factors in our feeding program. Specifically, we disseminated knowledge to parents and providers with relevance to feeding methods and related aero-digestive symptoms that may need personalization. Preterm infants need time for maturation of the central and the enteric nervous system mediated reflexes that participate in activation, control, coordination, and adaptation of oromotor, aero-digestive, and peristaltic function.^{4,16,28,29,32,34,35,82,85-89} However, these reflexes can only be activated by a stimulus, i.e., feeds. In our approach, the feeding stimulus was provided during critical windows of opportunity across a maturational timeline. This was an all-inclusive provider- and infant- driven feeding program, targeting SIMPLE (simplified, individualized, milestone-targeted, pragmatic, longitudinal, and educational) feeding

strategies to improve overall feeding and outcome metrics, while monitoring balancing measures which included growth velocities, co-morbidities and length of hospital stay. Process optimization, implementation of feeding strategy, monitoring compliance, multidisciplinary feeding rounds, and continuous education strategies were employed. The ability to reach full enteral feeds and full oral feeds sooner in over 81% and 72% of the subjects respectively is noteworthy.⁹⁰ Furthermore, this standardized approach yielded positive economic outcomes in lowering the length of hospital stay as well as gastrostomy rates compared to the baseline period. Both these key outcome measures are dependent on adequacy of aerodigestive systems and overall maturation.

4) SUMMARY

Technological advances and cutting edge research permitted understanding of vagal pathobiology and functional aerodigestive connectivity involved in regulating swallowing and aerodigestive functions. We recognized that the neurosensory and neuromotor pathways are influenced by pathologies during perinatal events, prematurity, inflammatory states and coexisting medical and surgical conditions. We translated this knowledge to crib-side by clarifying symptom occurrences and precision medicine based personalized feeding strategies. Approaches to clarify pathophysiologic mapping of aerodigestive interactions, as well as translating these discoveries into the development of personalized and simplified feeding strategies to advance child health are detailed. Coordinated interdisciplinary feeding management strategies are essential as the problems pertinent to the aerodigestive systems 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. Further studies are needed to generalize our approaches to improve better feeding outcomes. In addition, clarification of aerodigestive symptoms and malfunctions among infants with birth asphyxia, GERD, dysphagia, CLDI, and infants undergoing prolonged intensive supports are needed so as to develop targeted therapeutic strategies.

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ABBREVIATIONS

UES	upper esophageal sphincter
LES	lower esophageal sphincter
GER	gastroesophageal reflux
GERD	gastroesophageal reflux disease
TLESR	transient LES relaxation

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Figure 1. Schematic representation cumulative reflexes to pharyngo-esophageal stimuli
Pharyngeal (blue) or esophageal (green) stimulus evokes regional (pharyngo-esophageal reflex responses within the upper digestive tract), extraregional (responses within pulmonary and cardiac systems), and neurocognitive (sensation, perception, regulation of integrative reflexes) responses. Shaded color coded insets represent functional disturbances in the respectively shaded organs.

Figure 2. Mapping of pharyngo-esophageal reflexes in response to stimulation (pharyngeal: A, B and esophageal: C,D)

Potential pharyngo-esophageal responses to pharyngeal stimulation are *A) Pharyngeal Reflexive Swallowing* characterized by pharyngeal contraction, UES relaxation, esophageal body peristalsis, and pharyngo-LES-relaxation reflex, and *B) Pharyngo-UES-Contractile Reflex* characterized by UES contraction and pharyngo-LES-relaxation reflex. Potential responses to esophageal stimulation are *C) Esophago deglutition reflex* characterized by pharyngeal contraction, UES relaxation, esophageal body peristalsis, and esophago-LES-relaxation reflex and *D) Secondary Peristalsis* characterized by UES contraction, esophageal body peristalsis and esophageal-LES-relaxation reflex. DMN-Dorsal Motor Nucleus, NTS-Nucleus tractus solitaries, NA-Nucleus ambiguus, Px-pharynx, UES-upper esophageal

sphincter, PE-proximal esophagus, ME-middle esophagus, DE-distal esophagus, LES-lower esophageal sphincter, Sto-stomach

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A. Maturation Responses to Pharyngeal Infusion

B. Media and Maturation Responses

Figure 3. Characterizing maturation effects of pharyngeal stimulus induced reflexes

A) Maturation comparison of responses to air and water pharyngeal infusion. (a) Response to air infusion 35 wk postmenstrual age. (b) Response to air infusion 39 wk postmenstrual age. (c) Response to water infusion 35 wk postmenstrual age. (d) Response to water infusion 39 wk postmenstrual age. Maturation differences are evident in both air and water infusion responses. Notice more rapid PRS onset in response to air infusions vs. water during both time-1 and time-2. Additionally, PLESRR onset time significantly decreases in response to air with time-2 infusions (vs. time-1). The magnitude of PLESRR is greater in response to water (vs. air) during time-2, as well as compared to water time-1. The duration of PLESRR is increases in response to water infusions (vs. air) at each time; however, PLESRR duration in response to water infusions decreases with maturation. LES, lower esophageal sphincter; PLESRR, pharyngo-lower esophageal sphincter relaxation reflex; PRS, pharyngeal reflexive swallow; UES, upper esophageal sphincter. *B) Characterization of media and maturational responses.* (a) Response latency to pharyngeal reflexive swallow (in seconds); * $P = 0.04$; ** $P = 0.007$; triangle with a stroke: air; square with a stroke: water. (b) Frequency of pharyngeal reflexive swallow, %; * $P = 0.0004$; ** $P = 0.002$; gray box: air; black box: water.

(c) Frequency of complete propagation, %; *P = 0.01; **P = 0.007; gray box: air; black box: water. (d) Frequency of multiple pharyngeal reflexive swallows; %; *P < 0.0001; **P = 0.0003; gray box: air; black box: water. (e) Response latency to pharyngo-LES relaxation reflex (in seconds); *P = 0.05; triangle with a stroke: air; square with a stroke: water. (f) Frequency of pharyngo-LES relaxation reflex, %; *P = 0.01; gray box: air; black box: water. (g) Duration of LES nadir (in seconds); *P = 0.05; **P = 0.006; gray box: air; black box: water. (h) Magnitude of LES relaxation; mmHg; *P = 0.03; **P = 0.05; gray box: air; black box: water. Infants respond differently to air vs. water stimulus with maturation (time 1–35 wk postmenstrual age vs. time 2–39 wk postmenstrual age). Panels a–d characterize PRS responses to both media and maturation. Panels e–h characterize PLESRR responses to both media and maturation. PLESRR, pharyngo-lower esophageal sphincter relaxation reflex; PRS, pharyngeal reflexive swallow. *Source: Jadcherla et al, Ped Research 2015.*

Figure 4. Genesis of cough reflex: effect of esophageal and pharyngeal stimulus

Stimulus induced coughing associated with aerodigestive mechanisms: (a) Cough reflex in response to esophageal stimulation: Note (i) 2 ml air introduced into the mid-esophagus, (ii) associated with upper esophageal sphincter contractile reflex as the initial aerodigestive mechanism with respiratory rhythm disturbance (10.8 s) characterized by cessation or respiratory activity, (iii) cough, and (iv) complete primary peristalsis restoring aerodigestive and respiratory quiescence. (b) Cough reflex in response to pharyngeal stimulation: Note (i) 0.3 ml water introduced into the pharynx, the respiratory rhythm disturbance (74.7 s) characterized by irregularly spaced bursts of rapid breathing efforts during which there is (ii) multiple failed swallowing attempts as the initial aerodigestive mechanism, and (iii) multiple cough events, (iv) attempts of aerodigestive restoration, and (v) complete peristalsis restoring aerodigestive and respiratory quiescence. *Source: Jadcherla et al, Ped Research 2015.*

Figure 5. Pathophysiology of Aerodigestive reflexes: contributory factors and mechanisms

Contributory factors and potential central and regional mechanisms associated with neonatal dysphagia. BPD, bronchopulmonary dysplasia; CPG, central pattern generator; CNS, central nervous system; ENS, enteric nervous system; GERD, gastroesophageal reflux disease; GI, gastrointestinal; NEC, necrotizing enterocolitis. *Source: Jadcherla, Am J Clin Nutr 2016.*