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Effects of Esophageal Acidification on Troublesome Symptoms: An Approach to Characterize True Acid GERD in Dysphagic Neonates

Maneesha Sivalingam, BS¹, Swetha Sitaram, MS¹, Kathryn A. Hasenstab, BS, BME¹, Lai Wei, PhD⁴, Frederick W. Woodley, PhD^{2,3}, and Sudarshan R. Jadcherla, MD^{1,2,3,5}

¹Innovative Neonatal and Infant Feeding Disorders Program, Center for Perinatal Research, The Research Institute at Nationwide Children's Hospital, OH, USA

²Department of Pediatrics, The Ohio State University College of Medicine, Columbus, OH, USA

³Division of Pediatric Gastroenterology and Nutrition, Nationwide Children's Hospital, Columbus, OH, USA

⁴Center for Biostatistics, The Ohio State University College of Medicine, Columbus, OH, USA

⁵Division of Neonatology, Nationwide Children's Hospital, Columbus, OH, USA

Abstract

Objective—To quantify and compare maximal extent (height) of acid reflux events (AREs) on symptom generation in dysphagic neonates.

Methods—Dysphagic neonates (N=53), born at 30 ± 5.3 wks gestation, underwent 24-hour pH-impedance study for the evaluation of troublesome symptoms purported to be due to gastroesophageal reflux disease (GERD). AREs (pH < 4 for > 4 seconds) detected by impedance (Z) were categorized by maximal extent as refluxate reaching distal (Z6, Z5), middle (Z4, Z3), or proximal (Z2, Z1) impedance channels. AREs reaching the pH sensor only were categorized as distal. Symptom correlation (%), symptom index (SI), symptom sensitivity index (SSI), and

Address correspondence to: Sudarshan R. Jadcherla, MD, FRCPI, DCH, AGAF, Professor of Pediatrics and Associate Division Chief, Divisions of Neonatology, Pediatric Gastroenterology and Nutrition, 700 Children's Drive, Nationwide Children's Hospital, Columbus, OH 43205, **Phone:** 614-355-6643; **Facsimile:** 614-355-5899.

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Contributors' Statements:

1. **Maneesha Sivalingam:** procedures, design, data verification and statistical analysis, interpretation, figures/tables, writing and revisions, critical review, approval of final draft.
2. **Swetha Sitaram:** Biostatistician, statistical design, manuscript writing, critical review, and approval of final draft.
3. **Kathryn A. Hasenstab:** data verification and statistical analysis, interpretation, figures/tables, editing the revisions, critical review, approval of final draft.
4. **Lai Wei:** Biostatistician, statistical design, manuscript writing, critical review, and approval of final draft.
5. **Frederick W. Woodley:** validation of methods, manuscript writing and revisions, critical review, approval of final draft.
6. **Sudarshan R. Jadcherla:** concept and relevance, design and procedures, analysis, validation and interpretation, writing 1st draft and revisions, critical review, approval of final draft, IRB correspondence, securing funding.

symptom associated probability (SAP)) and temporal characteristics (clearance times) of AREs were analyzed using linear mixed and GEE models comparing height categories presented as mean $\pm$ SEM, median (IQR), and OR (95% CI).

Results—Of the 2003 AREs: 1) distal extent AREs (n=1642) had increased frequency ($p < 0.05$), decreased ACT ($p < 0.05$), and decreased acidity ($p < 0.05$), 2) in middle and proximal AREs, acid clearance was longer than bolus clearance, $p < 0.01$, and 3) the odds of having cardiorespiratory (cough or sneeze) symptoms are increased with proximal and middle AREs ($p < 0.05$).

Conclusion—Most proximal ascent of AREs into middle or proximal esophagus likely activates protective aerodigestive reflexes (peristalsis) or vigilant states to facilitate bolus and chemical clearance. Heightened esophageal sensitivity, acid neutralization delays, or clearance mechanism delays may accentuate multi-systemic troublesome symptoms.

Keywords

GERD; dysphagia; deglutition; deglutition disorders; swallowing; acid reflux

INTRODUCTION

Swallowing disorders among infants manifesting as feeding difficulties, oral aversion or troublesome aerodigestive symptoms are often indistinguishable from symptoms of gastroesophageal reflux disease (GERD). GERD is a common condition in infants with feeding difficulties affecting about 10.3% of convalescing ICU infants (1–3). Immature regulation and coordination of the lower esophageal sphincter contractile and relaxation characteristics (4–6) or anatomical defects in the esophagus, stomach, or gastroesophageal junction increases the prevalence of GER (7). Large feeding volumes, immature pharyngo-esophageal motility mechanisms, and maladaptation of aerodigestive reflexes may contribute to the inadequate clearance of acid reflux events (AREs), thus contributing to prolonged esophageal stimulus and ensuing symptoms (8–10). However, the magnitude or prevalence of reflux-symptom relationship is unclear.

As GERD is often suspected based on symptoms, acid-suppressive therapies (histamine-2 receptor antagonists, proton pump inhibitors), non-pharmacological strategies (thickening feeds, positioning), or surgical approaches (gastrostomy and/or fundoplication) are considered as clinically indicated (3, 11–16). However, objective diagnosis of symptoms specific to acid-GER events or of its proximal migration remains to be clarified in infants. Since GERD testing can be expensive, labor intensive, time consuming, and not readily available, providers prescribe acid suppressive medications that are easily available (17, 18). Even though the use of acid suppressive medication is associated with nosocomial infections, enterocolitis, nutrient malabsorption, and osteopenia, the widely held belief that it can easily assuage the problematic cardiorespiratory, sensory, and physical symptoms has not waned (17, 19–21). Hence objective evaluation of GERD is important prior to instituting therapy.

Using 24 hr pH-Impedance studies, the chemical (acid or nonacid), physical (liquid, gas, or mixed), spatial (height), and temporal (clearance time) characteristics of GER (1, 19) in

relation to the symptom occurrence can be defined (22–24). Ascending AREs can expose the esophageal column, upper esophageal sphincter, pharynx, oral cavity, and/or nares to gastric contents depending on the height reached. The maximal extent (height) of refluxate is especially important as the presence and magnitude of troublesome symptoms may be dependent upon the spread of the acid or of its clearance (19).

Although the distal esophagus is known to be the more common site of GERD pathogenesis, there has been great debate as to what extent pH-only events represent true GERD. It has been shown that the proximal esophagus is more sensitive than the distal esophagus during acidic stimulation (19, 25, 26). However, it is unclear how the maximal extent of acid bolus differs and its effect on symptoms in infants with dysphagia, and further scrutiny is needed to provide clues for appropriate treatment. Therefore, our objectives were to quantify and compare ARE height on symptom generation. We hypothesized that proximal AREs are distinct from distal AREs with regards to: 1) the chemical and temporal characteristics, and 2) provocation of troublesome symptoms. Understanding the characteristic differences may pave the way for objective, evidence-based therapeutic strategies for improvement of dysphagia likely related to reflux-type symptoms.

MATERIALS AND METHODS

Participants and Study Design

Participants were 53 dysphagic (clinically defined as oral feeding difficulties or aerodigestive symptoms in the post prandial state) neonates (27 males) born at 30 ± 5.3 (mean $\pm$ SD) weeks gestation (birth weight 1.7 ± 1.3 kg, postmenstrual age 44 ± 6.9 wk) referred for the evaluation of troublesome symptoms suspected to be due to GERD. All studies were performed in the neonatal intensive care unit at Nationwide Children's Hospital, Columbus, OH. Informed consent was obtained from the parents, and Health Insurance Portability and Accountability Act guidelines were followed. Permission was granted by the Institutional Review Board at Nationwide Children's Hospital to report the data retrospectively. Infants were excluded from this study if they had genetic or chromosomal abnormalities, or if receiving acid suppressive medications or prokinetics. Feeding methods at evaluation and discharge respectively, were 28: 72 and 47: 53 (% oral, % transitional, $p < 0.01$).

pH-Impedance study methods and protocol

Twenty-four hour pH/Impedance methods were utilized as previously published (1, 19, 27). Studies were performed using antimony single use pH-impedance catheters (Greenfield MMS-Z1-I, 6.4 French, Medical Measurements Systems USA, Inc. Dover, NH). The catheters contained a total of seven impedance electrodes spaced 1.5 cm apart to create six impedance channels (Z1 – Z6) with a pH sensor between impedance sensors 6 and 7 (Figure 1). The pH probe was calibrated with pH 4.0 and pH 7.0 buffer solutions prior to placement. In the absence of manometric evaluation, expert ESPGHAN guidelines were considered for an emphasis on generalizability, feasibility, safety, and hospital policy compliance (28). ESPGHAN guidelines state that the pH electrode should be positioned 2 vertebrae above the diaphragm and confirmed by chest x-ray, yet this method has its own limitations (28–30). In

an effort to closely place the pH sensor in the distal esophagus yet being pragmatic, feasible and safe, predicted averages from published estimation formulas (based on somatic esophageal growth characteristics) were used and verified by chest x-ray (28, 30–32). As the diaphragmatic hiatus or upper border of the lower esophageal sphincter junction is located at T10 vertebral level, pH probe position was verified by chest x-ray if the pH sensor was at the T7–T8 vertebral level to comply with ESPGHAN guidelines (28, 33). The pH-impedance probe was connected to a portable pH/Impedance device (Ohmega, Medical Measurements System USA, Inc. Dover NH) for proper recording of the pH-impedance tracings.

Documentation of Symptoms

Symptoms and meal times of the infants were documented and recorded by trained nurse assistants who were blinded to the pH-impedance recordings. They worked in 6–8 hour shifts over the study duration to ensure real time symptom documentation at bedside (1, 19, 27). Event markers were placed directly using the button interface of the recording system. The following events of interest were documented: coughing, gagging, sneezing, bradycardia, emesis, flushing, grimacing, grunting, and arching/irritability. The recorded symptoms were correlated with the reflux events to calculate the symptom index (SI), symptom sensitivity index (SSI), and Symptom Association Probability (SAP) (23, 24, 34).

Data Analysis

An ARE was defined as a drop in pH < 4.0 for > 4 s and verified manually. ARE maximal extent, or height, was arbitrarily defined as distal (Z6, Z5), middle (Z4, Z3), or proximal (Z2, Z1) extent detected by the pH-impedance probe (Figure 1) (9, 19, 35, 36). To be detected by impedance sensors, an ARE must drop 50% from baseline originating in the Z6 channel. It is well known that multiple AREs are not detected by impedance but do ascend to only the pH sensor (pH-only events). To alleviate under-representation of these events on symptom generation, these pH-only events were also categorized as distal AREs. False pH-refluxes caused by pH-fluctuations or electrode drift were ruled out, and not included.

Maximal ARE Extent Characteristics—ARE characteristics were compared between distal, middle, and proximal extent (Figure 1): *Acid Clearance Time (ACT)*, *nadir pH*, *SI*, *SSI*, *SAP*, and *frequency of liquid swallows* (1, 19, 37–39). ACT was defined as the time that the esophageal mucosal pH took to normalize to pH 4.0. *Bolus Clearance Time (BCT)* indicated the duration (s) from a drop in impedance to 50% of the baseline impedance to when impedance returns to 50% baseline (Figure 1) (9, 19). BCTs were only documented for impedance detected AREs as the nature of pH-only events have no detectable impedance drops. For each ARE, the lowest (nadir) pH value reached, was documented to indicate the degree of acidity of the bolus (lower pH = higher acidity).

Since, post reflux clearance mechanisms in infants include deglutition and secondary peristaltic responses (40–42), we also measured post reflux swallowing as a measure of clearance. *Liquid swallows* were classified by a drop in impedance 50% from baseline impedance moving in the antegrade direction from Z1 to Z6 (37, 39). A liquid swallow

was associated with GER if it occurred within two minutes after the onset of the ARE (Figure 2).

Effect of ARE Height on Symptom Generation—Symptoms exhibited by the subjects were considered to be temporally associated with an ARE if the symptoms occurred 120 sec from ARE onset. Documented symptoms were further classified into one of three groups: *cardiorespiratory* (coughing, gagging, sneezing, bradycardia, apnea, periodic breathing, desaturation), *sensory* (emesis, flushing, grimacing, grunting, startle), and *physical* (back arching and irritability). SI and SSI were calculated as $(\text{number of symptoms associated with AREs} \div \text{total number of symptoms}) \times 100$ per patient and $(\text{number of AREs associated with symptom} \div \text{total number of AREs}) \times 100$ per patient, respectively (23, 34). SAP was calculated to provide the probability that the observed associations between symptom and ARE did not occur due to chance (24).

We also evaluated the effect *Acid Reflux Index (ARI)*, defined as the percent of total time pH < 4.0, on temporal and symptom correlations of maximal extent AREs classified by severity. Per NASPGHAN guidelines, ARI is with ARI < 3% was defined as normal, ARI between 3% – 7% (inclusive) as indeterminate, and ARI > 7% as abnormal (3).

Statistical Analysis

Since multiple measures within each patient may be correlated, linear mixed models were used to measure chemical and temporal characteristics of ARE maximal extent categories (distal, middle, and proximal). Generalized estimating equations were used to compare outcomes that were categorical such as symptom associations. SI, SSI, and SAP for each individual subject was calculated and median (IQR) was used to summarize associations for the entire population. Wilcoxon signed-rank test was used to compare SI, SSI, and SAP between ARE height. Results are presented as mean $\pm$ SEM, OR (95% CI), percentage (%), or as otherwise indicated. A p-value < 0.05 was considered significant. All statistical analyses were performed using SAS v9.3 (SAS Institute, Cary, NC).

RESULTS

Refluxate Characteristics

A total of 2003 AREs over 1007 hours of study time comprised of the following maximal extent height classifications: distal in 1642 (82%), middle in 160 (8%), and proximal in 201 (10%). Characteristics (frequency of ARE, ACT, and nadir pH) of ARE height comparisons are shown (Table 1).

Symptom Associations

A total of 4780 symptoms were recorded and analyzed. While 8% of the total symptoms were associated with AREs (SI), 20% of the total AREs were associated with at least one symptom (SSI). A detailed analysis comparing frequency of symptoms (%), SI, SSI, and SAPs for the maximum extent AREs are shown with the symptom subcategories (cardiorespiratory, sensory, and physical) and the top 2 most frequent symptoms in each respective subcategory (Table 2). Additionally, in our investigation, we determined that the

odds (OR, 95% CI) of having a cardiorespiratory symptom association was 2.6 (1.7 – 3.8) times higher with proximal AREs and 1.6 (1.1 – 2.3) times higher with middle AREs vs distal AREs ($p < 0.05$). A sensory symptom association was 2.6 (1.5 – 4.4) times higher with proximal AREs vs distal AREs ($p < 0.01$). No significant associations were observed between physical type symptoms and ARE height.

Symptom Associations within the ARI Severity Groups

Of the 53 infants, 20 (38%) had a normal ARI, 17 (32%) had an indeterminate ARI, and 16 (30%) had an abnormal ARI. A total of 332 (17%) AREs were positively associated with symptoms of which 18% had normal ARI, 27% had indeterminate ARI, and 55% had severe ARI. Further analyses were conducted to calculate the odds of having a cardiorespiratory event, sensory and physical symptom association between ARE height within each ARI severity group (Table 3).

Relationship of Acid Clearance Time between ARE Height within ARI Severity

Maximal ARE extent (distal: middle: proximal, %) was 37:29:34, 25:40:35, and 11:36:53 in normal, indeterminate, and abnormal ARI groups, respectively ($p < 0.05$ vs abnormal ARI group). Additionally, proximal and middle AREs have prolonged ACT when ARI is Abnormal (Figure 3).

ARE Swallowing Relationships

The odds of having a swallow associated with ARE increases by 2.1 (1.7 – 2.5) times per one unit decrease in pH. The odds (OR, 95% CI) of having a swallow associated are higher with proximal 2.0 (1.4 – 2.9) and middle AREs 1.8 (1.2 – 2.7) vs. distal AREs ($p < 0.05$). There was no significant difference in the odds of swallowing between proximal 1.1 (0.8 – 1.7) vs. middle events ($p = 1.0$).

DISCUSSION

The primary aim of this study was to quantify and compare the effects of maximal ascent of AREs on symptom generation in dysphagic neonates. In this selected population, the most prevalent cardiorespiratory symptoms observed were coughing and sneezing, and the most prevalent sensory symptoms were grunting and grimace. Importantly, proximal and middle AREs were distinct from distal AREs with respect to the spatial and temporal characteristics and magnitude of associated troublesome symptoms. However, proximal vs middle AREs generally did not significantly differ. The efficiency with which rapidly ascending reflux is cleared is a necessity for airway protection, considering the dangers of gastric contents from flowing toward the aerodigestive tract. Symptoms such as acute coughing, sneezing, grunting, and gagging as well as frequent swallowing (as in middle and proximal esophageal exposure) may be protective mechanisms that thwart digestive material from the airway, or, the airway may be hyper-vigilant and overtly sensitive to proximal esophageal stimulus exposure manifesting as troublesome symptoms (19). Nonetheless, persistent ascending reflux is known to evoke troublesome chronic aerodigestive tract consequences such as airway spasm, glottal closure, retrograde aspiration, chronic cough, lung infections and laryngeal disorders (43–45). Prolonged acid clearance associated with proximally ascending

AREs correlated with symptoms and delays in acid neutralization or clearance mechanisms may sensitize and accentuate multi-systemic troublesome symptoms.

Furthermore, contacting a larger surface area, the acidic refluxate stimulates the afferent pathways which in turn are evoking various efferent responses such as symptoms and esophageal peristaltic bolus clearance. Therefore, the normalization of acidic residue throughout the esophagus is crucial in AREs. This may be accomplished by two possibilities: volume clearance and chemical clearance (46, 47). Volume clearance is the clearance of the bulk of the acidic reflux by esophago deglutition response (manifested as swallowing upon middle or proximal esophageal exposure, in the current study) and/or secondary peristalsis stimulated by mechanosensitive (stretch) or chemosensitive receptors in the esophageal mucosa, with esophago deglutition response being predominant with acid (40, 42, 48, 49). Thus, acidity in the esophagus may accentuate swallowing. Chemical clearance to buffer the acidic pH (< 4.0) to a neutral pH ($\geq$ 4.0) occurs by mechanisms that include the swallowing of bicarbonate-rich saliva and the direct secretion of bicarbonate and proteins into the esophageal lumen by sub-mucosal glands (47). In the context of the present study, the odds of swallowing increase with increasing acidity and proximally ascending (proximal and middle extent) AREs. This is likely to be related to peristaltic attempts to clear the chemical residue from the esophageal mucosa resulting from exposure of the ascending acid bolus. However, the presence of prolonged mucosal acidic contact (due to delays in chemical clearance) may continue to provoke the troublesome symptoms. Given that acid clearance duration of ascending AREs was prolonged (vs. bolus clearance), it is likely that peristaltic reflex mechanisms alone may not be sufficient to neutralize esophageal acidity. While we can suggest that esophageal dysmotility is resulting in inadequate clearance of the acid, it is also feasible that other acid-neutralizing mechanisms may be flawed. Such inconsistent mechanisms may include production of salivary bicarbonate, mucosal secretions, and mucosal proteins which buffer H⁺ ions (50). In addition to its role in buffering, salivary factors protect and repair the esophageal mucosa (50).

In our study, a majority of the ascending AREs (between 83 – 87% depending on ARE height) did not result in troublesome symptoms (Table 2), likely due to timely operational aerodigestive mechanisms (glottal closure, upper esophageal sphincter contractile reflex, lower esophageal sphincter relaxation reflex, secondary peristalsis, and/or esophago deglutition reflex) to prevent the symptoms (4, 40, 41, 51, 52). The remaining percentage of ascending AREs are associated with symptoms, and may be explained by ineffective, delayed or malfunctioning aerodigestive reflexes in which prolonged and more proximal exposure of the esophagus to refluxed acid may be activating visceral, autonomic and sensory aerodigestive pathways (44, 51, 53, 54). Other explanations may include varying volume of the refluxate and/or sleep state (1, 19, 44, 53–55).

Application of established symptom indices (SI, SSI, and SAP) can be utilized to clarify the understanding of GERD severity as defined by the presence, magnitude, and probability metrics, and assist in the diagnosis of mechanistic basis of symptoms (23, 24, 34). SI gives a picture of GERD symptoms in relation to overall symptoms or a measure of the symptom specificity, and SSI quantifies a subject's symptom sensitivity to AREs (23, 34). Since SI and SSI do not take into account the total number of AREs and total number of symptoms,

respectively, and do not take into account association due to chance, SAP was developed (24). SAP is a single quantitative measure of the strength of the association between symptoms and AREs. A high SAP confirms the probability that the ARE-symptom association is not due to chance.

Since controversy still exists about the best index to detect GERD, multiple symptom indices can be utilized in conjunction for further characterization of symptom generation and development of individualized therapeutic strategies (56–58). As an example, in this population regarding cough symptoms, middle and proximal AREs have normal SI but abnormal SSI (Table 2). This suggests that higher extent AREs provoke the esophagus, those specific symptoms occur (evidenced by abnormal SSI), however other causes of the symptoms (cough in this case) should be explored as well (evidenced by normal SI) (58–60). Additionally, SI and SAP have been shown to be good predictors of therapy response (or symptom resolution) (24, 57, 61). Therefore, if an infant exhibited a positive SI and SAP for ascending AREs, symptoms may resolve after combined multi-pronged anti-reflux therapy that pays attention to feeding strategies, posture, and acid suppression. On the other hand if an infant exhibited a positive SI and SAP to distal AREs, the symptoms may resolve after acid-suppressive therapy. Based on our findings and prior work, empiric acid-suppressive therapies based on symptoms alone should not be recommended, as we run the risk of treating normals and miss abnormal causal mechanisms (non-GERD related) in several. Such a practice can prolong hospitalization amidst uncertainty of causal mechanisms. We believe the indication and duration of PPI use in infant-GERD should be based on objective testing by utilizing pH-impedance methods and symptom correlation metrics. Larger randomized control trials are needed to examine therapies in objective-evidence based GERD in infants. The lack of such approaches has resulted in an alarmingly high prescription of GERD therapies. Although this may be cumbersome, training approaches for generalization of such diagnostic strategies are needed. We typically prescribe PPI therapy for a limited duration if only when the acid reflux index is >7 and/or positive symptom correlation with acidic refluxate.

Neonates are highly susceptible to acid-induced inflammation when the ARI $> 7\%$ (3, 62). Consequently, the mechanisms by which neonates attempt to clear the refluxed acid were examined in our study. Inflammation of the esophagus due to constant acid exposure can lead to decreases in the permeability of the esophageal mucosa, activation of inflammatory mediators and stimulation of nerve/muscle interactions. These factors may cause activation of pain pathways, resulting in sensory, cardiorespiratory, and/or physical symptoms.

In the present study, within the abnormal ARI group (> 7), the odds of having cardiorespiratory symptoms was greater with more proximally ascending AREs than distal AREs (Table 3). Thus, the symptom generating mechanisms in the neonatal human esophagus, when chronically exposed to severe acidity, is likely due to inflammation and or repetitive multi-modal activation of mechano- or chemo-sensitive stimulation induced reflexes, albeit with troublesome symptoms. Additionally, acid clearance was significantly prolonged with AREs extending to proximal and middle esophagus in the Abnormal ARI group (Figure 2), suggesting a greater struggle to adequately clear higher ascending acid refluxate with increasing acid severity. Diagnoses such as this, therefore, may warrant acid

suppressive therapy and follow-up for resolution of constantly ascending acidic refluxate as well as the associated troublesome symptoms. Previously, Jadcherla *et al* (19) correlated the spatio-temporal relationship of ascending events to elicited symptoms and Woodley *et al.* compared the specific reflux characteristics (frequency, ACT, and BCT) between impedance positive and pH-only events (36). However, the current study is unique in that we have characterized an approach to define true GERD symptoms that merit appropriate management and follow up. In particular, we have addressed objectivity and tighter treatment criteria, i.e., ARI >7, middle- and proximal- extent of AREs, abnormal symptom correlation metrics based on impedance methods. Such approaches will prevent the use of empiric therapeutic strategies.

Limitations and Approaches to Overcome

We have classified distal, middle and proximal esophageal regions based on scientific reasoning, pragmatic generalizability of methods, while advocating for subject safety and quality assurance of tests. To this effect, a combination of estimating formulas were utilized for pH sensor location in the distal esophagus, and further confirmed by chest X-ray. We acknowledge pharyngo-esophageal manometric localization methods to be accurate; such approaches could not be performed due to ethical and feasibility limitations. Estimation formulas must be chosen and applied with caution for the age groups for which these were defined (29, 30) as esophageal growth patterns vary from subject to subject. Chest x-ray too has its own limitations based on subject positioning. Regardless, the vertebral body markers (T7–T8 junction) can be used for consistency in pH-sensor placement.

In conclusion, our study describes inefficiency of chemical clearance as an underlying pathophysiological mechanism specific to the development of infant-GERD; this is more so of a problem with acid migration to middle and proximal esophageal segments. On the other hand, distal AREs may only be relevant if associated with positive SAP values. Infants with troublesome symptoms and/or swallowing difficulties may merit personalized GERD management strategies, only if presenting with evidence of abnormal ARI and/or proximally ascending AREs with troublesome symptoms. Although decreasing the acidity of the stomach contents has been proven to correlate with alleviating esophagitis (63), it can be inferred from this study that more proximally extending esophageal stimulation compared to distal esophageal acidification may be strongly linked to dysphagia symptom generation mechanisms. Additional therapeutic regimens are needed to prevent or reduce contact of the proximal esophagus with refluxed acidic gastric content. Our study methods and approaches offer an ability to objectively test the effects of targeted therapeutic strategies.

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Abbreviations

GER	Gastroesophageal Reflux
GERD	Gastroesophageal Reflux Disease

ARE	Acid Reflux Event
ARI	Acid Reflux Index
SI	Symptom Index
SSI	Symptom Sensitivity Index
SAP	Symptom Association Probability

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Figure 1. Definitions of Maximal ARE Extent

Note on the left hand side a representative example of the pH-impedance probe (Model ZI - I) in the esophageal column with the pH sensor positioned at 1.5 cm above the upper border of the lower esophageal sphincter (LES UB). ARE maximal extent was defined as the maximum ascent or height of the refluxate detected by the pH-impedance probe as into distal (Z6, Z5), middle (Z4, Z3), or proximal (Z2, Z1) segments. A–C are representative examples. Note, events reaching the pH sensor only were also categorized as distal extent. BCT-bolus clearance time, ACT- acid clearance time.

Figure 2. Post ARE Swallowing Association

Depicted is a representative example of liquid swallowing (classified by a drop in impedance 50% from baseline moving in the antegrade direction from Z1 to Z6) occurring within 120 sec from ARE onset.

Figure 3. Impact of ARI Severity on Acid Clearance Time in Maximum Extent ARE groups

Comparisons were made: a) between ARE heights (distal, proximal, and middle) in each of the corresponding ARI severity (Normal, Indeterminate, and Abnormal) groups, * $p < 0.05$ vs distal, and b) within each ARE height category † $p < 0.05$ vs Normal ARI. Note, the ACT of proximal and middle AREs is increased in the abnormal ARI group.

Table 1

Characteristics of Maximal Extent AREs (N=2003) in the Esophageal Column

Characteristic	Distal (n=1642)	Middle (n=160)	Proximal (n=201)	p-value
ARE (per subject/24 hr), #	23(12–47) [*] [†]	3(2–5)	3(2–7)	<0.001
ACT, s	58±6.2 [*] [†]	181.3±13.5 [*] [‡]	139.2±12.4 [‡]	<0.001
BCT, s	11±1.1 [‡]	12.5±0.9	14±0.8	0.1
Degree of Acidity, pH nadir	3.1±0.06 [*] [‡]	2.4±0.07	2.5±0.07	<0.001

^{*}
p<0.05 vs middle,

[†]
p<0.05 vs proximal,

[‡]
p<0.001 vs BCT in the corresponding ARE extent category.

Data presented as median (IQR) or mean ± *SE*.

Table 2

Maximal Extent ARE (N=2003) Symptom Relationships

Characteristic	Distal (n=1642)	Middle (n=160)	Proximal (n=201)	p-value
Overall Symptom, %	17	13	16	0.4
SI	5(2–10) ^{*†}	1(1–2)	2(1–2)	<0.001
SSI	19(9–26)	20(14–25)	25(11–33)	0.5
SAP	86(80–96) ^{*†}	67(62–75)	78(64–89)	<0.001
Cardiorespiratory, %	6 [†]	10 [†]	17 [*]	<0.001
SI	8(4–17)	3(2–8)	5(3–11)	0.02
SSI	9(5–13) ^{*†}	24(20–42)	25(15–40)	<0.001
SAP	85(71–97)	88(74–91)	91(82–94)	0.5
Cough, n	5 ^{*†}	10	12	<0.001
SI	11(5–30)	4(3–11)	8(4–13)	0.04
SSI	9(6–11) ^{*†}	24(20–42)	25(13–40)	<0.001
SAP	86(70–99)	90(78–95)	92(81–97)	0.5
Sneeze, %	1 [†]	1 [†]	4	<0.01
SI	14(13–20)	20(20–20)	21(13–329)	0.6
SSI	3(2–8) [†]	9(9–9)	10(8–11)	0.02
SAP	75(67–91) [†]	92(92–92)	94(90–96)	0.04
Sensory, %	7 [*]	9	12	0.03
SI	16(5–29)	12(4–42)	5(3–18)	0.9
SSI	9(4–16) ^{*†}	20(20–50)	25(14–50)	<0.001
SAP	90(76–97)	94(84–99)	95(75–99)	0.5
Grunting, %	4%	3%	6%	0.4
SI	15(4–31)	2(2–26)	6(3–8)	0.2
SSI	8(6–16)	25(20–33)	14(10–25)	0.05
SAP	96(62–97)	73(68–84)	84(68–90)	0.6
Grimace, %	2%	2%	1%	0.8
SI	41(23–100)	55(11–100)	2(1–3)	0.3

Characteristic	Distal (n=1642)	Middle (n=160)	Proximal (n=201)	p-value
SSI	7(5–8) [*] [†]	18(17–20)	25(25–25)	<0.01
SAP	93(90–95) [†]	98(97–99) [†]	80(80–80)	<0.01
Physical (Arching/Irritability), %	16	22	15	0.1
SI	7(5–14) [*] [†]	3(2–5)	2(1–5)	<0.001
SSI	20(11–29)	29(16–45)	24(10–33)	0.07
SAP	88(78–97)	85(72–95)	77(72–90)	0.1

^{*} p<0.05 vs middle extent,

[†] p<0.05 vs proximal extent.

Data presented as %, median (IQR), or *mean* ± *SE*.

SI- symptom index, SSI- symptom sensitivity index, SAP- symptom associated probability

Table 3
Relationship of symptom correlations between ARE maximum extent related to acid reflux index (ARI) severity

ARI Group	Symptom Category	Proximal vs Distal*	p-value	Middle vs Distal*	p-value	Proximal vs Middle*	p-value
Normal (ARI <3)	Cardiorespiratory	0.9 (0.4–1.9)	1.0	1.9 (1.1–3.3)	0.07	0.5 (0.2–1.0)	0.2
	Physical	0.5 (0.2–1.0)	0.2	0.8 (0.3–2.0)	1	0.6 (0.2–1.8)	1.0
	Sensory	2.3 (1.0–5.2)	0.2	1.2 (0.3–4.6)	1	1.8 (0.3–10)	1.0
Indeterminate (ARI 3–7)	Cardiorespiratory	3.7 (2.2–6.0)	<0.01	1.5 (0.5–4.6)	1	2.4 (0.9–6.5)	0.3
	Physical	1.1 (0.5–2.6)	1.0	1.5 (0.9–2.7)	0.5	0.8 (0.3–2.2)	1.0
	Sensory	0.5 (0.09–2.7)	1.0	1.1 (0.3–3.7)	1	0.4 (0.07–2.9)	1.0
Abnormal (ARI >7)	Cardiorespiratory	3.0 (2.1–4.1)	<0.01	2.0 (1.2–3.2)	0.03	1.5 (1.0–2.4)	0.2
	Physical	1.5 (0.9–2.7)	0.14	1.8 (1.2–2.9)	0.02	0.8 (0.5–1.5)	1.0
	Sensory	1.9 (1.1–3.3)	0.05	2.1 (1.1–4.1)	0.07	0.9 (0.5–1.8)	1.0

Data presented as OR (95% CI).

* represents reference group. Interpretation example: Within the Abnormal group, the odds of having a cardiorespiratory event is 3.0 times greater with a proximal extent ARE vs a distal extent ARE.