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Symptom Scores and pH-Impedance: Secondary Analysis of a Randomized Controlled Trial in Infants Treated for Gastroesophageal Reflux

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Abstract

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Authors' Contributions:

Lai Wei and Sudarshan R. Jadcherla designed the study. Sudarshan R. Jadcherla secured NIH funding. Sudarshan R. Jadcherla and Rebecca K. Moore attained institutional review board approval. Zakia Sultana, Kathryn A. Hasenstab, Rebecca K. Moore, Erika K. Osborn, and Sudarshan R. Jadcherla performed studies. Zakia Sultana, Kathryn A. Hasenstab, and Vedat O. Yildiz analyzed data. Zakia Sultana, Kathryn A. Hasenstab, and Sudarshan R. Jadcherla drafted the initial manuscript. Zakia Sultana, Kathryn A. Hasenstab, Rebecca K. Moore, Erika K. Osborn, Vedat O. Yildiz, Lai Wei, Jonathan L. Slaughter, and Sudarshan R. Jadcherla validated and interpreted data, critically reviewed and revised the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

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The authors disclose no conflicts.

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The data that support the findings of this study are available upon reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Supplementary Materials

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BACKGROUND AND AIMS: To evaluate and compare gastro-esophageal reflux (GER) symptom scores with pH-impedance and test the effects of acid-suppressive medications with or without feeding modifications on pH-impedance in high-risk infants.

METHODS: Infant Gastroesophageal Reflux Questionnaire Revised (I-GERQ-R) and 24-hour pH-impedance data were analyzed from 94 infants evaluated in a tertiary care setting for GER disease. Longitudinal data from 40 infants that received randomized GER therapy (proton pump inhibitor [PPI] with or without feeding modifications) for 4 weeks followed by 1-week washout were analyzed. Relationships between I-GERQ-R and pH-impedance metrics (acid reflux index, acid and bolus GER events, distal baseline impedance, and symptoms) were examined and effects of treatments compared.

RESULTS: (A) Correlations between I-GERQ-R and pH-impedance metrics were weak. (B) I-GERQ-R sensitivity, specificity, and positive predictive values were suboptimal when correlated with pH-impedance metrics. I-GERQ-R negative predictive value (NPV) was high for acid symptom–association probability (NPV = 84%) and distal baseline impedence (NPV = 86%) thresholds. (C) PPI with feeding modifications (vs PPI alone) did not alter pH-impedance metrics or symptom scores ($P > .05$); however, bolus clearance metrics worsened for both treatment groups ($P < .05$).

CONCLUSIONS: In high-risk infants (1) I-GERQ-R may be a helpful clinical screening tool to exclude acid-GER disease diagnosis and minimize unnecessary acid-suppressive treatment, but further testing is needed for diagnosis. (2) Acid-suppressive therapy with feeding modifications has no effect on symptom scores or pH-impedance metrics. Clearance of refluxate worsened despite PPI therapy, which may signal development of pharyngoesophageal dysmotility and persistence of symptoms. (3) Placebo-controlled trials are needed in high-risk infants with objective pH-impedance criteria to determine efficacy, safety, and underlying mechanisms. Clinicaltrials.gov ID: NCT02486263.

Keywords

Gastroesophageal Reflux Disease; Symptom Questionnaire; pH-Impedance; Proton Pump Inhibitor; Infant

Introduction

Gastroesophageal reflux (GER) is a physiological process defined as the passage of gastric contents into the esophagus with or without regurgitation and vomiting, while GER disease (GERD) is pathophysiologic and occurs when GER is associated with troublesome symptoms and/or complications.[1,2] This distinction between GER and GERD remains enigmatic among survivors in the neonatal intensive care unit (NICU). Reflux-type symptoms (arching, irritability, acute life-threatening events, coughing, failure to thrive, and swallowing difficulties) in this high-risk infant population can be troublesome to the parent and provider, and empiric management using pharmacological and dietary changes are common albeit with consequences.[1,3–5] The ambiguous definition of ‘troublesome or bothersome symptoms’ in infants with GERD makes diagnosis challenging. Therefore, the scientific rationale remains obscured for differential diagnosis based solely on symptoms and GERD therapies, particularly with treatment initiation, duration, treatment stopping

rules, and follow-up for consequences from effects of diagnosis or of therapies. The possibility of other diagnoses being missed puts these infants at risk for unintended problems. Consequently, infants convalescing in the NICUs spend longer durations to achieve airway-digestive milestones as a necessary step for discharge. A lack of proper diagnostic testing among NICUs precludes the understanding of normal vs abnormal GER and a wide practice variation is evident as shown by symptom-based diagnostic rates varying from 2% to 30% across the United States.[6,7] This type of practice is associated with additional economic burden of more than $70k per NICU admission and an average 30 days increase in length of hospital stay.[6]

Symptom-Based Questionnaires and pH-Impedance Testing

Psychometric questionnaires can be better than empiric therapies but still run the risk of overtreating patients who may have symptoms but not actual GERD pathophysiology. A validated 12-item Infant Gastroesophageal Reflux Questionnaire Revised (I-GERQ-R) questionnaire has been developed for infants aged <18 months with uncomplicated GERD.[8] Some studies have noted that the I-GERQ-R does not distinguish GERD from colic in children aged <3 months.[9,10] A prospective study that measured reflux symptoms using I-GERQ-R found that while the I-GERQ-R score decreased over time, the frequency of regurgitation was constant until 6 months of age suggesting better adaptation with maturation.[9] Regardless, I-GERQ-R has been a widely accepted tool used in clinical trials to evaluate interventions and treatments[11–13] but is unclear whether this questionnaire correlates with objectively determined GER characteristics in infants in the NICU setting.

Twenty four–hour pH testing is another common tool used to determine GERD in infants.[1,2] A primary metric for determining treatment is the acid reflux index (ARI) or % of time of esophageal acid exposure.[1,14,15] Ambiguity still exits regarding abnormal ARI threshold values for infants.[1,2,16,17] The 2009 North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) clinical practice guidelines proposed ARI threshold values <3% as normal, 3%–7% as indeterminate, and >7% as abnormal.[2] Currently, 2018 NASPGHAN guidelines mention ARI >10% for infants aged <1 year[1] but true normative values are still needed. Distal baseline impedance (DBI) is a newer pH-impedance metric being used to evaluate damage to the esophageal mucosa with DBI values <900 Ω predicting severe esophagitis in children.[18] In infants, DBI values are correlated with ARI and those with DBI <900 Ω have increased prevalence of tube feeding at discharge.[19] In addition, symptoms may be unrelated to acid and persist even after treatment, which may be due to the variability of GER properties (acid/nonacid, liquid/gas/mixed, proximal/distal) within each infant. With the implementation of impedance methods and symptom association probability (SAP),[1,14,20] it is possible to determine whether acute symptoms such as coughing, apnea/bradycardia/desaturation, and arching/irritability are correlated with GER events and specific properties of refluxate.[14,21]

Current Management Therapies

Off-label use of pharmacologic (histamine-2 receptor antagonists, proton pump inhibitors (PPIs), and alginates)[3,22–24] and empiric nonpharmacologic treatments (body positioning, formula thickening, intake volume, feeding frequency, and tube feeding) has been

attempted.[13,25,26] An increased use of empiric acid-suppressive therapies exists worldwide despite potential side effects,[3,22–24,27] although these medications are not adequately tested for efficacy based on objective metrics in infants. Although current NASPGHAN guidelines recommend acid suppressive therapy for 4–8 weeks and wean if symptoms improve,[1,2] many infants remain on acid suppression well beyond discharge.[6,22,28] It is unknown if 4 or 8 weeks duration is truly sufficient to completely resolve GERD symptoms. We recently reported that 4 weeks of randomized GERD therapy (acid suppression alone vs acid suppression with feeding modifications) did not improve primary clinical outcomes (total I-GERQ-R score or tube-feeding prevalence)[28] or esophageal reflexes[29] between randomized groups. However, lower esophageal sphincter and distal esophageal motility functions worsened at follow-up for both treatment groups despite acid suppressive therapy.[29] Individual pH-impedance characteristics and actual symptoms have not been evaluated before.

Rationale, Aims, and Hypothesis

Definitions and diagnostic criteria to treat NICU infants for GERD remain enigmatic. Therefore, a secondary analysis of data was undertaken to add further insight into GER symptom scores, pH-impedance metrics, and the effects of acid-suppressive medications with or without feeding modifications in infants. This work will likely have clinical and translational research implications for future work. Therefore, our aims were (1) to understand relationships between parent/provider perception of symptom burden vs objective GERD metrics, by determining if the overall I-GERQ-R score or individual components in the questionnaire are correlated with any pH-impedance metrics of interest in infants evaluated for GERD and (2) to examine treatment effects (acid suppressive therapy with or without feeding modifications) on symptom burden scores and pH-impedance metrics. We tested the hypothesis that symptom scores and pH-Impedance metrics improve with simultaneously employed pharmacological and feeding-modification approaches. To our knowledge, this is the first report of longitudinal effects of treatments on pH-impedance metrics and symptom correlation in high-risk infants.

Methods

Study Design, Participants, and Setting

This is a secondary analysis of data obtained during a single-center, blinded, randomized clinical trial [28,29] (Clinicaltrials.gov: NCT02486263) performed in the NICU units at Nationwide Children's Hospital, Columbus, Ohio. Symptom scores and 24-hour pH-impedance data from convalescing NICU infants evaluated for GERD were analyzed. Informed parental consent and approval from the Institutional Review Board at The Research Institute at Nationwide Children's Hospital (IRB #11–00734) were obtained prior to testing. Health Insurance Portability and Accountability Act guidelines were followed. All authors had access to the study data and reviewed and approved the final manuscript.

As the original study began in 2012, the study design of the trial was based-off of the 2009 NASPGHAN ARI threshold values.[2] Infants were eligible for GERD therapy if their ARI was ≥3%. Additional inclusion/exclusion criteria were (a) clinical suspicion of GERD, (b)

pH-impedance evaluation with I-GERQ-R between 34 and 60 weeks postmenstrual age, (c) on full enteral feeds ≥150 mL/kg/d, (d) breathing room air or supplemental oxygen ≤1 liter per minute, and (e) absence of known genetic, metabolic, or syndromic disease, severe neurologic disease, gastrointestinal malformations, or conditions. Aim-1 data included all subjects evaluated for GERD, while Aim-2 data included only treated infants with one week of PPI washout (Figure 1).

Experimental Protocol

Measuring Symptom Burden Using I-GERQ-R.—To measure parental/provider perception of symptom burden, the I-GERQ-R survey[8,30,31] was administered by the infant's primary caretaker (parent or bedside registered nurse) prior to the pH-impedance study. In brief, the I-GERQ-R is comprised of 12 questions about symptoms related to infant GERD including questions about emesis, arching/irritability, hiccups, breathing difficulties, and symptoms with feeds.[8] Responses range from 2 to 5 categories for each question, while total scores can range from 0 to 42 with scores ≥16 indicating an increased symptom burden.[8] To further examine the effect on acute airway and pulmonary symptoms, and growth, we posed 3 additional questions to reflect changes over the week prior to testing: (1) administration of any cardiopulmonary resuscitation or positive pressure ventilation; (2) coughing events during, before, or after feeds; and (3) adequate weight gain.

Twenty Four–Hour pH-Impedance Testing.—All infants underwent multichannel intraluminal pH-impedance testing over a 24-hour period as per previously published approaches.[14,15,19,21,32,33] Briefly, a single-use antimony pH-impedance probe, with 6 impedance channels spaced 1.5 cm apart and a pH sensor in the most distal impedance channel (Greenfield MMS Z1-I or ZandorpH MMS 6Z1P-I01, Laborie Medical Technologies, Mississauga, Ontario, Canada) was calibrated prior to the study using pH buffer solutions (pH 4 and pH 7) to assure accuracy. The probe was connected to a portable recorder (Ohmega, Laborie Medical Technologies, Mississauga, Ontario, Canada) and positioned nasally and secured. Probe position was initially calculated based on predicted averages from previously published equations [34,35] and confirmed by chest x-ray so that the pH probe was located between T7 and T8 vertebrae so as to comply with ESPGHAN guidelines.[14,36] At the infant's bedside, trained patient care assistants who were blinded to the pH-impedance recording used event markers on the recording device to document and record any symptoms or mealtimes for the duration of the study. Infants were categorized by ARI severity (normal: <3%, indeterminate: 3%–7%, and abnormal: >7%) per NASPGHAN guidelines.[2]

GERD Interventions.—If the infant had an ARI ≥3% as detected by the pH-impedance the infant was able to be enrolled into the GERD management trial (Clinicaltrials.gov: NCT02486263). Subjects were allocated using a 1:1 ratio by ARI severity (3%–7% or >7%) and birth gestation (preterm or full-term) and randomized into conventional (PPI alone which was the standard of care) or study (PPI + feeding modifications) arms.[37] PPI (omeprazole) therapy was recommended off-label at 0.75 mg/kg/dose twice a day. Feeding modifications included feeding in right lateral position for a duration of >30 minutes, postprandial supine position, and total fluid volume restricted to ≤140 mL/kg/d. After 4

weeks of therapy and 1 week of PPI washout, infants were re-evaluated at week 5 to determine if 4 weeks of therapy was sufficient to improve pH-impedance characteristics and resolve symptoms.

Data Analysis

pH-Impedance Metrics (All Data Excluded Mealtimes).—Characteristics of pH-impedance were analyzed using MMS analysis software (v. 9.5, Laborie Medical Technologies, Mississauga, Ontario, Canada). Acid and bolus GER components were evaluated as validated before.[14,15,32,33] Acid GER was defined as events with pH <4 for >5 second duration and bolus GER events were defined as retrograde movement (50% drop in impedance) originating in the Z6 channel and reaching at least the Z5 impedance channel. Additional characteristics analyzed from the pH sensor included ARI defined as the percentage of time that acid was present in the esophagus, the number of acid reflux events per day, the number of acid reflux events >5 minutes per day, the longest duration of acid reflux, the number of pH-only events (acid events not reaching Z5 impedance channel), and acid clearance time. Characteristics specific to the impedance sensors only included DBI categorized by severity (<900 Ω, 900–2000 Ω, and >2000 Ω), bolus exposure time (%), number of liquid, mixed and gas events, and bolus clearance times of impedance events at Z3 and Z6 channels.[14,19,21] Characteristics common to both pH and impedance sensors included the number of acid (pH <4) and weakly acid events (pH 4–7) at Z3 and Z6 impedance channels, acid bolus exposure time (%), and non–acid bolus exposure time (%).[14,15] Total number of symptoms (#/day) were collected. A symptom was attributed to a GER event, if the GER event occurred within 2 minutes prior to the symptom onset. This information was used to calculate SAP for individual symptoms with values ≥95% considered abnormal.[1,14,20] SAP values were calculated for acid GER (pH <4) and bolus GER (retrograde bolus in at least the most distal 2 impedance channels) events.[14,21] If SAP ≥95% was detected for any individual symptom the infant was considered as having a positive symptom correlation for acid GER and/or bolus GER.[21,36]

Statistical Analysis

The data were analyzed using Statistical Analysis System, version 9.4 (SAS Institute Inc., Cary, North Carolina). P values of < .05 were considered statistically significant. Descriptive statistics were reported as median (interquartile range [IQR]), mean ± standard deviation or total number and percentage for demographics and clinical characteristics. Normality was assessed using Shapiro–Wilks test and visual inspection of the Q-Q plot (normality) and residual plots. Analysis of variance (ANOVA) or Kruskal–Wallis test were used, as appropriate, to compare the demographics and I-GERQ-R between ARI severity groups. Two-sample t-test, paired t-test, or Wilcoxon signed rank test for the continuous variables and Chi-squared or Fisher's exact tests for the categorical variables, whichever was appropriate, were used to compare the GERD treatments on pH-impedance metrics between PPI and PPI + feeding modification groups and within groups Bonferroni correction was used for multiplicity adjustment to conserve the overall type 1 error at $\alpha = 0.05$. We examined the relationships between composite I-GERQ-R and individual components of I-GERQ-R score vs markers of GERD (ARI, number of acid events per day, and number of weakly acid events per day), symptoms, DBI using Spearman's correlation, and Pearson's

correlation. Correlation was defined as weak if |r | < 0.4.[38] Sensitivity, specificity, (negative predictive value [NPV]), and positive predictive values (PPVs) were calculated to assess the reliability of I-GERQ-R (≥16) detecting frequently collected GERD metrics during 24-hour pH-impedance including acid SAP ≥95%, bolus SAP ≥95%, acid or bolus SAP ≥95%, overall symptoms >127 /d, ARI >7%, ARI >10%, and DBI <900 Ω.[1,8,17,21]

Results

Participant Characteristics

A total of 94 convalescing infants underwent GERD evaluation via 24-hour pH-impedance testing with I-GERQ-R. Frequency of abnormal I-GERQ-R (≥16) was 43 (46%) with median (IQR) score of 16 (range: 12–20). Comparison of demographic and clinical characteristics categorized by ARI severity is shown in Table 1. Note, within the severe ARI group, increase in respiratory support and length of hospital stay were noted. Among the 72 infants treated for GERD, 40 underwent repeat testing with pH-impedance and I-GERQ-R at week 5.

Relationships Between I-GERQ-R and pH-Impedance Metrics

Comparison of I-GERQ-R scores and additional questions categorized by ARI severity are shown in Table 2. Note, there were no significant differences stratified by ARI severity. Relationships between composite I-GERQ-R score and pH-impedance metrics are shown in Figure 2. Note, correlations did not exist or were weak between composite I-GERQ-R score and pH-impedance metrics. Relationships between individual components of I-GERQ-R and pH-impedance metrics are also shown in Table 3. Note, most individual survey questions were not correlated with objective GER metrics; if correlation was noted it was weak. Further analysis was performed to investigate the relationship between weight gain and DBI. In infants with reported adequate weight gain (89%, N = 84) vs inadequate weight gain (11%, N = 10), respectively, (a) DBI (Ω) was 1512 [1184–1934] vs 1097 [680–1574], P = .02 and (b) DBI category (<900 Ω: 900–2000 Ω: >2000 Ω) was 13: 67: 20 vs 50: 50: 0, P = .01.

Sensitivity, Specificity, and Predictive Values.—The sensitivity, specificity, PPV, and NPV are shown for I-GERQ-R and common objective GERD metrics using 24-hour pH-impedance (Table 4). Note that a normal composite I-GERQ-R (<16) has a high NPV for both symptoms due to acid SAP and DBI < 900 Ω and even higher in infants with bronchopulmonary dysplasia.

Effect of GERD Therapies (N = 40)

Comparison of pH-impedance characteristics between treatment groups is shown in Table 5. Note, there were no significant differences between PPI or PPI + feeding modification groups at baseline, at follow-up, and the change from baseline to follow-up. However, bolus clearance times worsened in both treatment groups at follow-up. In addition, there were no significant differences between PPI + feeding modification vs PPI treatment groups with each individual survey question, composite I-GERQ-R score, and frequency of individual symptoms detected during pH-impedance (all P > .05, not reported).

Discussion

Summary

The relationships between composite and individual components of I-GERQ-R score and pH-impedance metrics were examined in NICU infants. In addition, the effect of acid-suppressive therapy with or without feeding modifications on symptom burden scores and pH-impedance metrics was examined. The salient findings are as follows: (A) Weak or no correlation was noted between I-GERQ-R (composite score and individual components) and pH-impedance characteristics; (B) Sensitivity, specificity, and PPVs of I-GERQ-R were suboptimal when compared to pH-impedance metric abnormalities, but NPV was high for acid SAP (NPV = 84%) and DBI (NPV = 86%) thresholds when the I-GERQ-R was normal; (C) PPI with feeding modifications (vs PPI without feeding modifications) did not alter pH-impedance metrics. GER frequency and bolus clearance metrics worsened for both treatment groups ($P < .05$).

I-GERQ-R and Comparison to Other Studies

In infants, ARI <3% is considered physiological.[2] After that, ambiguity still exists regarding true GERD definition and treatment strategies as different ARI threshold values have been proposed by multiple expert groups [2,16] and there are no clear data from high-risk infants, which is the focus of the present study. In addition to ARI, the DBI and SAP values may have some utility in GERD diagnosis.[19,21] Symptoms may be unrelated to acid and persist even after treatment, the etiology/pathophysiology of which remains obscure. Perception of symptom burden can be evaluated with I-GERQ-R. The original I-GERQ survey from 1992 aided physicians in history-taking[30] and was refined in 1996.[31] The latter version included 138 questions from caregivers of infants aged <14 months.[31] Comparisons were performed between 100 infants from a single-center well-baby clinic vs 35 infants who tested positive for GERD via pH probe or esophageal suction biopsy.[31] PPV and NPVs were more than 94% using a cutoff score of ARI >7%.[31] However, a 2005 study of infants reported that GERD questionnaires do not correlate with esophageal acid exposure or GERD severity.[39] The I-GERQ score was revised (I-GERQ-R) in 2006 to evaluate response to therapeutic interventions by documenting change in score.[8] That multinational observational I-GERQ-R survey of 12 questions was administered to primary caregivers of infants aged <18 months, and the sensitivity was 0.65 and specificity was 1.00 using a cut-point score of 16.[8] From our study, importantly, I-GERQ-R has low sensitivity, low specificity, low PPV, but high NPV for acid SAP ≥95%, and DBI <900 Ω. In addition, I-GERQ-R had low sensitivity, low specificity, low PPV and low NPV for ARI, symptoms >127 per day, and bolus SAP ≥95% (Table 4).

Clinical and Translational Research Implications Based on Physiological Reasoning

This study has several clinical and translational research implications aimed to define GERD diagnosis and develop optimal treatment strategies for management in high-risk NICU infants, as discussed below:

1. Potential utility of composite I-GERQ-R: There is a current push for exercising caution with the prescription of acid-suppressive medications as there may be

consequences with short-term or long-term use.[2,40–42] In addition, as GERD frequently resolves with maturation, exit strategies with deprescription are not known. The I-GERQ-R may be useful in screening to rule out acid-GERD if the composite score is <16 (as only NPV was high for acid SAP and DBI <900 Ω). In such situations, acid-suppressive therapies may not be indicated, and differential diagnoses should be considered. However, those with a composite I-GERQ-R score ≥16 likely still need further testing to determine true diagnosis as sensitivity, specificity, and PPV values were low. These findings may be due to the unique nature of NICU circumstances, as these nonverbal infants require continuous care with frequent change in providers and parents may not always be available. Further investigations would allow accuracy with sorting out differential diagnosis so that evidence-based strategies can be applicable.[43]

2. Potential utility of individual I-GERQ-R components: Airway-digestive symptoms are heterogeneous and individual questions may have some merit. For example, in Table 3, I-GERQ-R questions #1, 3, 4, 5, 11, and the additional question of ‘coughing with feeds had more than one correlation with pH-impedance. Specific modification of the questionnaire may result in improved predictive values. On the other hand, these symptoms also frequently occur with other comorbidities with dysfunctional mechanisms.[44–46] Examples may include swallowing and feeding difficulty, infantile colic, maturational neuropathology, and chronic lung disease.[47] Hence, consideration of symptom clusters may be beneficial in narrowing differential diagnosis as follows: emesis and regurgitation factors (items #1–3), feeding management related symptoms (items #4, 5), painful discomfort (items #6, 7, 8), respiratory effects (items #9,10,11), and cardiac effects (item #12). Esophageal and pharyngeal provocation can activate adaptive reflexes and bodily movements, which are often misconstrued as pathologic symptoms.[45,48,49]

3. Reasoning for complicated GERD situations: A complication of chronic GERD may be failure to thrive and/or esophagitis. It is not a common practice to biopsy, the esophagus in infants, and diagnoses esophagitis. However, in the current report it is interesting that DBI <900 Ω and inadequate weight gain are related. Therefore, lower DBI, feeding difficulties, and failure to thrive may be markers of complicated GERD and require further assessment. Acid exposure (ARI) and (DBI) are also correlated and may contribute to pharyngoesophageal dysmotility.[44,50–52] In addition, delays with maturation and adaptation to stimulus can be due to immaturity of sensory-motor aspects of esophageal motility and aerodigestive reflexes.[45,53,54] All these factors prolong bolus clearance along with abnormal pharyngoesophageal functions[29] and these metrics worsen despite PPI therapy. Whether GERD pathophysiology or PPI therapy is responsible for worsening of these metrics cannot be answered by this study. On the other hand, GERD and maturational esophageal dysmotility may be coexisting comorbidities, either dependent or independent.

4. Physiological reasoning for troublesome symptoms: Presence of cough, sneeze and/or emesis, and overall symptom burden (as measured

objectively by frequency of symptoms) may indicate the need for GERD screening.[14,21] Symptoms rarely occur with acid alone[21] but rather due to other refluxate properties or resultant aerodigestive reflexes evoked by provocation from refluxate.[14,33,44–46,55] Rather such reflexes are signals toward pharyngoesophageal-airway adaptation thus enhancing arousal responses and clearance, as in post-tussive swallowing[46] or esophagodeglutition response[53] or effortful swallowing after upper esophageal contractile reflex.[54] Furthermore, factors such as DBI (a potential marker of esophagitis),[18] SAP ≥95% (likelihood of distal acid, acid bolus, or nonacid bolus causing symptom), and proximal extent (activating proximal aerodigestive reflexes) can modify the activation of pharyngoesophageal motility and airway interactions based on cross-systems effect[48,49] and result in symptoms.[33] On the other hand, inefficient or exaggerated pharyngoesophageal motility reflexes contributed to symptom generation, some of which may be troublesome as persistent difficulties with feeding.[43]

Limitations and Future Directions

1. Further development of objective criteria: Current diagnostic criteria are largely subjective and provider dependent. Objective criteria are needed for establishing true acid-GERD and non–acid- GERD diagnosis to develop evidence-based treatment strategies. Components of such criteria may include ARI, DBI, acid-SAP, proximal extent of acid and nonacid bolus, bolus-SAP, growth trends, presence of comorbidities, and difficulties with feeding.

2. Treatment strategies for GERD: Acid-GERD is commonly assumed for symptom-based treatment with PPI or H2 receptor antagonist.[22] However, this study and prior works have demonstrated that symptoms may likely decrease with time and/or may likely be due to nonacid components of GER.[21,29,56] To further highlight the complexity of GER-inducing symptoms,[21] positive symptom association with acid only is prevalent in 10%, acid and bolus in 23%, and bolus only in 34%.[21] In addition, it is plausible that symptoms may also cause reflux but we did not test this in the present study design. Therefore, future approaches need to choose appropriate therapeutic targets (symptoms causing reflux, reflux causing symptoms, esophagitis markers, ARI severity, acidity-induced symptoms, and bolus-induced symptoms) in well-designed studies involving placebo. Potential treatments may include alginates or added rice formulas but a rigorous study is needed as there may be consequences to their use.[12,57]

3. Targeted therapies for GERD in high-risk infants: Pathophysiology-guided therapy can provide basis for optimal healing toward restoration of normalcy. However, true definition requires implementation of pH-impedance methods along with symptom scores and the use of placebo in future trials is justifiable, particularly as the use of PPI therapy can have direct effects, that is, worsening of bolus clearance metrics amidst persistence of symptoms (as shown from our data) and altered pharyngoesophageal motility.[29]

Conclusion

We evaluated and compared composite I-GERQ-R score and its individual components characteristics collected during pH-impedance in a high-risk NICU infant population. I-GERQ-R may be a useful screening tool to rule-out acid-GERD diagnosis because of its high NPV for positive symptom correlation with acid (acid-SAP) and DBI <900 Ω, but further testing is warranted to confirm specific abnormalities and whether any treatment is indicated. In addition, we tested the effects of acid-suppressive medications with or without feeding modifications on I-GERQ-R symptom scores and pH-impedance metrics. Acid-suppressive therapy or feeding modifications had no longitudinal effect on symptom scores or pH-impedance metrics. Clearance of refluxate worsened despite PPI therapy (as evidenced by prolonged bolus clearance times), which may signal pharyngoesophageal dysmotility as a contributing mechanism for the persistence of symptoms. Future placebo-controlled trials with objective pH-impedance criteria of GERD are needed to develop the true definition and prevalence of GERD in this NICU population and develop strategies to diagnose and treat acid-GERD and non–acid-GERD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used in this paper:

DBI	distal baseline impedance
I-GERQ-R	Infant Gastroesophageal Reflux Questionnaire Revised
GER	gastroesophageal reflux disease
GERD	GER disease
NICU	neonatal intensive care unit
NPV	negative predictive value
PPI	proton pump inhibitor
PPV	positive predictive value
SAP	symptom association probability

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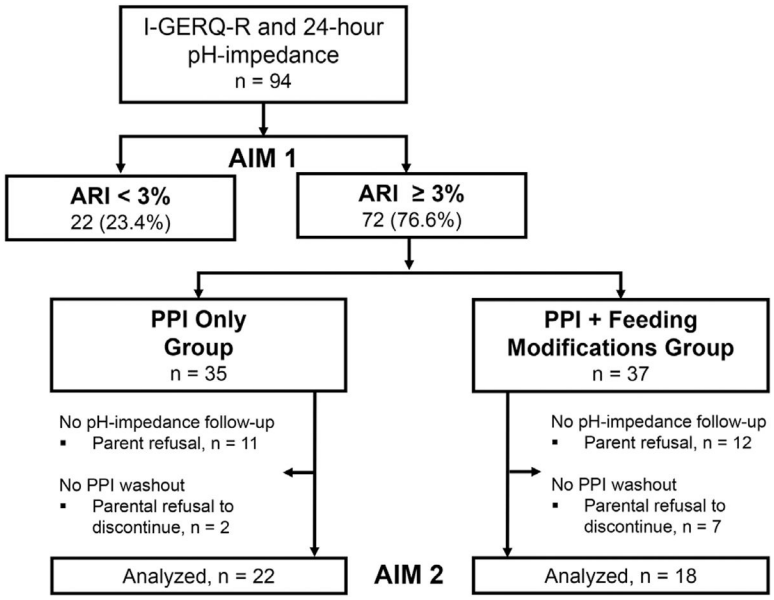

Figure 1.

Study flow diagram. This is a secondary analysis of data from NCT02486263. A total of 94 infants met inclusion/exclusion criteria of the current aims. All infants underwent pH-impedance testing and filled out I-GERQ-R questionnaire for potential GERD therapy. As determined by pH-impedance testing, infants with acid reflux index (ARI) >3% were enrolled and randomized into the GERD management trial for therapy [proton pump inhibitor (PPI) only or PPI + feeding modifications]. Feeding modifications included feeding in right lateral position, postprandial supine position, restricted fluid volume, and prolonged feeding duration. Infants were studied longitudinally after 4 weeks of treatment and one week of PPI washout.

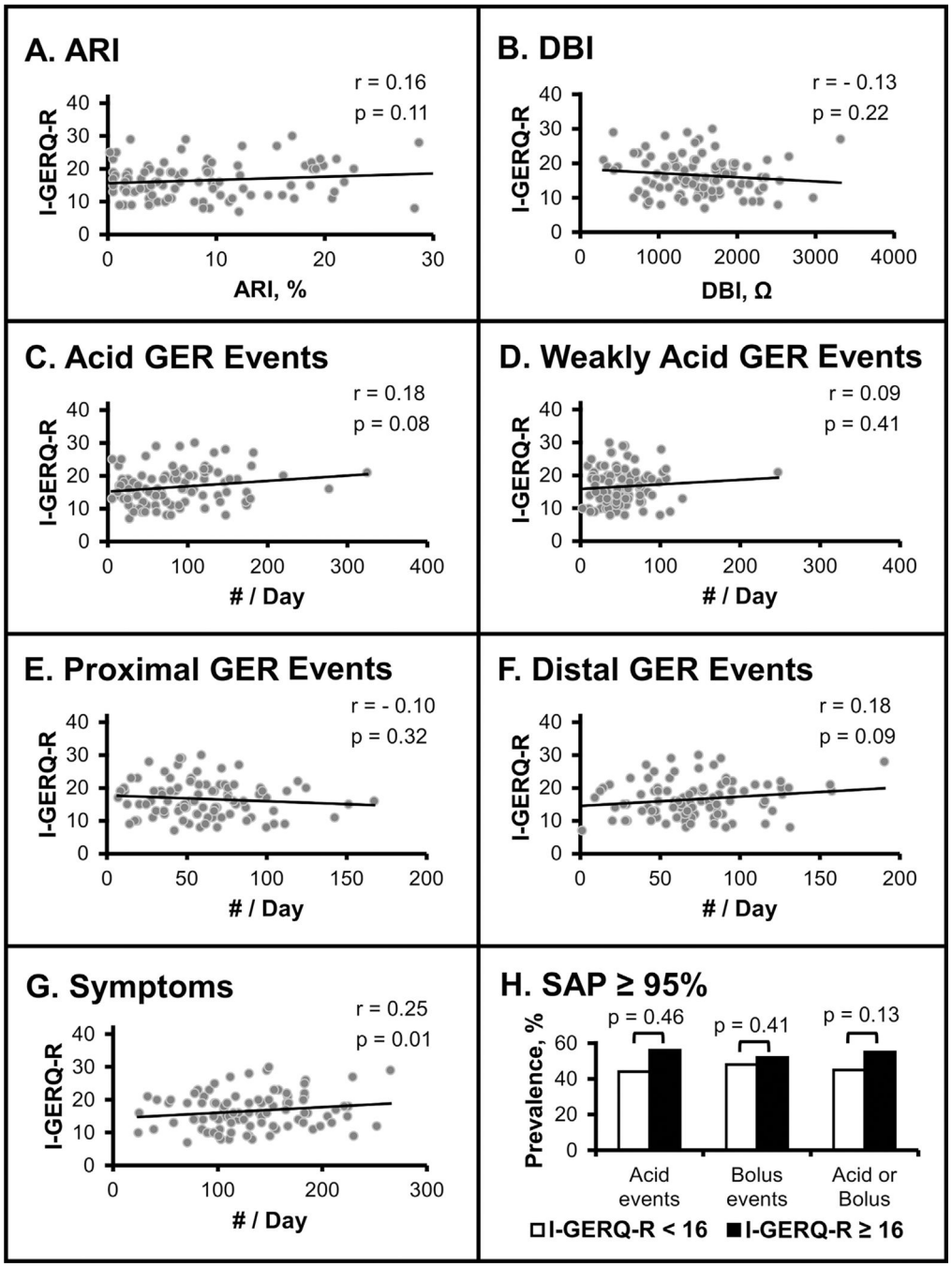

Figure 2.

Relationships between composite I-GERQ-R score and pH-impedance metrics at baseline evaluation. No correlations were noted with: (A) acid reflux index (ARI) or % of time the esophagus was exposed to acid; (B) distal baseline impedance (DBI) a potential marker of esophagitis[18]; (C) number of acid (pH <4) GER events; (D) number of weakly acid (pH ≥4) GER events; (E) number of proximal GER events, and (F) number of distal GER events. (G) I-GERQ-R had a weak correlation with the total number of symptoms. (H) Symptom association probability (SAP) ≥95% indicates that GER events are likely to cause

symptoms.[20,21] There were no significant differences between infants with abnormal and normal I-GERQ-R scores for positive symptom correlation with acid GER events, bolus GER events, or any (acid or bolus) GER events.

Table 1.

Clinical Characteristics of Infants Evaluated for GERD as Categorized Based on Acid Reflux Index (ARI) Severity

Characteristic	Overall N = 94	ARI <3% N = 22	ARI 3%–7% N = 25	ARI >7% N = 47	ANOVA *P* value
At birth					
Gestational age, wk	30.5 ± 4.1	31.9 ± 3.6	31.3 ± 4.1	29.4 ± 4.1	**.03**
Weight, kg	1.6 ± 0.9	1.8 ± 0.9	1.8 ± 1.0	1.4 ± 1.0	.11
Length, cm	40.0 ± 6.7	41.7 ± 7	41.9 ± 6.4	38.3 ± 6.4	**.03**
Gender (female), %	51	64	52	45	.34
Race, %					.11
African American or Black	18	27	8	19	
Other/Unknown	1	0	0	5	
White	74	73	92	66	
Ethnicity (non-Hispanic or Latino), %	96	100	96	94	.93
At evaluation					
Postmenstrual age, wk	40.9 ± 2.5	40.4 ± 2.3	40.9 ± 2.5	41.1 ± 2.5	.99
Weight, kg	3.5 ± 0.9	3.3 ± 1.1	3.7 ± 0.6	3.4 ± 0.9	.31
Length, cm	49.2 ± 3.6	48.6 ± 4.0	50.6 ± 2.7	48.7 ± 3.8	.08
Respiratory support (nasal cannula oxygen), %	28	14	16	40	**.02**
Feeding method (oral: oral + gavage: Gavage), %	51: 47: 2	64: 36: 0	40: 60: 0	51: 45: 4	.39
Mild neuropathology, %	23	5	32	28	**.04**
Bronchopulmonary dysplasia, %	40	55	44	32	.15
At discharge					
Weight, kg	4.2 ± 0.9	3.9 ± 0.9	4.3 ± 7.3	4.3 ± 1.0	.21
Length, cm	52.6 ± 3.9	51.2 ± 4.1	53.1 ± 3.4	52.9 ± 4.0	.18
Respiratory support (nasal cannula oxygen), %	19	9	4	32[b]	**.01**
Feeding method (oral: oral + gavage: Gavage), %	77: 17: 6	82: 9: 9	76: 20: 4	75: 19: 6	.82
Length of stay, d	96.5 ± 45	70.3 ± 40.6	85.4 ± 40.4	114.1 ± 42.3[a,b]	< **.01**

Data presented as % or mean ± SE. Pairwise comparisons were performed between all 3 ARI groups adjusted using Bonferroni method. Bold values indicate statistical significant ($P < .05$).

[a] $P < .05$ vs ARI <3%.

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[b] $P < .05$ vs ARI 3%–7%.

Table 2.

Individual Components of I-GERQ-R and Composite Score as Categorized Based on Acid Reflux Index (ARI) Severity

Survey question	ARI <3% N = 22	ARI 3%–7% N = 25	ARI >7% N = 47	ANOVA *P* value
I-GERQ-R [a]				
1. Emesis occurrence	1 [1–2]	1 [1–1]	1 [1–1]	.71
2. Emesis amount	1 [1–2]	1 [1–1]	1 [1–2]	.32
3. Emesis tolerability	2 [1–3]	2 [1–2]	2 [1–4]	.21
4. Feeding refusal occurrence	0 [0–1]	0 [0–2]	1 [0–2]	.44
5. Stopped feeding shortly after begun	2 [0–3]	2 [0–3]	2 [0–2]	.46
6. Crying during or after feeds	1.5 [1–2]	1 [1 –2]	2 [1–2]	.82
7. Crying frequency	1.5 [1–2]	1 [0–1]	1 [0–2]	.23
8. Crying duration	1 [1–2]	1 [1–1]	1 [1–2]	.56
9. Hiccup frequency	2 [1–3]	2 [1–2]	2 [1–3]	.84
10. Arching frequency	3 [2–3]	2 [2–3]	3 [1–3]	.93
11. Stopped or struggled to breathe, n (%)	10 (45%)	6 (24%)	22 (47%)	.15
12. Turned blue or purple, n (%)	8 (36%)	3 (12%)	14 (30%)	.13
Composite score, score	15 [13–19]	16 [11–19]	16 [12–21]	.44
Abnormal score (≥ 16), n (%)	10 (45%)	10 (40%)	23 (49%)	.77
Additional questions				
CPR or PPV provided in prior week, n (%)	0 (0%)	2 (8%)	2 (4%)	.40
Coughing before, during, or after feeds, n (%)	9 (41%)	12 (48%)	26 (55%)	.52
Adequate weight gain, n (%)	19 (86%)	24 (96%)	41 (87%)	.45

Data presented as Median [IQR] or n (%). Comparisons were performed between ARI groups; no significant differences were noted for I-GERQ-R individual questions or composite score.

CPR, cardiopulmonary resuscitation; PPV, positive pressure ventilation.

[a] I-GERQ-R: infant gastroesophageal reflux questionnaire revised by Kleinman et al[8] (2006).

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Table 3.

ERD Survey Questions and pH-Impedance Metrics

I-GERQ-R question																				Additional questions					
2. Emesis amount		3. Emesis tolerability		4. Feeding refusal occurrence		5. Stopped feeding		6. Crying feeds		7. Crying frequency		8. Crying duration		9. Hiccups frequency		10. Arching frequency		11. Breathing		12. Turned blue		CPR or PPV		Cough		Weight gain	
r_s	*P* value	r_s	*P* value	r_s	*P* value	r_s	*P* value	r_s	*P* value	r_s	*P* value	r_s	*P* value	r_s	*P* value	r_s	*P* value	r_s	*P* value	r_s	*P* value	r_s	*P*val	r_s	*P*-val	r_s	*P*-val
0.13	.20	0.20	.06	0.15	.16	−0.04	.71	0.07	.50	0.01	.95	0.06	.58	0.00	.97	−0.07	.52	0.06	.57	−0.03	.74	0.02	.84	0.10	.34	0.05	.66
0.16	.11	0.09	.37	0.10	.33	0.11	.28	−0.01	.94	−0.16	.11	−0.19	.07	0.05	.63	0.07	.50	−0.11	.29	−0.07	.51	−0.01	.95	0.10	.35	−0.14	.17
0.08	.43	0.12	.26	0.04	.72	−0.10	.35	0.01	.90	−0.14	.19	−0.12	.25	0.00	.10	0.00	.98	−0.07	.48	−0.01	.94	0.05	.63	0.09	.38	−0.16	.13
0.08	.46	**0.28**	**.01**	−0.10	.33	**−0.20**	**.05**	0.02	.84	0.03	.77	−0.02	.84	0.06	.57	0.19	.07	**0.22**	**.04**	0.19	.06	0.03	.81	**0.25**	**.01**	0.05	.61
0.17	.10	**0.26**	**.01**	−0.09	.36	**−0.22**	**.04**	0.05	.64	−0.01	.95	−0.08	.45	0.06	.55	0.15	.16	0.19	.07	0.05	.66	0.07	.49	**0.21**	**.04**	−0.02	.85
0.15	.15	**0.29**	**.00**	−0.15	.15	**−0.23**	**.02**	0.08	.43	0.06	.58	0.02	.82	0.10	.32	0.11	.31	**0.25**	**.02**	0.07	.49	0.02	.88	0.14	.18	0.04	.73
0.01	.96	0.17	.09	0.03	.80	−0.06	.54	0.10	.35	0.08	.44	0.05	.63	0.06	.55	0.06	.60	−0.05	.60	−0.03	.80	−0.15	.15	0.06	.54	0.04	.72
0.14	.19	0.04	.69	−0.05	.65	−0.03	.80	0.06	.59	0.07	.53	0.11	.31	0.07	.50	−0.06	.57	0.05	.64	0.04	.70	−0.09	.41	−0.05	.61	0.10	.36
0.21	**.04**	**0.24**	**.02**	0.05	.66	−0.12	.23	0.16	.13	−0.01	.89	0.02	.84	−0.04	.67	0.17	.10	0.15	.14	0.03	.74	0.08	.46	0.19	.07	−0.04	.73
0.03	.78	**0.27**	**.01**	**−0.24**	**.02**	**−0.26**	**.01**	0.04	.73	−0.01	.92	0.02	.82	0.14	.17	0.05	.64	**0.20**	**.05**	0.08	.43	0.03	.81	0.18	.08	−0.04	.71
0.18	.09	**0.21**	**.04**	0.05	.64	−0.10	.35	0.12	.27	0.03	.75	0.02	.88	−0.01	.93	0.14	.19	0.16	.13	0.01	.90	0.06	.56	0.16	.14	−0.03	.79
0.05	.66	**0.24**	**.02**	**−0.21**	**.04**	**−0.23**	**.02**	0.02	.82	−0.01	.96	−0.03	.76	0.15	.15	0.02	.88	**0.21**	**.04**	0.04	.73	0.00	.97	0.16	.12	−0.04	.73
0.20	.05	**0.25**	**.02**	−0.02	.82	−0.13	.23	0.14	.17	0.07	.50	0.05	.65	0.02	.82	0.14	.17	0.18	.09	0.01	.93	0.07	.52	0.17	.11	−0.03	.79
0.02	.83	**0.24**	**.02**	**−0.23**	**.03**	**−0.25**	**.02**	0.05	.61	0.02	.84	0.03	.78	0.10	.32	0.04	.68	**0.25**	**.02**	0.09	.37	0.01	.90	0.11	.31	0.03	.81

I-GERQ-R question																				Additional questions					
2. Emesis amount		3. Emesis tolerability		4. Feeding refusal occurrence		5. Stopped feeding		6. Crying feeds		7. Crying frequency		8. Crying duration		9. Hiccups frequency		10. Arching frequency		11. Breathing		12. Turned blue		CPR or PPV		Cough		Weight gain	
r_s	*P* value	r_s	*P* value	r_s	*P* value	r_s	*P* value	r_s	*P* value	r_s	*P* value	r_s	*P* value	r_s	*P* value	r_s	*P* value	r_s	*P* value	r_s	*P* value	r_s	*Pval*	r_s	*P*-val	r_s	*P*-val
0.15	.16	0.14	.19	0.14	.19	−0.02	.87	0.14	.19	0.02	.82	−0.07	.50	0.14	.17	0.07	.48	**−0.21**	**.04**	−0.06	.57	−0.08	.47	0.14	.19	−0.07	.53
0.08	.45	0.17	.10	−0.06	.57	−0.08	.46	0.00	1.00	0.05	.62	0.08	.47	0.02	.88	0.02	.82	0.05	.65	0.01	.91	−0.15	.16	0.02	.82	0.07	.53
0.07	.51	−0.10	.34	0.05	.65	0.01	.93	0.00	1.00	−0.16	.12	−0.11	.30	−0.12	.24	−0.07	.51	−0.12	.23	−0.04	.69	**0.22**	**.03**	0.13	.23	**−0.22**	**.03**
0.07	.48	0.01	.95	−0.03	.77	−0.02	.82	0.15	.15	0.17	.10	0.10	.35	0.07	.52	**0.22**	**.03**	0.11	.28	**0.21**	**.04**	0.09	.38	−0.13	.21	0.06	.54

per day unless otherwise stated.

pearman correlation.

k correlation defined as $p < .05$ with $|r| < 0.4$.

Table 4.

Sensitivity, Specificity, and Predictive Values of I-GERQ-R Among Objective GERD Metrics Derived Using 24-H pH-Impedance Testing

Abnormal threshold criteria	Sensitivity, %	Specificity, %	PPV, %	NPV, %
All subjects, N = 94				
Acid SAP ≥95%	61	47	22	**84**
Bolus SAP ≥95%	60	51	51	60
Acid or bolus SAP ≥95%	63	54	59	58
Symptoms >127/d	61	53	59	56
ARI >7%	57	48	51	53
ARI >10%	56	47	35	67
DBI <900 Ω	63	47	20	**86**
Subjects without BPD, N = 51				
Acid SAP ≥95%	58	46	25	**78**
Bolus SAP ≥95%	57	47	43	61
Acid or bolus SAP ≥95%	61	50	50	61
Symptoms >127/d	65	54	54	65
ARI >7%	60	48	43	65
ARI >10%	60	47	32	74
DBI <900 Ω	56	45	18	**83**
Subjects with BPD, N = 43				
Acid SAP ≥95%	67	49	17	**90**
Bolus SAP ≥95%	64	57	61	60
Acid or bolus SAP ≥95%	64	61	70	55
Symptoms >127/d	58	53	65	45
ARI >7%	54	47	61	40
ARI >10%	47	46	36	57
DBI <900 Ω	71	50	22	**90**

ARI, acid reflux index; BPD, bronchopulmonary dysplasia; DBI, distal esophageal baseline impedance; SAP, symptom association probability.

Bolded values indicate probabilities >75%.

Sensitivity: Probability of a positive test given the individual has disease.

Specificity: Probability of a negative test given the individual does not have the disease.

Positive Predictive Value (PPV): Probability of disease given a positive test.

Negative Predictive Value (NPV): Probability of no disease given a negative test.

Table 5.

Effect of GERD Treatments on pH-Impedance Metrics Among PPI Infant's vs PPI and Feeding Modification

Characteristic	Baseline at Week-0				Follow-up at Week-5				Baseline vs follow-up *P* values			Baseline to follow-up difference Week 5–Week 0	
		Treatment group				Treatment group				Treatment group			
	Overall N = 40	PPI N = 22	PPI + FM N = 18	*P* value	Overall N = 40	PPI N = 22	PPI + FM N = 18	*P* value	Overall N = 40	PPI N = 22	PPI + FM N = 18	Difference between treatment groups	Adjusted *P* value
Acid reflux index, %	11 ± 1	11 ± 1	11 ± 2	.99	11 ± 1	10 ± 2	11 ± 2	.99	0.99	0.99	0.99	1 ± 3	.99
Acid reflux events	97 ± 9	107 ± 12	88 ± 13	.99	106 ± 9	98 ± 12	113 ± 14	.99	0.99	0.99	0.73	34 ± 23	.74
Longest acid reflux, min	21 ± 3	20 ± 3	21 ± 4	.99	21 ± 3	22 ± 4	20 ± 4	.99	0.99	0.99	0.99	−3 ± 6	.99
Bolus exposure time, %	1 ± 0	1 ± 0	1 ± 0	.99	2 ± 0	1 ± 0	2 ± 0	.96	**0.01**	0.52	**0.02**	0 ± 0	.99
Bolus events	70 ± 6	76 ± 8	65 ± 9	.99	86 ± 6	86 ± 7	87 ± 8	.99	**<0.01**	0.39	**0.01**	11 ± 8	.86
Liquid events	66 ± 5	71 ± 7	61 ± 8	.99	75 ± 5	76 ± 6	75 ± 7	.99	0.21	0.99	0.22	9 ± 9	.99
Mixed events	5 ± 2	2 ± 3	8 ± 3	.90	10 ± 2	11 ± 3	10 ± 3	.99	0.21	0.06	0.99	−7 ± 5	.85
Gas events	4 ± 2	4 ± 1	5 ± 2	.99	6 ± 2	9 ± 3	4 ± 3	.93	0.99	0.20	0.99	−7 ± 4	.44
Proximal bolus clearance time, s	6 ± 0	6 ± 1	7 ± 1	.12	8 ± 0	7 ± 1	8 ± 1	.41	**<0.01**	**<0.01**	**0.04**	−1 ± 1	.99
Proximal acid events	17 ± 3	19 ± 3	15 ± 4	.99	31 ± 3	28 ± 4	34 ± 4	.99	**<0.01**	0.24	**<0.01**	1 ± 7	.61
Proximal weakly acid event	40 ± 4	39 ± 5	41 ± 6	.99	46 ± 4	52 ± 6	41 ± 7	.99	0.62	0.13	0.99	12 ± 8	.69
Distal bolus clearance time, s	13 ± 1	12 ± 1	14 ± 1	.11	15 ± 1	14 ± 1	16 ± 1	.19	**<0.01**	**<0.01**	**0.04**	0 ± 1	.99
Distal acid events	24 ± 3	26 ± 4	21 ± 5	.99	38 ± 3	34 ± 5	42 ± 5	.99	**<0.01**	0.66	**<0.01**	13 ± 8	.52
Distal weakly acid events	47 ± 4	48 ± 6	47 ± 6	.99	49 ± 4	52 ± 6	45 ± 6	.99	0.99	0.99	0.99	−7 ± 7	.99
Liquid acid events	22 ± 3	25 ± 4	19 ± 4	.99	31 ± 3	28 ± 4	34 ± 4	.99	0.09	0.99	**0.04**	13 ± 7	.45
Liquid weakly acid events	45 ± 4	47 ± 5	43 ± 6	.99	44 ± 4	48 ± 5	40 ± 6	.99	0.99	0.99	0.99	−4 ± 7	.99
Mixed acid events	2 ± 1	1 ± 1	2 ± 1	.97	5 ± 1	6 ± 2	5 ± 2	.99	**0.01**	**<0.01**	0.75	−3 ± 2	.99
Mixed weakly acid events	4 ± 1	1 ± 2	6 ± 2	.97	5 ± 1	5 ± 2	5 ± 2	.99	0.99	0.73	0.99	−4 ± 4	.99
DBI, ohms	1581 ± 96	1478 ± 117	1684 ± 129	.99	1535 ± 96	1474 ± 139	1596 ± 154	.99	0.99	0.99	0.99	−85 ± 227	.99
Symptoms	172 ± 12	182 ± 16	162 ± 18	.99	120 ± 12	112 ± 16	128 ± 18	.99	**0.02**	0.99	0.99	−37 ± 33	.99

Units for pH-impedance metrics are # per day unless otherwise stated. Data presented as Mean ± SE. Bold values indicate statistical significant ($P < .05$).

PPI, proton pump inhibitor; FM, feeding modification bundle including prolonged feeding duration (>30 min) in right side lying position at ≤140 mL/kg/d and postprandial supine position; DBI, distal baseline impedance.