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Extra-Esophageal Manifestations of Gastroesophageal Reflux in the Premature Infant: New Clinical Methods of Evaluation

In this Issue...

Gastroesophageal reflux (GER) may be an important factor in the persistence of chronic lung disease and cardio-respiratory events in the extremely premature infant. Improving our ability to detect the cardio-pulmonary complications of GER may help to prevent further lung damage and poor outcomes of premature infants.

In this issue, we review how tracheal pepsin has been used as a marker of reflux aspiration in the premature infant, and report on how the combined impedance-pH probe monitoring system may improve the association of GER symptoms with cardio-respiratory (CR) events.

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1 contact hour Nurses

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Guest Faculty Disclosure

Jeanne Nunez, MD has indicated that she has received grants/research support from INO Therapeutics.

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LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Describe how GER may be associated with feeding disorders, chronic lung disease, and persistent cardio-respiratory events (apnea and bradycardia)
- Describe how the impedance-pH probe technique improves sensitivity for diagnosis and may allow association of GER with cardio-respiratory events
- Discuss how tracheal pepsin may be used as a marker of reflux aspiration in the premature infant

COMMENTARY

While chronic lung disease (CLD), cerebral palsy, and mental retardation are well known complications of extreme prematurity, less well known is the increased prevalence of feeding dysfunction. At the Mount Washington Pediatric Hospital in Baltimore, 41% of infants born at less than 25 weeks gestation receive surgically placed feeding tubes for feeding problems.¹ According to a study done as part of the Nationwide Inpatient Sample, 48,000 anti-reflux surgeries have been done over the period from 1996 to 2003.² Almost half of those were in infants less than one year old, and the incidence was found to have almost doubled during that period. Dysfunctional swallow associated with immaturity, brain damage, and poor respiratory reserve seen in infants with CLD, as well as GER, are believed to be causal factors leading to feeding dysfunction in extremely premature infants.

While GER is essentially seen in all newborn infants and improves with maturation, the condition is believed to contribute to several important consequences, including: CR events, reflux aspiration, feeding aversion, and swallowing dysfunction.^{3,4} These events increase length of hospitalization, worsen CLD, and may increase the risk of sudden death.

In the Collaborative Home Infant Monitoring Evaluation (CHIME) study (involving the largest longitudinal physiologic dataset of infants), persistent obstructive apneas were shown to be common beyond term in the recovering premature infant, and were associated with poor developmental outcome.^{5,6} GER may be suspected as a cause of persistent CR events at a gestational age (GA) when most premature infants have outgrown their apnea of prematurity. CR events induced by GER may be mediated through vagal reflexes or reflux aspiration. Acute pulmonary aspiration is often suspected in infants with CLD when they develop new signs of apnea, respiratory distress, and chest X-ray changes. Acute aspirations occur with both nipple feedings and gavage feedings, suggesting GER. In infants with CLD, GER may become "non-physiologic" because of increased transient lower esophageal

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sphincter relaxation,⁷ and may be especially associated with increased work of breathing and intra-abdominal pressures. Also, "non-physiologic" GER may be further complicated by swallowing/laryngeal dysfunction preventing airway protection.

However, obtaining direct proof of aspiration due to GER or proving an association of a GER event with a CR event is, at present, very elusive. Esophageal pH monitoring explores only the esophageal consequences of GER, and is accurate only when the gastric pH is low. Clinical history, pattern of abnormalities on chest X-ray, and tracheobronchial aspiration during barium contrast or scintigraphic studies lack sensitivity and/or specificity. Similarly, determination of fat-laden macrophages in tracheal aspirates has been shown to be poorly specific, with about half of both the children presenting with GER and respiratory symptoms as well as controls testing positive for macrophages containing fat.⁸

Each of the studies discussed herein sought to explore new methods of investigation to associate cardiopulmonary events, especially aspiration and CR events, with GER. The presence of tracheal pepsin has been used as a marker of aspiration in older children, adults, and experimental studies.⁹⁻¹² Several studies have attempted to correlate CR events with GER as detected by impedance in diverse pediatric populations.¹³⁻¹⁸ Results and interpretations of these clinical studies have been conflicting secondary to major methodological differences, including subject selection, methods of exploration, and temporal association statistical analysis.

By identifying the reflux bolus itself in the esophagus and its pH, the combined impedance-pH probe has the potential to more accurately establish a temporal correlation with CR events. Sandhill Scientific, the manufacturer of the combined impedance pH probe in the US, has developed several statistical tools to explore symptom association. The symptom index (SI) is calculated as the number of symptoms with reflux times 100 divided by the total number of symptoms, and is expressed as a percentage. A second method is the Symptom Associated Probability (SAP), which is a Fisher exact test. The advantage of these statistical methods is that a correlation between reflux and CR events may be established for each individual infant.

Sandhill has released their proprietary software with two different techniques to statistically correlate GER and respiratory symptoms for the SAP. In the first method of SAP, the recording is divided into 2 minute bins, and tested for the presence of GER in bin n and symptom in bin n+1. A symptom occurring in the same bin n after a GER event is not counted as being correlated. Whether this assumption is appropriate or not is unclear. The second method of SAP is based on research by Bredenoord et al.¹⁹ The recording is divided into two minute bins and tested for the presence of GER. A symptom is determined to be temporally correlated if the beginning of a GER event occurs within the 2 minute segment before the symptom. This method seems more appropriate, and new software with this SAP method has recently been released by Sandhill.

In summary, further studies are needed in infants suspected of cardiopulmonary complications of GER as seen in the recovering premature infant with persistent CLD and/or persistent CR events. GER should be considered in these infants when they should have outgrown their CLD and/or apnea of prematurity. The association of CR events with GER may help determine the optimal medical and surgical management of GER to improve poor outcome.

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USE OF GASTRIC PEPTIDES TO IDENTIFY ASPIRATION IN INTUBATED INFANTS

Farhath S, Aghai ZH, Nakhla T, et al. **Pepsin, a reliable marker of gastric aspiration, is frequently detected in tracheal aspirates from premature ventilated neonates: Relationship with feeding and methylxanthine therapy.** *J Pediatr Gastroenterol Nutr*. 2006 Sep;43(3):336-341.

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As gastric pepsin is normally absent in tracheal secretions, its presence has been used as a marker of aspiration in adults, in older children, and in experimental models. In this 2006 report, the authors sought to determine if tracheal pepsin can serve as a reliable marker of reflux aspiration in neonates.

The investigators collected tracheal aspirates in intubated infants born at less than 32 weeks gestation on postnatal days 1, 3, 5, 7, 14, 21, 28, and after 28 days if still ventilated. Tracheal pepsin levels were measured with an enzymatic method using a fluorescein isothiocyanate casein (a procedure described by Krishnan et al¹). The

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authors report that pepsin levels were found to be lower on day 1 when compared with all other time points. Further, the mean concentration of pepsin in aspirates was found to be significantly lower during those periods when infants were unfed compared to levels during feedings.

Finding the presence of gastric pepsin in the trachea suggests reflux aspiration in infants intubated with uncuffed endotracheal tubes. However, the enzymatic method may not be specific to gastric pepsin, as it may detect other proteases normally present in the lungs; a better technique would have been to use Western blots, allowing specific identification of pepsin by molecular weight and the use of pepsin antibodies. With further studies, tracheal pepsin could help determine the role of reflux aspiration in the persistence and worsening of CLD. Of note is that the measurement of tracheal pepsin may be useful for determining optimal feeding methods for intubated infants.

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GER DETECTED BY COMBINED IMPEDANCE-PH PROBE MONITORING SYSTEM

Peter CS, Wiechers C, Bohnhorst B, Silny J, Poets CF. **Detection of small bolus volumes using multiple intraluminal impedance in preterm infants**. *J Pediatr Gastroenterol Nutr*. 2003 Mar;36(3):381-384.

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Esophageal pH monitoring, the standard method for diagnosing GER in infants, will not detect non-acid GER (the most common GER seen in infants). The pH probe may also falsely detect low pH from the clearance of a previous episode of reflux. Intra-esophageal impedance measurement at multiple sites can detect bolus movements in the esophagus independently of the pH. The presence of fluid inside the esophagus can be identified based on the differing electrical resistance of air, muscle, and fluids to alternating current generated between multiple pairs of electrodes. Intraluminal impedance is increased in the presence of air, and decreased in the presence of fluid, compared to the baseline impedance of the esophagus.

Because there is no fundamental difference between changes of impedance induced by GER and swallowing, the authors sought to test the sensitivity of the impedance monitoring system to small bolus volumes via induced swallows. Ten preterm infants at median GA 33 weeks and 9 days old underwent 10 instillations each of 0.1 ml to 0.5 ml of saline.

The investigators report that all 100 instillations were detected by the impedance monitoring system. They further note that liquid volumes as small as 0.1 ml may be detected by multiple intraluminal impedance, suggesting that this technique is very sensitive.

Available infant commercial probes have 6 impedance channels, contained in a 7.2FR catheter, and measure change of impedance at various levels in the esophagus, allowing differentiation between antegrade (swallow) and retrograde (reflux) fluid movements. As this study demonstrates, the impedance method is very sensitive, and consistent association with manometric events has demonstrated good specificity as well. A pH probe included in the catheter allows simultaneous measurement of esophageal pH.

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ESTABLISHING ESOPHAGEAL IMPEDANCE NORMATIVE DATA IN HEALTHY PREMATURE INFANTS

Lopez-Alonso M, Moya MJ, Cabo JA, et al. **Twenty-four-hour esophageal impedance-pH monitoring in healthy preterm neonates: Rate and characteristics of acid, weakly acidic, and weakly alkaline gastroesophageal reflux.** *Pediatrics*. 2006 Aug;118 (2):e299-308.

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The investigators replaced a conventional feeding tube with a specially designed feeding tube that included 9 impedance channels. This feeding tube/impedance probe was placed in the stomach (8 FR), with esophageal and gastric pH monitored using a separate parallel 6 FR catheter. Twenty-six healthy premature infants (median postmenstrual age (PMA) 32 weeks, median postnatal age (PA) 12 days) were recruited for the study. Esophageal impedance was recorded for 24 hours. Infants were fed through a feeding tube over one hour, with 2-hour breaks between feedings.

The authors report that the median number of reflux events in 24 hours was 71: of these, 25.4% were acidic and 72.9% weakly acidic. The median number of reflux events during fasting was 37 (42% acid, 57.8% weakly acid). Feeding periods were associated with a higher number of reflux/hour and a higher number of weakly acid reflux events. Ninety percent of reflux events were only liquid, as opposed to the mixed gaseous/liquid GER mostly observed in adults. About 90% of reflux episodes reached the proximal esophageal segments. Median bolus clearance time was 9.2 seconds, while chemical clearance (pH) was 20.8 seconds. Total acid exposure (pH drops both associated and not associated with reflux detected by impedance) was 5.59% (fed 2.35%, fasting 7.23%), while reflux-related acid exposure (pH drops associated with reflux detected by impedance) was 1.66% (fed 0.10% fasting 1.36%).

pH-only reflux events (with no impedance changes and slow drifts of impedance in one or two channels) might be explained by very short reflux events that did not meet the definition criteria of GER detected by impedance (50% drop of impedance in at least two consecutive impedance channels). This finding confirms the need for the use of impedance together with pH. For example, temporal correlation with cardio-respiratory events may be underestimated if pH-only GER events representing short reflux that have not reached the proximal esophagus are included.

While this study provides normative data at 32 weeks PMA, it raises the questions of what the normative data would be at other GA and ages. In addition, further studies are needed to correlate normal and abnormal data with outcome. Furthermore, while these data demonstrate the utility of the combined impedance-pH probe in identifying GER, the results are not extended to association of GER with CR events. CR events and reflux aspiration complicating GER are mediated through a combination of vagal reflexes and oromotor dysfunction associated with immaturity, brain damage, and poor respiratory reserve in infants with CLD. These infants may have cardio-pulmonary complications of GER despite having a normal lower esophageal sphincter (LES). Moreover, the specially designed feeding tube used in this study had impedance channels that transcended the LES, thereby potentially compromising it. These findings may therefore overestimate the actual normal GER data.

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ASSOCIATION OF APNEA AND GER VIA INTRALUMINAL IMPEDANCE (1)

Wenzl TG, Schenke S, Peschgens T, Silny J, Heimann G, Skopnik H. **Association of apnea and Non-acid GER in Infants: Investigations with the Intraluminal Impedance Technique.** *Pediatr Pulmonol.* 2001 Feb;31(2):144-149.

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Twenty-two patients at mean age 69 (+/- 38) days were enrolled in this study: of these, 10 had a history of recurrent regurgitations, 12 had respiratory symptoms and recurrent respiratory infections, and 2 were SIDS siblings. An apnea event was defined as a breathing arrest of more than or equal to 5 seconds; for detection, oronasal airflow was registered by thermistor, and chest wall movement was recorded by induction plethysmography with an Alice II polygraph. Occurrence of an apneic episode during the 30 seconds preceding or following the beginning of GER detected by esophageal impedance was defined as temporal association. Sleep state was not part of the study design.

No statistical differences were found between the patient groups; therefore, they were merged into one group for statistical analysis. The investigators report that 86.5% of GER occurred during the first two postprandial hours, with 71.4% reaching the hypopharynx. 29.75% of apneas were associated with GER (with most apneas central), and 77.65% of GER episodes associated with apnea were non-acidic. Regarding the association found between apnea and GER, the mean time spent apneic during GER (40.2 seconds/hour) was greater than the mean time spent apneic without GER (6.8 seconds/hour [$p < 0.001$ paired Wilcoxon test]). Furthermore, GER episodes lasting longer than 30 seconds were more often associated with apnea than shorter GER episodes ($p < 0.03$). Because the data contained outliers, an underlying normal distribution was not assumed. Therefore, non-parametric tests were used.

Unfortunately, the results of the pH probe are not reported. As normative data are known for the pH probe, these results could have been used to assess the significance of GER at the lower esophageal sphincter in these infants. Further, it may be questioned whether the mean time spent apneic during reflux, compared to the mean time spent apneic between reflux, is the best way to demonstrate temporal correlation. In addition, this statistical analysis of the temporal correlation looked at a heterogeneous population and not at each specific child; therefore this method of analysis may not be clinically useful. Also, sleep state was not recorded during the study, an important measure since swallowing and esophageal bolus clearance might be impaired during sleep.

ASSOCIATION OF APNEA AND GER VIA INTRALUMINAL IMPEDANCE (2)

Peter CS, Sprodowski N, Bohnhorst B, Silny J, Poets CF. **Gastroesophageal reflux and apnea of prematurity: No temporal relationship.** *Pediatrics.* 2002 Jan;109(1):8-11.

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Nineteen premature infants ranging from 24 to 34 weeks gestation at median age of 26 (13-93) days with apnea of prematurity (AOP) underwent recording of esophageal impedance in conjunction with a pneumogram. Apnea was defined as cessation of breathing efforts and/or nasal airflow for at least 4 seconds. A temporal relationship was defined if both GER and CR events commenced within 20 seconds of each other. The frequency of apneas associated with GER was calculated by

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dividing the number of pauses during these reflux epochs by the total time of these epochs, and comparing the resulting values with those calculated for reflux-free epochs using the Wilcoxon's matched pairs test.

The investigators reported that the frequency of apneas occurring within +/- 20 seconds of a GER was not significantly different from those occurring during reflux-free epochs. They concluded that in the majority of premature infants, GER is probably not the underlying cause of AOP, and the widespread use of anti-reflux medications in premature infants is probably not justified. However, these infants were young (on average at 33 weeks PMA) and still at significant risk for AOP. Thus, the temporal correlation may be underestimated if the majority of apneas seen were due to prematurity, and only a few were associated with GER. Since the risk of AOP decreases around term, a temporal correlation could have been easier to demonstrate in former premature infants with persistent CR events at term.

ASSOCIATION OF APNEA AND GER VIA INTRALUMINAL IMPEDANCE (3)

Mousa H, Woodley FW, Metheney M, Hayes J. **Testing the association between gastroesophageal reflux and apnea in infants.** *J Pediatr Gastroenterol Nutr.* 2005 Aug;41(2):169-177.

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The investigators enrolled 25 patients at a median age of 4 months with history of acute life threatening events (ALTE), and synchronized the combined Impedance-pH probe data with the pneumography data. Apnea was defined as a decrease in airflow to 10% of baseline lasting 10 seconds or more (derived from that of Loughlin's 2000 study, which defined apnea as a pause in breathing lasting at least 2 breathing cycles¹). An apnea event was defined as temporally linked if the apneic event occurred during the episode or within the ensuing 5 minutes.

The authors report that scatterplots revealed no significant correlation between apnea and frequency or duration of reflux episodes. Four of the 25 patients showed a significant correlation of apnea duration with duration of GER; these 4 patients had significant apnea and were subsequently treated with fundoplication or gastrojejunal feedings. Individual Chi-square analysis found association between apnea and reflux only in 2 patients.

The temporal association found in the few patients in this study may suggest (but not prove) a cause-effect relation. An improvement of the apneas after GER treatment by Nissen fundoplication would have demonstrated a cause-effect relation. The Chi-square, an estimate of the Fisher exact test, used in this study has the advantage of exploring the temporal association between apnea and reflux for each individual patient.

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At the conclusion of this activity, participants should be able to:

- Describe how GER may be associated with feeding disorders, chronic lung disease, and persistent cardio-respiratory events (apnea and bradycardia)
- Describe how the impedance-pH probe technique improves sensitivity for diagnosis and may allow association of GER with cardio-respiratory events
- Discuss how tracheal pepsin may be used as a marker of reflux aspiration in the premature infant

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