Symptomatic Gastroesophageal Reflux in the Preterm Infant: Fantasy or Real?

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Objectives

- Identify the pathophysiology of gastroesophageal reflux (GER) in the preterm infant.
- Discuss diagnostic modalities for GER.
- Explain the possible causal relationship of GER and apnea of prematurity.
- Identify effects of treatment of GER in the preterm infant.
Case

- You are taking care of a 3-week-old former 26-week GA 800 g baby, on NCO2 and caffeine. She has recurrent apnea and bradycardia events recorded by the nurses.
- “Apnea is much worse with feeding, and I’ve noticed the baby swallowing a lot with the spells, and she spits up all the time. I think it’s reflux!”
  - “Do something!”
Apnea and Reflux: Cause and Effect?

- Most (all) premature babies have reflux.
- Most premature babies < 32 weeks have apnea.
- Does reflux cause or worsen apnea of prematurity?
Ontogeny of GER in Preterm Infants

Adapted from Poets CF, Brockmann PE. Myth: gastroesophageal reflux is a pathological entity in the preterm infant. *Semin Fetal Neonatal Med*. 2011;16(5):259–263.
Is there a physiologic basis for the “connection” of GER with “idiopathic” apnea of prematurity?
Laryngeal Stimulation Results in Reflex Apnea in Preterm Infants

Methods to Diagnosis GER

- pH probe – measures for acid reflux in lower esophagus
- Esophageal impedance – measures electrical esophageal signals occurring with reflux and swallows
- Combined impedance/pH probe
- Clinical: Can you see it?
How is GER Diagnosed in the NICU?

Most Common Clinical Criteria for GER Diagnosis in the NICU

Is there evidence that GER precipitates “idiopathic” apnea of prematurity?
No Relationship between GER (pH) and Apnea

Proportion of GER Episodes Preceded by Cardiorespiratory Event

Lower Esophageal Sphincter (LES) Pressure Falls Coincident with Apnea

Case Continued (4 Weeks Later)

- The baby is now 33 weeks PMA. She is noted to have repeated apnea, bradycardia, and desaturation with PO feeding.

- Her nurse also notes that she spits up occasionally, and then cries—acts “uncomfortable” and is “gassy.”

- The mother tells you her other baby had “reflux” and got better with an unidentified medication.
  - “Do something!”
## Relationship of Post-prandial Reflux and Apnea

<table>
<thead>
<tr>
<th></th>
<th>Total GER (per hr)</th>
<th>Acidic GER</th>
<th>Non-acidic GER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-feed</strong></td>
<td>2 (0–11)</td>
<td>2 (0-11)</td>
<td>0 (0-4)</td>
</tr>
<tr>
<td><strong>Post-feed</strong></td>
<td>4 (0-16)</td>
<td>0 (0-10)</td>
<td>4 (0-11)</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>0.012</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Apnea &gt; 5 s</th>
<th>Brady &lt; 85</th>
<th>Desat &lt; 85%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-feed</strong></td>
<td>7 (0-86)</td>
<td>0 (0-4)</td>
<td>0 (0-25)</td>
</tr>
<tr>
<td><strong>Post-feed</strong></td>
<td>6 (0-60)</td>
<td>0 (0-4)</td>
<td>0 (0-40)</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>0.30</td>
<td>0.42</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Signs Attributed to GER in Preterm Infants

- Apnea and desaturation
- Failure to thrive
- Feeding intolerance
- Nipple aversion
- General irritability (especially post-prandial)
- Worsening lung disease
### Differences of Opinion Amongst Subspecialties on GER Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Pulmonologist (%)</th>
<th>Gastroenterologist (%)</th>
<th>Neonatologist (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening Lung Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheezing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apnea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeding Intolerance</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Failure to Thrive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
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</tbody>
</table>

Temporal Association of Reflux “Behaviors” and Measured GER

Does treatment of clinical reflux affect the incidence of cardiorespiratory events or other GER symptoms in preterm infants?
Medications Used for Anti-reflux Treatment in Preterm Infants

- **Pro-kinetic agents**
  - Metoclopramide (cisapride)

- **Gastric acid suppression**
  - Proton pump inhibitors
  - Histamine antagonists
Anti-reflux Treatment Does Not Improve Apnea

Cross-over Trial of Metoclopramide for Bradycardia Events

Efficacy and Safety of Proton Pump Inhibitor in Treatment of GER in Infants < 1 Year Old

<table>
<thead>
<tr>
<th></th>
<th>Lansoprazole (N=81)</th>
<th>Placebo (N=81)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy (%)</strong></td>
<td>54</td>
<td>54</td>
<td>NS</td>
</tr>
<tr>
<td><strong>All Adverse Events (%)</strong></td>
<td>62</td>
<td>46</td>
<td>0.058</td>
</tr>
<tr>
<td><strong>Severe Adverse Events (%)</strong></td>
<td>12</td>
<td>2</td>
<td>0.032</td>
</tr>
</tbody>
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* All infants with severe adverse events required hospitalization.

Ranitidine Associated with Increased Risk of Sepsis, Necrotizing Enterocolitis, and Death in Very Low Birth Weight Infants

Other Suggested Treatment Strategies in Preterm Infants

- Body positioning (head-up angle, left lateral)
- Change in feeding approach (continuous intra-gastric or trans-pyloric)
- Milk thickeners (xanthan gum, starch, rice cereal)
- Hydrolyzed protein formulas

None of these have been systematically studied in the preterm population and do not appear to reduce GER “behaviors.”
Case Continued (4 Weeks Later)

- The baby is now 39 weeks PMA. She was transferred 2 weeks ago to a community hospital.
- Her mother calls to tell you “The docs here finally listened to me, and put her on ranitidine and metoclopramide, and she is SO much better and going home tomorrow!”
  - “They are ‘good’ doctors”
  - “They did something!”
Use of Reflux Meds in Extremely Low Birth Weight Infants at Discharge in NICHD Network

Conclusions/AAP Committee on Fetus and Newborn (COFN) Recommendations

- Little evidence that GER is associated with apnea of prematurity or other “reflux-like” behaviors
- No evidence that treatment of suspected or proven GER is beneficial in preterm infants, and may be harmful
- Broad diagnostic and therapeutic variation in practice
- “Watchful waiting” best approach (new AAP COFN recommendations)
Selected References


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