Reflux and Apnea: Real or Reflex

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The speaker has signed a disclosure form and indicated he has no significant financial interest or relationship with the companies or the manufacturer(s) of any commercial product and/or service that will be discussed as part of this presentation.

Session Summary

Reflux is a frequent diagnosis in preterm infants. Whether apnea of prematurity can be precipitated by reflux, and whether treatment of reflux can ameliorate apnea, remain controversial. This talk will view the evidence for and against a role of reflux in apnea of prematurity.

Session Objectives

Upon completion of this presentation, the participant will be able to:

- describe the epidemiology of apnea of prematurity;
- summarize the evidence for the possible role of GER in apnea;
- understand the effects and side effects of treatment for GER in premature infants.

References


**Session Outline**

See presentation handout on the following pages.
Apnea, Reflux, Both or Neither: A Source of Unwarranted Practice Variation?

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Apnea of Prematurity: Why is it Important?
- One of the most common diagnoses in the Newborn Intensive Care Unit
- Resolution of apnea usually precondition for discharge
- Significant contribution to length of hospital stay for preterm infants
- Significant practice variation
- Is it harmful?

Incidence of Apnea Inversely Proportional to Gestational Age

<table>
<thead>
<tr>
<th>Gestational Age (weeks)</th>
<th>n = 226</th>
<th>n = 435</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>90%</td>
<td>80%</td>
</tr>
<tr>
<td>26</td>
<td>80%</td>
<td>70%</td>
</tr>
<tr>
<td>28</td>
<td>70%</td>
<td>60%</td>
</tr>
<tr>
<td>30</td>
<td>60%</td>
<td>50%</td>
</tr>
<tr>
<td>32</td>
<td>50%</td>
<td>40%</td>
</tr>
<tr>
<td>34</td>
<td>40%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Proportion of Infants with Persistent Apnea/Bradycardia Events

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenstrual Age</td>
</tr>
<tr>
<td>26 wk</td>
</tr>
<tr>
<td>28 wk</td>
</tr>
<tr>
<td>30-32 wk</td>
</tr>
</tbody>
</table>

Site Differences in Day of Last Documented Apnea Event in 30 to 34 wk infants

<table>
<thead>
<tr>
<th>Postmenstrual Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>34.1 wks</td>
</tr>
<tr>
<td>35.8 wks</td>
</tr>
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</table>

Variation in Diagnosis of Apnea in 33 to 34 week Infants

<table>
<thead>
<tr>
<th>Hospital Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Earliest to Latest Discharge</td>
</tr>
<tr>
<td>24%</td>
</tr>
<tr>
<td>76%</td>
</tr>
</tbody>
</table>
Late Preterm Infants Diagnosed with Apnea are Discharged Later

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 C, Semin Fetal Neonatal Med 2011

Diagnosis of 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 NICU?

Most Common Clinical Criteria for GER Diagnosis

Dhillon AS, Acta Paediatr 2004

Dhillon AS, Acta Paediatr 2004
Is there a physiologic basis for the “connection” of GER with “idiopathic” apnea of prematurity?

Apnea and Reflux
- Infants have very active laryngeal reflex
- Stimulation with acid or water precipitates apnea rather than cough reflex
- Serves as “rationale” for relationship between apnea of prematurity and reflux

Types of Apnea
- Central: cessation of breathing efforts
- Obstructive: upper airway obstruction with breathing effort
- Mixed: both central and obstructive

Reflex response to upper airway obstruction is to swallow repeatedly

Laryngeal Stimulation Results in Reflex Apnea in Preterm Infants

Is there evidence that GER precipitates “idiopathic” apnea of prematurity?

No Relationship Between Gastroesophageal Reflux (pH) and Apnea

De Ajuriaguerra, AJDC 1991
No Relationship Between Gastroesophageal Reflux (pH) and Apnea

Proportion of Cardiorespiratory Events Preceded by GER (MII and pH)

Proportion of GER Episodes Preceded by CR Event

LES Pressure Falls Coincident with Apnea

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>Pre-feed</td>
<td>2 (0–11)</td>
<td>2 (0–11)</td>
<td>0 (0–4)</td>
</tr>
<tr>
<td>Post-feed</td>
<td>4 (0–16)</td>
<td>0 (0–10)</td>
<td>4 (0–11)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.012 &lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Pre-feed&lt;br&gt;7 (0–86)&lt;br&gt;0.30</th>
<th>Brady &lt; 85&lt;br&gt;6 (0–4)</th>
<th>Desat &lt; 85%&lt;br&gt;0 (0–25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-feed</td>
<td>6 (0–65)</td>
<td>0 (0–4)</td>
<td>0 (0–40)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.30</td>
<td>0.30</td>
<td>0.23</td>
</tr>
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Does treatment of clinical reflux affect the incidence of cardiorespiratory events 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 Metaclopramide for Bradycardia Events

Transpyloric Feedings Decrease Apnea in Infants with Suspected GER

Efficacy and Safety of PPI in Treatment of GER in Infants < 1 year

<table>
<thead>
<tr>
<th></th>
<th>Lansoprazole (N=81)</th>
<th>Placebo (N=81)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy (%)</td>
<td>54</td>
<td>54</td>
<td>NS</td>
</tr>
<tr>
<td>All Adverse Events (%)</td>
<td>62</td>
<td>46</td>
<td>0.058</td>
</tr>
<tr>
<td>Severe Adverse Events (%)</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, NEC and Death in VLBW Infants
Conclusions

- Little evidence that GER associated with apnea of prematurity
- No evidence that treatment of clinical GER beneficial, and may be harmful
- Recommend hefty dose of therapeutic nihilism

Use of Reflux Meds in ELBW at Discharge

Malcolm WF, Pediatrics 2008

Apnea and Reflux: Buyer Beware!

"We don't have a dog but we felt a need to offer a warning anyway."