Apnea and Gastroesophageal Reflux in the Premature Infant: Two Intersecting Dilemmas

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The Dilemmas

- Aspirate
- Apnea
- Bradycardia
- Spitting
- Desat
- Regurgitation
Apnea and GER: Common Features

- May be physiologically linked
- Manifestations of developmental immaturity
- Exhibit natural resolution

APNEA  GER
Apnea and GER

Physiologic basis for a relationship
Clinical basis for a relationship
Diagnostic options and dilemmas
Rationale for therapeutic approaches
Anatomy of the Gastroesophageal Junction

Epstein, NEJM 1997
Possible Causal Relationships Between Apnea in Preterm Infants

GER  APNEA
Gastroesophageal Reflux and Apnea

Herbst, J Pediatr 1979
Reflex Pathways Involved in Central Apnea, Laryngeal Closure, Airway Constriction, Bradycardia and Reflux
Possible Causal Relationship Between Apnea in Preterm Infants

GER

APNEA
Respiratory Control and LES Pressure

Hypoxia-induced apnea

DIA EMG (AU)

PLES (mmHg)

Kiatchoosakun, Pediatr Res 2002
LES Pressure Associated with Apnea Onset

LES Pressure

Apnea

Time Relative to Apnea Onset (sec)

mmHg

Omari, J Pediatr 2009
Apnea and GER

Physiologic basis for a relationship

Clinical basis for a relationship

Diagnostic options and dilemmas

Rationale for therapeutic approaches
GER versus GERD!!

“Infants suspected of GERD have more frequent regurgitation, vomiting and crying than healthy control infants. However, clinical history and questionnaires cannot predict the severity of GERD. Therefore a highly sensitive and specific method to select infants for investigation and empiric pharmacotherapy still needs to be developed.”

Salvatore S, J Pediatr Gastroenterol Nutr 2005
Physician Perceived Symptoms Do Not Identify Healthy Preterm Infants with Significant GER

Hibbs AM, PAS 2010
Most Common Clinical Criteria for GER Diagnosis (UK NICU Center Survey)

Percent of Centers

- Feeding Intolerance
- Apnea
- Bradycardia
- Desaturation
- Milk in Mouth or Oropharynx
- Respiratory Problems

Dhillon, Acta Paediatr 2004
Apnea and Gastro-Esophageal Reflux in the Preterm Infant

Number of Acid-Based Reflux Episodes (per 12h) vs. Number of Apnea (per 12h)

Barrington, J Perinatol 2002
Effect of GER on Apnea Duration

Apnea before GER

Apnea during GER

30sec Before Acid Gastroesophageal Reflux During

30sec After

DiFiore, Pediatrics 2005
Effect of GER on Apnea Duration
(n=27 infants)

DiFiore, Pediatrics 2005
Apnea and GER

Physiologic basis for a relationship
Clinical basis for a relationship
Diagnostic options and dilemmas
Rationale for therapeutic approaches
Role of Upper Airway Dilator Muscles During Development

- Alae nasi (AN)
- Genioglossus (GG)
- Sternohyoid (SH)
- Posterior Cricoarytenoid (PCA)
# Mixed Apnea

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate (BPM)</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>60</td>
</tr>
<tr>
<td>Chest Wall Movement</td>
<td>15</td>
</tr>
<tr>
<td>Tidal Volume (cc)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>15</td>
</tr>
</tbody>
</table>

[Graph showing heart rate, chest wall movement, and tidal volume over 10 seconds.]
Decreased Respiratory Drive

APNEA, HYPOVENTILATION

incr. vagal tone

BRADYCARDIA

decr. O₂ delivery

carotid body

DESATURATION
Diagnostic Modalities

- Esophageal pH probe
- Multiple intraluminal impedance
- Combined pH and impedance
Reflux Index* Percentiles in Healthy Infants

*percent of time with pH <4

Vandenplas, Pediatrics 1991
Gastroesophageal Reflux and Apnea of Prematurity

GER (Impedance)

Pharynx

Esophagus

Airflow Effort

Peter CS, et al, Pediatr 2002
Rates of Reflux Events Before and After Feeding

Median GER Events/hr

Before Feed

After Feed

Acid
Non-Acid

Slocum, J Perinatol 2009
Median Height of Esophageal Reflux in Preterm Infants

Slocum, J Perinatol 2009
Relationship between Ph-MII Impedance Determined *Reflux* and PSG Determined *Apnea* in Preterm Infants

![Graph showing the relationship between reflux and apnea in preterm infants. The x-axis represents time periods: GER free period, 1 min around GER, 30 sec before GER, and 30 sec after GER. The y-axis represents the number of apneas per minute. There are significant differences marked with asterisks (*all p<0.05*).](attachment:image-url)

*Corvaglia L, et al. Arch Dis Child 2008*
Incidence of Cardiorespiratory Events Preceded by GER

- **All Events:** 2.7%
- **Apnea >10 sec:** 3.4%
- **Desaturation <85%:** 2.8%
- **Bradycardia <80bpm:** 2.9%

*DiFiore, J Perinatol 2010*
Apnea and GER

Physiologic basis for a relationship
Clinical basis for a relationship
Diagnostic options and dilemmas
Rationale for therapeutic approaches
Rationale for Apnea Therapy

- Enhance spontaneous respiratory efforts
- Minimize intermittent hypoxia ± bradycardia
Therapeutic Approaches for Apnea

**Accepted Interventions**
- CPAP
- Xanthine therapy

**Interventions Needing Further Study**
- “Kangaroo” care
- Enrichment of sensory environment
- Change in baseline $\text{SaO}_2$, hematocrit, or $\text{↑CO}_2$
Effect of CPAP on Incidence of Apnea

(p<0.02)
Nasal CPAP for Neonatal Apnea

- Decrease in upper airway resistance
- Increase in FRC
- Improvement in oxygenation
Theophylline

Pre

Post

Caffeine

Pre

Post

Mean Daily Number of Apneic Episodes

Number of Apneic spells per day

Aranda, J Peds 1977

Uauy, Pediatr 1975
DECAFE OR CAFFE

CAP TRIAL

Schmidt B.
# Effect of Caffeine Therapy for Apnea of Prematurity

<table>
<thead>
<tr>
<th></th>
<th>Caffeine Group (n=1006)</th>
<th>Placebo Group (n=1000)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenstrual age at last use of endotracheal tube Median</td>
<td>29.1 weeks</td>
<td>30.0 weeks</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postmenstrual age at last use of supplemental oxygen Median</td>
<td>33.6 weeks</td>
<td>35.1 weeks</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Schmidt, NEJM 2006*
Proposed Beneficial Effects of Xanthine on BPD

CAFFEINE

Lower concentration

Adenosine receptor blockade
\( (A_1, A_{2A}, A_{2B}, A_3) \)

INCREASED RESPIRATORY DRIVE

Higher concentration

\( \uparrow \text{cAMP} \)

(phosphodiesterase inhibition)

BRONCHODILATION

INFLAMMATORY RESPONSE MODULATION
Caffeine Therapy for Apnea Trial: Outcome at 18-21 Months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Caffeine</th>
<th>Placebo</th>
<th>OR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or disability</td>
<td>40%</td>
<td>46%</td>
<td>0.77</td>
<td>0.006</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>4.4%</td>
<td>7.3%</td>
<td>0.58</td>
<td>0.009</td>
</tr>
<tr>
<td>MDI&lt;85</td>
<td>34%</td>
<td>38%</td>
<td>0.80</td>
<td>0.035</td>
</tr>
<tr>
<td>Severe ROP</td>
<td>5.1%</td>
<td>7.9%</td>
<td>0.63</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Schmidt, NEJM 2007
Proposed Beneficial Effects of Xanthine on Neurodevelopment

xanthines

- Altered CNS neurotransmission (adenosine, GABA)
- Less apnea
- Less hypoxemic events
- Downregulation of cytokine release from immune cells

Improved Neurodevelopmental Outcome
Rationale for GER Therapy

- Feeding intolerance-symptomatic GERD
- Apnea, bradycardia, desaturation episodes
- Growth failure
- ? Risk of respiratory morbidity, e.g. wheezing disorders, worsening BPD
% of Physicians reporting likelihood that Symptoms are caused by GERD, based on overall clinical impression

Golski C., Pediatrics 2009
Non-Pharmacologic Approaches

- Thickened feeds
- Positioning
- Nasojejunal feeds
- Avoidance of tobacco exposure
# Thickened Feeds and Reflux: Frequency of Emesis

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n</th>
<th>Control n</th>
<th>Standardized Mean Difference 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moya 1999</td>
<td>14</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Orenstein 1987</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Wenzl 2003</td>
<td>14</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Total (95%CI)</td>
<td>6</td>
<td>20</td>
<td>-4.0 -2.0 0 2.0 4.0</td>
</tr>
</tbody>
</table>

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FDA Warns Not to Feed SimplyThick to Premature Infants

UPDATE: June 5, 2011: Simply Thick Recalled, FDA Continues to Investigate Necrotizing Enterocolitis and SimplyThick
Positioning and Reflux

- Postprandial GER is enhanced in the right lateral [right side down] and supine positions.
- However, the right lateral position promotes gastric emptying.
- Potential benefit of these positions for inpatients must be balanced against the *back to sleep* message for SIDS prevention.
Positioning and Reflux

Vandenplas, Arch Dis Child 2010
Major Candidates for Pharmacotherapy in Neonates

- **Prokinetics**
  - metoclopramide, cisapride, erythromycin
- **Acid suppression**
  - proton pump inhibitors
  - histamine (H₂ receptor) antagonists
ELBW Infants Discharged on Anti-Reflux Medication

Percent Going Home on GER Medications

- All ELBW Infants: 24.8%
- Discharged <42 weeks: 19.3%
- Discharged >42 weeks: 47.6%

WF Malcolm, Pediatrics 2008
Efficacy of Oral Erythromycin for Treatment of Feeding Intolerance in Preterm Infants

Cross-Over Trial of Treatment for Bradycardia Attributed to Gastroesophageal Reflux

Number of Bradycardia Episodes

Drug
Metoclopromide or Ranitidine

Placebo

* $p = 0.04$

Wheatley, J Pediatr 2009
## Efficacy and Safety of Proton Pump Inhibitor Therapy in Infants with GERD

<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 rate</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>NS</td>
</tr>
<tr>
<td><strong>Severe adverse events</strong></td>
<td>12%</td>
<td>2%</td>
<td><strong>.032</strong></td>
</tr>
</tbody>
</table>

*Orenstein, J Pediatr 2009*
## Medications Commonly Used to Treat Gastroesophageal Reflux Disease in Infants in the United States

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Robust Evidence for Effectiveness in Infants</th>
<th>Safety Concerns</th>
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</thead>
<tbody>
<tr>
<td>Gastric Acid Suppression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H₂ Receptor Antagonists</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Proton pump Inhibitors</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Prokinetics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Hibbs A, NeoReviews 2011*
GER Pharmacotherapy: Recommendations

Recognize that...

- Therapy started in the NICU may be continued indefinitely
- Natural history supports resolution of GER
- Short and long term safety of pharmacotherapy must be a high priority
GER Pharmacotherapy: Recommendations

Meanwhile...

- Avoid “therapeutic exuberance”
- Seek evidence for benefit in the individual patient
- Discontinue therapy if symptoms not improved
Evidence Basis for Pharmacotherapy:

Apnea
Benefit outweighs Risk

GER
Risk may outweigh Benefit
Acknowledgement

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