GE Reflux Disease in Neonates

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Objectives

• Name the physiologic basis of gastroesophageal reflux in infants
• Systematically evaluate the evidence for therapeutic approaches

Disclosure

I have no actual or potential conflict of interest in relation to this program.

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

Reflux in Infants

Magnitude of pharmacotherapy
Basis for a relationship with apnea
Diagnostic options and dilemmas
Rationale for therapeutic approaches
Recommendations+

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Possible Causal Relationship Between Apnea in Preterm Infants

Anatomy of the Gastroesophageal Junction

Gastroesophageal Reflux and Apnea
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GE Reflux Disease in Neonates

Apnea and Gastro-Esophageal Reflux in the Preterm Infant

- Number of Reflux Episodes (per 12h)
- Number of Apnea (per 12h)

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Diagnostic Modalities

- Esophageal pH probe
- Multiple intraluminal impedance
- Combined pH and impedance
- Gastric emptying ($^{13}$C exhalation)
- Ultrasonography
- Manometry

Reflux Index* Percentiles in Healthy Infants

*percent of time with pH <4

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

Pre-Feed Post-Feed

p=0.02

Slocum, J Perinatol 2009

Comparison of Apnea Rates Before and After Feeding

Apnea events/hr (≥15 sec)

Pre-Feed Post-Feed

Slocum, J Perinatol 2009

Relationship between Ph-MII Impedance Determined Reflux and PSG Determined Apnea in Preterm Infants


Incidence of Cardiorespiratory Events Preceded by GER

Percent of Events

DiFiore PAS 2009

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DiFiore PAS 2009
Rationale for Therapy

- Feeding intolerance—symptomatic GERD
- Apnea, bradycardia, desaturation episodes
- Growth failure
- \( ? \) Risk of respiratory morbidity, e.g., wheezing disorders, worsening BPD
- \( ?? \) Risk for adult esophageal cancer

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</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moya 1999</td>
<td>14</td>
<td>6</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Orenstein</td>
<td>20</td>
<td>20</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Wenzl 2003</td>
<td>14</td>
<td>14</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total (95%CI)</td>
<td></td>
<td></td>
<td>-4.0 -2.0 0 2.0 4.0</td>
<td></td>
</tr>
</tbody>
</table>

Positioning and Reflux

- Postprandial GER is enhanced in the right lateral [right side down] and supine positions
- \( \textit{However}, \) the right lateral position promotes gastric emptying
- Potential benefit of these positions for inpatients must be balanced against the \( \textit{back to sleep} \) message for SIDS prevention

Major Candidates for Pharmacotherapy in Neonates

- Prokinetics
  - metoclopramide, cisapride, erythromycin
- Acid suppression
  - proton pump inhibitors
  - histamine (H\(_2\) receptor) antagonists
**Changes in Use of GI Medications With Time (All NICU Admissions)**

- Cimetidine (tagamet)
- Famotidine (pepcid)
- Lansoprazole (prevacid)
- Omeprazole (prilosec)

**Gastroesophageal Reflux Medications for Apnea**

- Cisapride
- Metoclopramide

- Before Treatment
- After Treatment

* p < 0.05

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

- Drug: Metoclopramide or Ranitidine
- Placebo

* p = 0.04

**Efficacy and Safety of Proton Pump Inhibitor Therapy in Infants with GERD**

- Lansoprazole
- Placebo

<table>
<thead>
<tr>
<th></th>
<th>Lansoprazole</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy rate</td>
<td>54%</td>
<td>54%</td>
<td>NS</td>
</tr>
<tr>
<td>All adverse events</td>
<td>62%</td>
<td>46%</td>
<td>NS</td>
</tr>
<tr>
<td>Severe adverse events</td>
<td>12%</td>
<td>2%</td>
<td>0.32</td>
</tr>
</tbody>
</table>

**“pet peeves of mine and many peds pulmonology colleagues..In the NICU, the neonatologist have an incredibly high threshold for even considering treating obvious GER” .. Pulmonologist**

**“GERD is very vexing and overdiagnosed..we have no definitive protocol for dealing with it”.. Neonatologist**

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**Golski C., Pediatrics 2009**

**Kimball and Carlton, J Pediatr 2001**

**Wheatley, PAS 2008**

**Orenstein, J Pediatr 2009**

**Golski C., Pediatrics 2009**
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**Recommendations**

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

**Meanwhile...**
- Avoid “therapeutic exuberance”
- Seek evidence for benefit in the individual patient
- Discontinue therapy if symptoms not improved

**Suggested Treatment Algorithm for GER(D) in Premature Infants**

<table>
<thead>
<tr>
<th>Concern for harmful sequelae</th>
<th>No evidence for harmful sequelae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial non-pharmacologic therapies (e.g., feeds).</td>
<td>No intervention.</td>
</tr>
<tr>
<td>Consider diagnostic testing if readily available.</td>
<td></td>
</tr>
<tr>
<td>Improves</td>
<td>Does not improve</td>
</tr>
<tr>
<td>No further intervention.</td>
<td></td>
</tr>
<tr>
<td>Diagnostic testing if readily available (e.g., pH/MII probe with pneumogram).</td>
<td></td>
</tr>
<tr>
<td>No pathologic reflux</td>
<td>Excessive reflux or diagnostic study not available</td>
</tr>
<tr>
<td>No further GER(D) treatment; Work-up for other causes of symptoms.</td>
<td>Trial of pharmacologic therapy (H2-blocker ± prokinetic).</td>
</tr>
<tr>
<td>Does not improve, or side-effects</td>
<td>Improves</td>
</tr>
<tr>
<td>Stop pharmacologic therapy; Consider subspecialist referral.</td>
<td>Continue therapy; Trial off therapy in 1-6 mos.</td>
</tr>
</tbody>
</table>

Acknowledgement

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