Is Gastroesophageal Reflux a Problem in Preterm Infants?

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Professor, Pediatrics
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Reflux in Infants

- Magnitude of pharmacotherapy
- Basis for a relationship with apnea
- Diagnostic options and dilemmas
- Rationale for therapeutic approaches
- What about ALTE’s?
- Overall recommendations
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
Variation in Use of Antireflux Medication at Discharge Among Network Centers

Percent going home on GER medications

Discharged <42 weeks
Discharged >42 weeks

Individual Centers

1 2 3 4 5 6 7 8 6 10 11 12 13 14 15 16

Proposed Overused Neonatal Therapies:  
Survey of US Neonatologists*

All Treatment Clusters

- IMV
- bedside tasks
- bicarbonate
- PDA ligation
- PRBC transfusion
- medical treatment for PDA
- iNO for ELBW
- bronchodilators
- diuretics
- antibiotics
- GER Medication

*personal communication, DeWayne Pursley, M.D., 2012
Reflux in Infants

- Magnitude of pharmacotherapy
- **Basis for a relationship with apnea**
- Diagnostic options and dilemmas
- Rationale for therapeutic approaches
- What about ALTE’s?
- Overall recommendations
Most Common Clinical Criteria for GER Diagnosis
(UK NICU Center Survey)

Dhillon, Acta Pædiatr 2004
Apnea and GER: Common Features

- May be physiologically linked
- Manifestations of developmental immaturity
- Exhibit natural resolution
Anatomy of the Gastroesophageal Junction

Epstein, NEJM 1997
Possible Causal Relationship Between Apnea in Preterm Infants
Respiratory Control and LES Pressure

Hypoxia-induced apnea

DIA EMG (AU)

PLES (mmHg)

30 s

Kiatchoosakun, Pediatr Res 2002
LES Pressure Associated with Apnea Onset

Omari, J Pediatr 2009
Possible Causal Relationship Between Apnea in Preterm Infants

GER  APNEA
Gastroesophageal Reflux and Apnea

Herbst, J Pediatr 1979
Apnea and Gastro-Esophageal Reflux in the Preterm Infant

Number of pH Based Reflux Episodes (per 12h)

Number of Apnea (per 12h)

Barrington, J Perinatol 2002
Reflux in Infants

- Magnitude of pharmacotherapy
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- **Diagnostic options and dilemmas**
- Rationale for therapeutic approaches
- What about ALTE’s?
- Overall recommendations
Diagnostic Modalities

- Esophageal pH probe
- Multiple intraluminal impedance
- Combined pH and impedance
- Gastric emptying
- Ultrasonography
- Manometry
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

<table>
<thead>
<tr>
<th></th>
<th>Pre-Feed</th>
<th>Post-Feed</th>
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<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
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<tr>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

The frequency of apneas in very preterm infants is increased after non-acid gastro-esophageal reflux

L. CORVAGLIA, D. ZAMA, M. SPIZZICHINO, A. ACETI, E. MARIANI, M. G. CAPRETTI, S. GALLETTI & G. FALDELLA

Neonatology and Neonatal Intensive Care Unit, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy

“Non-acid (as opposed to acid)-GER is responsible for a variable amount of apnea detected after GER.”
Incidence of Cardiorespiratory Events Preceded by GER

DiFiore, J Perinatol 2010
Reflux in Infants

- Magnitude of pharmacotherapy
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- Diagnostic options and dilemmas
- **Rationale for therapeutic approaches**
- What about ALTE’s?
- Overall recommendations
Rationale for GER Therapy

- Feeding intolerance - symptomatic GERD
- Apnea, bradycardia, desaturation episodes
- Growth failure
- ? Risk of respiratory morbidity, e.g. wheezing disorders, worsening BPD
GER versus GERD!!

“...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
% of Physicians reporting likelihood that Symptoms are caused by GERD, based on overall clinical impression

- Irritability
- Failure to Thrive
- Feeding Intolerance
- Apnea
- Wheezing
- Worsen lung disease

Golski C., Pediatrics 2009
The Reliability of the Assessment of Endoscopic Laryngeal Findings Associated With Laryngopharyngeal Reflux Disease

Ryan C. Branski, MA; Neil Bhattacharyya, MD; Jo Shapiro, MD

“Our data indicate that otolaryngologists vary significantly in their ratings of the various laryngoscopic physical findings that could be associated with LRPD. We found relatively poor inter-rater reliability for all of the visually assessed variables.”
Non-Pharmacologic Approaches

- Thickened feeds
- Positioning
- Nasojejunal feeds
## 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>
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<tbody>
<tr>
<td>Moya 1999</td>
<td>14</td>
<td>6</td>
<td>-4.0</td>
<td>-2.0</td>
</tr>
<tr>
<td>Orenstein 1987</td>
<td>20</td>
<td>20</td>
<td>0</td>
<td>2.0</td>
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<tr>
<td>Wenzl 2003</td>
<td>14</td>
<td>14</td>
<td>4.0</td>
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</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>-4.0</td>
<td>-2.0</td>
</tr>
</tbody>
</table>

*Copyright © 2007 The Cochrane Collaboration, John Wiley & Sons, Ltd*
**Effect of Increased Enteral Viscosity (Sodium Alginate) on Apnea and Reflux in Preterm Infants**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Treatment</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Apnea Index</td>
<td>9.5 (0-35)</td>
<td>9.5 (0-44)</td>
<td>NS</td>
</tr>
<tr>
<td>Acid GER Index</td>
<td>3 (0-16)</td>
<td>1 (0-5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Non-acid GER Index</td>
<td>6 (1-21)</td>
<td>4.5 (0-22)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Corvaglia, et al., Early Hum Dev, 2011
FDA Warns Not to Feed SimplyThick to Premature Infants

UPDATE: June 5, 2011: Simply Thick Recalled, FDA Continues to Investigate Necrotizing Enterocolitis and SimplyThick
Effect of pH on Thickened Formula Viscosity

J.A. Vanderhoof, 2003
Positioning and Reflux: How Do They Do It?
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
Efficacy of Oral Erythromycin for Treatment of Feeding Intolerance in Preterm Infants

Nuntnarumid P, Kiatchoosakun P, Tantiprapa W and Boonkasidecha S


*p value = <0.001
Gastroesophageal Reflux Medications for Apnea

Kimball and Carlton, J Pediatr 2001

* p < 0.05

Before Treatment

After Treatment

Cisapride
Metoclopramide

Frequency of Apnea (events/day)
Cross-Over Trial of Treatment for Bradycardia Attributed to Gastroesophageal Reflux

Number of Bradycardia Episodes

Drug
Metoclopramide or Ranitidine

Placebo

* $p = 0.04$

Wheatley, J Pediatr. 2009
Association of H2-Blocker Therapy and Higher Incidence of Necrotizing Enterocolitis in Very Low Birth Weight Infants

NICHD Neonatal Research Network
<table>
<thead>
<tr>
<th></th>
<th>Lansoprazole n=81</th>
<th>Placebo n=81</th>
<th>p value</th>
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</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>.032</td>
</tr>
</tbody>
</table>

*term infants or preterms >44 wk PMA

Orenstein, J Pediatr 2009
Ranitidine is Associated with Infections and Necrotizing Enterocolitis in Preterm Infants (24-32 weeks’ Gestational Age)

<table>
<thead>
<tr>
<th></th>
<th>No Treatment</th>
<th>Treatment</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection (%)</td>
<td>9.8</td>
<td>37.4</td>
<td>5.5 (2.9-10.4), p&lt;0.001</td>
</tr>
<tr>
<td>NEC (%)</td>
<td>1.6</td>
<td>9.8</td>
<td>6.6 (1.7-25.0), p=0.003</td>
</tr>
</tbody>
</table>

Terrin G, Pediatrics 2012
Histamine-2 Receptor Blockers Alter the Fecal Microbiota in Premature Infants

“These alterations in fecal microbiota may predispose the vulnerable immature gut to necrotizing enterocolitis and suggest prudence in the use of H2-blockers in the premature infant”.

Gupta RW: JPGN 2013
Gastric Microflora
[in children & adolescents]

Staphylococcus
Veillonella
Streptococcus
Rothia
Dermabacter
Neisseria
Corynebacterium
Candida
Bacillus
Prevotella
Capnocytophaga

Prevalence Ratio

No therapy  Acid suppression therapy

Rosen R: JAMA 2014
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>H$_2$ 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
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Case Scenario

- Former 37 weeks male now 42 weeks post menstrual age
- Found 1 hour after feeding; coughing and choking with formula in nose and mouth; face turned blue and reported apneic
- Mother picked him up, blew in his face, rubbed his back, gave rescue breaths and called Emergency Medical Service (EMS)
- When EMS arrived he appeared well
- Admitted for overnight, pneumogram (respiratory inductance plethysmography, pulse oximetry), and esophageal pH with impedance
Apparent Life-Threatening Event Admissions and GERD

Doshi A, Pediatr Emer Care 2012
Disposition of ALTE Admissions at Rainbow (2008-2011) n=100

- No Intervention
- Home Monitor
- GI Meds
- Other
- Feeding Intervention
- Home Monitor
- Other
- No Intervention
- GI Meds
- Feeding Intervention
Potential Perpetuating Cycle of Apnea and GER

- Apnea
- Decreased LES Pressure
- Activation of Upper Airway Receptors
- GER/Regurgitation
Reflux in Infants

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GER Pharmacotherapy: Recommendations

- Avoid “therapeutic exuberance”
- Recognize higher risk groups of infants
  - e.g., neurologic impairment
  - Anatomic disorders, e.g., TEF, CDH
- Short and long term safety of pharmacotherapy must be a high priority
GER Pharmacotherapy: Recommendations [continued]

- Seek evidence for benefit in the individual patient
- Discontinue therapy if symptoms not improved
- Therapy started in the NICU may be continued “indefinitely”
GI Medications Use Rates
(Per 1000 Patients Based Counted Only Once Per Patient)

Pantoprazole
Cisapride
Famotidine
Omeprazole
Lansoprazole
Metoclopramide

Courtesy: R Clark, Pediatrix Clinical Data Warehouse
Children at Higher Risk for Developing Severe Chronic Gastroesophageal Reflux Disease

- History of neurologic impairment
- Esophageal and anatomical disorders [e.g., tracheoesophageal fistula]
- ? Chronic respiratory disorders
- ? History of prematurity
- ? Obesity
- ? Certain genetic disorders

Gestational Age at Birth and Risk of Gastric Acid-Related Disorders in Young Adulthood

Casey Crump, MD, PhD, Marilyn A. Winkleby, PhD, Jan Sundquist, MD, PhD, and Kristina Sundquist, MD, PhD

Ann Epidemiol 2012

“Gestational age at birth was inversely associated with antisecretory (acid suppression) medication prescription in young adulthood”
Thank You!

Juliann Di Fiore, BSSE
Peter MacFarlane, PhD
Anna Maria Hibbs, MD, MSCE
Mary Elaine Patrinos, MD
Marina Arko, RN
Mary Jo Joyce, RN