Aerodigestive Disorders in the NICU

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Attending in Pediatric Pulmonary Medicine
## Personal/Professional Financial Relationships with Industry

<table>
<thead>
<tr>
<th>External Industry Relationships *</th>
<th>Company Name</th>
<th>Role</th>
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<tr>
<td>Equity, stock, or options in biomedical industry companies or publishers</td>
<td>None</td>
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<tr>
<td>Board of Directors or officer</td>
<td>None</td>
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<tr>
<td>Royalties from Emory or from external entity</td>
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<tr>
<td>Industry funds to Emory for my research</td>
<td>None</td>
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<td>Other</td>
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</table>
Aerodigestive Disorders in the NICU

- GERD
  - Apnea
  - Malacia (laryngeal, tracheal, bronchial)
  - BPD
- Aspiration
  - Primary from dysphagia
  - Secondary from GERD
Aerodigestive Protective Mechanisms

Aerodigestive Protective Mechanisms

Cough Provocation and Resolution in BPD

- 16 of 69 preterm infants w/ BPD had coughing during basal and provocative esophageal manometry.
Most cough events had upper aerodigestive origins with only 20% due to GER.
Patients did have lower UESp which may lead to decrease protection from aspiration
90% of cough followed by swallowing (increased from adults of 50%)
GER AND APNEA
Apnea and GER in the Preterm Infant

- 45 premature infants (born <32 weeks GA) monitored for apneas >10 seconds, bradycardia, desaturation and GER by pH probe

- No correlation between apnea frequency or duration and GER frequency or duration
Lack of Relationship to Apnea

- 137 premature infants (born <32 wks GA) with clinical symptoms of GER (ave corrected GA was 37 weeks)
- 63% were confirmed by pH probe
Apnea Not Prolonged by GER
DiFiore et al. Pediatrics. 2005

• 119 preterm infants w/ clinical GER underwent cardioresp. and pH monitoring.
GER and Apnea: No Temporal Relationship

- 19 preterm infants (<37 wks GA) with AOP had MII
- No correlation between apnea, bradycardia or desaturation and GER.
  - Equal number of events before, during and after GER episodes.
  - Some GER events were temporally associated with apnea/desaturation, esp if refluxate reached the pharynx.
Cardiorespiratory Events and GER in Preterm Infants
Nunez et al. JPGN. 2011.

• 7 premature infants (born <29 wk GA) with persistent symptoms at 39-48 wk PMA despite antireflux meds.

• Synchronized PSG and pH-MII

• Single-subject-level analysis found a temporal association between CR events and GER
Effect of Trans-pyloric Feedings

• 72 premature infants with trans-pyloric feeding tubes had fewer A/B events
Malacia

GER in Airway Malacia

- 116 children aged 3-28 mo with chronic respiratory symptoms
  - 54 (nearly ½) found to have malacia
  - Improved after anti-reflux therapy
GER and Its Relationship to BPD

- Reflux is common in premature infants but does it contribute to respiratory disease?
  - Does GER contribute to BPD? OR
  - Does BPD contribute to GER?
• Mild: need supp. $O_2 > 28$ days, but not at 36 weeks PMA
• Moderate: need supp. $O_2 > 28$ days and $FiO_2 < 0.30$ at 36 weeks PMA
• Severe: need supp. $O_2 > 28$ days and $FiO_2 > 0.30$ and/or PPV at 36 weeks PMA
Mechanisms BPD Contributes to GER

- Increased respiratory effort with increased intra-abdominal pressure
- Decreased LES tone
- Frequency of gastric feeding tubes
- Respiratory medications
  - Theophylline and caffeine stimulate acid secretion and may relax LES
  - Beta agonists may relax LES
Mechanisms GER Contributes to BPD

- Micro-aspiration of refluxate
- Reduced airway conductance via stimulation of esophageal receptors
GER Not Correlated With CLD

- Retrospective study of 137 premature infants (born <32 wks GA) w/ clinical symptoms of GER (ave corr GA 37 wks)
- No difference in GER in BPD or CLD versus those without BPD or CLD

<table>
<thead>
<tr>
<th>Table 3</th>
<th>GER and BPD at 28 d</th>
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</thead>
<tbody>
<tr>
<td>Status</td>
<td>GER</td>
</tr>
<tr>
<td>BPD (n = 102)</td>
<td>64 (63%)</td>
</tr>
<tr>
<td>No BPD (n = 35)</td>
<td>23 (65%)</td>
</tr>
</tbody>
</table>

Data shown as frequency (%); chi-square p = 0.99.
GER, gastroesophageal reflux; BPD, bronchopulmonary dysplasia.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>GER and CLD at 36 wk Postmenstrual Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status</td>
<td>GER</td>
</tr>
<tr>
<td>CLD (n = 76)</td>
<td>46 (60%)</td>
</tr>
<tr>
<td>No CLD (n = 60)</td>
<td>41 (68%)</td>
</tr>
</tbody>
</table>

Data shown as frequency (%); chi square p = 0.38.
GER, gastroesophageal reflux; CLD, chronic lung disease.
Reflux to Proximal Esophagus

- Measure GER by pH probe T1-T2 in 14 infants with BPD, 13 infants without BPD
- Infants with BPD had less GER: less time pH <4, fewer episodes per hour, fewer prolonged episodes
- Did not account for non-acid GER or how occasional episodes may aggravate lung disease
Height of Refluxate Determines Symptoms in BPD

• 9 infants with CLD evaluated by manometry, pH-MII and symptom diary

Table 3. Symptom Sensitivity Index (SSI) Based on the Proximal Extent of AREs

<table>
<thead>
<tr>
<th>Extent of Refluxate (# AREs)</th>
<th>Composite SSI</th>
<th>Respiratory</th>
<th>Sensory</th>
<th>Movements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharynx (N = 30)</td>
<td>77% (23/30)</td>
<td>47% (14/30)</td>
<td>47% (14/30)</td>
<td>7% (2/30)</td>
</tr>
<tr>
<td>Proximal esophagus (N = 36)</td>
<td>50% (18/36)</td>
<td>22% (8/36)</td>
<td>22% (14/36)</td>
<td>19% (7/36)</td>
</tr>
<tr>
<td>Middle esophagus (N = 36)</td>
<td>50% (18/36)</td>
<td>28% (10/36)</td>
<td>28% (10/36)</td>
<td>31% (11/36)</td>
</tr>
<tr>
<td>Distal esophagus (N = 409)</td>
<td>27% (109/409)</td>
<td>11% (44/409)</td>
<td>17% (68/409)</td>
<td>12% (48/409)</td>
</tr>
</tbody>
</table>

SSI value >10% was considered to be abnormal (8).

• Frequency and character of symptoms depend on most proximal extent of refluxate.
• 46 preterm infants
  – 12 with BPD and 34 without.
  – Increased pH only events
  – 25% of symptoms a/w GER

<table>
<thead>
<tr>
<th>Table III. Effect of BPD, caffeine treatment, and orogastric tube feeding on GER events: results of the quantile regression analysis</th>
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<tbody>
<tr>
<td><strong>Coefficient</strong></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Total number of reflux events</td>
</tr>
<tr>
<td>BPD (yes vs no)</td>
</tr>
<tr>
<td>Caffeine (yes vs no)</td>
</tr>
<tr>
<td>Orogastic tube feeding (yes vs no)</td>
</tr>
<tr>
<td>Total acid reflux events</td>
</tr>
<tr>
<td>BPD (yes vs no)</td>
</tr>
<tr>
<td>Caffeine (yes vs no)</td>
</tr>
<tr>
<td>Orogastic tube feeding (yes vs no)</td>
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<tr>
<td>Total weakly acid reflux events</td>
</tr>
<tr>
<td>BPD (yes vs no)</td>
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<tr>
<td>Caffeine (yes vs no)</td>
</tr>
<tr>
<td>Orogastic tube feeding (yes vs no)</td>
</tr>
<tr>
<td>Total gas reflux events</td>
</tr>
<tr>
<td>BPD (yes vs no)</td>
</tr>
<tr>
<td>Caffeine (yes vs no)</td>
</tr>
<tr>
<td>Orogastic tube feeding (yes vs no)</td>
</tr>
<tr>
<td>Total pH-only events</td>
</tr>
<tr>
<td>BPD (yes vs no)</td>
</tr>
<tr>
<td>Caffeine (yes vs no)</td>
</tr>
<tr>
<td>Orogastic tube feeding (yes vs no)</td>
</tr>
</tbody>
</table>
Anti-reflux Surgery in Symptomatic Infants

• 51 patients <2 years old with pulmonary symptoms of GER
  – Recurrent aspiration: 91% resolved
  – Unexplained apnea: 88% marked benefit
  – BPD: 83% clinical improvement

• 9 premature infants with severe BPD (ventilator dependent) and GERD
  – 7/9 extubated within 1.5 weeks
  – Rapid decrease in O2 requirement with resolution of aspiration episodes

• 50 preterm infants with severe BPD: 22 w/ anti-GER surgery
  – This cohort was sicker—more PAH, airway malacia, tracheostomy, most fed NJ
  – Severity didn’t rapidly improve, there was modest reduction in RR and FiO2
    Jensen et al. Ped Pulm. 2015.
Aspiration
Why is it important?
Complications of Acute Aspiration

- Depends on what is aspirated and how much.
- Acute airway occlusion from large volume
- Reflex laryngospasm and apnea → vagally mediated by stimulation of supraglottic or tracheal mucosa
- Peanut aspiration → severe mucosal and parenchymal inflammation, rapidly evolving pneumonitis
- Vegetable or non-organic aspiration → residual chronic airway obstruction, atelectasis, recurrent pneumonia, bronchiectasis
- Chemical pneumonitis → diffuse alveolar damage or ARDS
- Aspiration pneumonia → delayed consequence of aspiration pneumonitis; bacterial
Complications of Chronic Aspiration

- Evolves into chronic interstitial inflammation ➔ interstitial thickening and even fibrosis
- Chronic bronchitis
- Bronchiectasis
Detection of Secondary Aspiration in NICU
Valat et al. Nucl Med Commun. 1986

- 31 mechanically ventilated neonates gavaged 99Tcm-sulphur colloid solution and tracheal aspirates measured for radioactivity.
- 42% +radioactivity
Airway Pepsin and BPD

• Pepsin was measured in serial tracheal aspirates (TA) of 59 mechanically ventilated preterm neonates (<28 days old).

• Pepsin in 91% of TA
Dysphagia and Primary Aspiration

- During oral feeding, minute ventilation decreases which may impair oxygenation/ventilation.
- Preterm infants tend to swallow during apnea or inhalation, increasing risk of aspiration.
- Many preterm infants have neurodevelopmental issues further increasing risk of aspiration.
Swallow Mechanism

• 3 phases
  – Oral: chewing, forming bolus and propelling bolus to the pharynx
  – Pharyngeal: transfer bolus past larynx into esophagus
  – Esophageal: transport bolus into stomach

• By 12 wks gestation, fetus sucks and swallows but it is not until 34wks gestation that sufficient coordination develops.
Oral Phase

- Saliva to moisten food and being enzymatic digestion
- Bolus extraction
- Mastication
- Bolus moved posteriorly
- Involves coordination of several structures
  - Lips
  - Teeth
  - Salivary glands (parasympathetic control)
  - Tongue
  - Jaw Muscles
- Voluntary neuromuscular control
Pharyngeal Phase

- Triggered when bolus reaches tonsils
- Other activities stop (chewing, breathing, coughing, vomiting)
- Automatic without conscious control
- Lasts approximately one second
- Several things have to happen:
  - Palate closes to prevent reflux into nose
  - Vocal cords close/adduct to prevent aspiration into trachea
  - Throat muscles coordinately constrict
  - Larynx pulls up and forward so epiglottis covers cords
  - Upper esophageal sphincter relaxes so bolus enters esophagus
- Easily fatigued
Laryngeal function: Airway Protection

The glottis: open for inspiration and closed for swallowing

Open

Closed
Effect of PDA Ligation

- 20-40% of premature infants will develop left vocal cord paralysis (LVCP) after patent ductus arteriosus ligation

<table>
<thead>
<tr>
<th></th>
<th>With LVCP</th>
<th>Without LVCP</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPD</td>
<td>82%</td>
<td>39%</td>
<td>0.002</td>
</tr>
<tr>
<td>Reactive airway disease</td>
<td>86%</td>
<td>33%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Feeding difficulties</td>
<td>63%</td>
<td>6%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Esophageal Phase

- Bolus is actively transported down to the stomach via peristalsis at a rate of 3-5 cm/sec.
- Involuntary neuromuscular control
OroPharyngeal Dysphagia (OPD)

- Problems in any phase can cause dysphagia (difficulty swallowing) and/or aspiration.
- Need perfect timing, adequate sensation, coordination.
Developmental Changes

- In infancy, larynx is high in the airway and glottal apparatus is immature. This makes infant prone to penetration of liquids and food.
- Recall that sufficient coordination for suck, swallow and breathe does not occur before 34 wks gestation so premature infants are at risk, particularly if they have continued lung disease.
- Mechanism is highly complex and easily fatigued especially with intercurrent illnesses, ie RSV.
- Infants not fed orally for prolonged periods have difficulty coordinating breathing and swallowing.
- Healthy, neurologically and anatomically normal infants generally outgrow by 15-24mo.
Evaluating Swallow

- Modified barium swallow (MBS/oropharyngeal motility study (OPMS)/videofluoroscopic swallowing study (VFSS))
- Different consistencies of liquid and food mixed with barium are fed under fluoro.
Aspiration prior to swallowing

Contrast enters pharynx
Contrast enters hypopharynx
Contrast enters larynx
Larynx elevates at start of swallow
Contrast down esophagus; larynx closes but contrast is already in trachea
Full closure of larynx
Summary

- Complex aerodigestive mechanisms involved in protecting airway and lungs.
- Infrequent association between GER and apnea of prematurity. GER may have role in persistent CR events in term corrected premature infants.
- GER complicates the management of BPD/CLD however it remains controversial if it plays a significant role in the pathogenesis of lung disease.
- Aspiration can cause significant lung injury.
  - Aspiration of stomach contents is common in mechanically ventilated preterm neonates and may contribute to the development of BPD.
  - Preterm infants have dysphagia and are at risk for aspiration.
THANK YOU!

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