Learning Objectives

- To determine the prevalence and economic burden of gastroesophageal reflux (GER) in infancy
- To appropriately utilize diagnostic testing in the evaluation of infants with complicated GER
- To understand the safety and outcome of current therapeutic approaches in the management of infants with clinical GER

GER is the passage of gastric contents into the esophagus and is a physiologic process

Variability in GERD Diagnosis Rates across the USA

- Rates of GERD diagnosis in preterm infants varied dramatically across NICUs from 2.4% to 29.9%¹

Prevalence of Neonatal Anti-reflux strategies

- Clinical significance of GERD also evident from the 7-fold increase in use of acid suppressive medications
- ~48% (range, 10% to 90%) of premature neonates are being discharged on acid suppressive medications
- ~45% of anti-reflux procedures are performed in infants

¹ Hospital Pediatrics 2013

Malcolm et al. 2008 Pediatrics
Clark et al. 2006 Pediatrics
GERD and Burden

• GERD diagnosis is associated with:
  
  • $70,489 additional costs per discharge and
  • 29.9 additional days in LOS

Lighter birth weights, age >7 days, Aged 28 to 33 weeks at birth, Non-Hispanic patients

How does it happen?

In infants with GERD, the number of TLESRs overall was similar to healthy controls...

• but the proportion of TLESRs accompanied by acid GER was significantly higher

Healthy infants vs infants with GERD

- TLESRs’ occurrence is not affected by postmenstrual age
- Weak correlation between postnatal age and the rate of TLESRs, with older infants having fewer TLESRs ($r=0.32, p<0.05$)

Mechanisms of reflux in neonates with GERD

- In infants with GERD, the number of TLESRs overall was similar to healthy controls...
- but the proportion of TLESRs accompanied by acid GER was significantly higher

In GERD patients, TLESRs, GER, distension of proximal stomach, and gastric emptying are increased in RLP compared to LLP. This effect is not seen in HC.

Infants with GERD have a significantly higher number and proportion of TLESRs associated with acid GOR ($p<0.0001$)
The occurrence of TLESRs in relation to feeds

- Feeding changed the pattern of occurrence of TLESRs and acid/non-acid GOR during the period 2–4 hours postprandially.
- No difference between EBM vs formula fed

Omar et al, Gut 2002;51:475–479

Do infants have higher gastric acid production?

<table>
<thead>
<tr>
<th>Mean age</th>
<th>Volume (mL/h)</th>
<th>Mean titratable acid (mEq/h)</th>
<th>Mean acid output (mEq/kg/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 d</td>
<td>3.3</td>
<td>8.1</td>
<td>0.01</td>
</tr>
<tr>
<td>4 wk</td>
<td>3.1</td>
<td>26.4</td>
<td>0.02</td>
</tr>
<tr>
<td>12 wk</td>
<td>13.4</td>
<td>34.8</td>
<td>0.10</td>
</tr>
<tr>
<td>16 wk</td>
<td>44.0</td>
<td>41.6</td>
<td>0.17</td>
</tr>
<tr>
<td>24 wk</td>
<td>64.0</td>
<td>49.2</td>
<td>0.24</td>
</tr>
<tr>
<td>&gt;4-9 yr</td>
<td>42.5</td>
<td>114.2</td>
<td>0.24</td>
</tr>
<tr>
<td>&gt;1 yr to adults</td>
<td>143.2</td>
<td>91.2</td>
<td>0.10</td>
</tr>
</tbody>
</table>


How is GER received?

GER
- The retrograde movement of stomach contents into the esophagus
- Refluxate can be stomach acid, feeds, bile, gastric or pancreatic juices, or even air
- It can be a normal physiologic process that occurs throughout the day in healthy neonates, infants, children, and adults

GERD
- GERD occurs when GER causes symptoms
- It is a pathological process manifesting as:
  - Poor Oral Feeding
  - Poor weight gain
  - Ascension
  - Irritability/Pain
  - Swallowing Problems
  - Esophagitis
  - Hematemesis
  - ENT problems
  - Airways symptoms (apnea, aspiration, recurrent pneumonia, chronic lung disease (CLD))

Jadcherla SR, Rudolph CD. NeoReviews 2005;6;e87–e98

Esophageal, Supra- and Extra-esophageal reflexes

GER in the NICU is still a controversy!!

Great divide remains
- Red flags
- Apnea??
- Aspiration!!

The use and abuse of anti-reflux medications is still a debate

How and when to evaluate?
How much is GER predictable with questionnaires, pH-metry, endoscopy and histology?

- Poor diagnostic accuracy of a clinical questionnaire (compared to pH monitoring and esophageal biopsy)
  - 100 infants suspected of having GER compared to 100 healthy controls.
- A normal questionnaire score in 26% of those with confirmed GERD.
- The score was abnormal in 81% of infants with a normal biopsy and pH study result.


Appropriate Use of the Upper GI Series to Evaluate for GERD

- Useful to detect anatomic abnormalities
  - Intestinal malrotation (or non-rotation), hiatal hernia, achalasia, stricture or mass
- Not a test to definitively diagnose reflux
- Many false positives and negatives ( < 50% sensitive/specific)

Intestinal malrotation in an 8 year-old with chronic vomiting and heartburn
Achalasia in a 14 year-old girl with chronic vomiting: Previous diagnosis ‘psychogenic vomiting’
Stricture in a 13 year-old post-bezoar removal


The benefits of UGI in evaluating a patient with GERD

Table 2 Abnormal findings on the UGI study other than GER that affected the operative management

<table>
<thead>
<tr>
<th>Finding</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malrotation</td>
<td>22 (3.3)</td>
</tr>
<tr>
<td>Esophageal stricture</td>
<td>4 (0.6)</td>
</tr>
<tr>
<td>Delayed gastric emptying</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Possible duodenal obstruction</td>
<td>1 (0.15)</td>
</tr>
</tbody>
</table>


Ph-metry vs Ph-impedance

- pH Reproducibility 70’s
- The sensitivity of the pH probe is 40% (compared with pH-MII)

Normal values for non-acid reflux

<table>
<thead>
<tr>
<th>Variable</th>
<th>Percentile</th>
<th>Variable</th>
<th>Percentile</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR)</td>
<td>1.8 (0.6–5.55)</td>
<td>Median (IQR)</td>
<td>0.4 (0.1–1.1)</td>
<td>0.7 (0.45–1.2)</td>
</tr>
<tr>
<td>Infants</td>
<td>2.7</td>
<td>Infants</td>
<td>1.74</td>
<td>1.76</td>
</tr>
<tr>
<td>&lt;1yrs</td>
<td>3.4</td>
<td>&lt;1yrs</td>
<td>2.15</td>
<td>2.68</td>
</tr>
<tr>
<td>(birth–11.9 mo)</td>
<td>N/A</td>
<td>(birth–11.9 mo)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>11 (6–19.5)</td>
<td>Median (IQR)</td>
<td>11 (2–23)</td>
<td>12 (16–40)</td>
</tr>
<tr>
<td>Birth (11.9 mo)</td>
<td>N/A</td>
<td>Birth (11.9 mo)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>42.5 (16–62)</td>
<td>Median (IQR)</td>
<td>48.1</td>
<td>67.3</td>
</tr>
<tr>
<td>&lt;1yrs</td>
<td>38.2</td>
<td>&lt;1yrs</td>
<td>44.3</td>
<td>57.6</td>
</tr>
<tr>
<td>(birth–11.9 mo)</td>
<td>45.5</td>
<td>(birth–11.9 mo)</td>
<td>48.1</td>
<td>67.3</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>7.5 (3–15.5)</td>
<td>Median (IQR)</td>
<td>7.5 (2–15.5)</td>
<td>7.5 (2–25.5)</td>
</tr>
<tr>
<td>Proximal NAGER Episodes</td>
<td>22.5 (0.9–</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25.5)</td>
<td>Proximal NAGER Episodes</td>
<td>27.6</td>
<td>48.6</td>
</tr>
<tr>
<td></td>
<td>45.5</td>
<td></td>
<td>48.6</td>
<td>57</td>
</tr>
</tbody>
</table>


- Ability to measure nonacid reflux
- Ability to assess chemical clearance vs bolus clearance
- Ability to evaluate the possible association between GER and other symptoms

Acta Paediatr. 2007;96(7):956-62
Gastroenterology. 2001;120(7):1599-606
MH1  add graph
Mousa, Hayat, 10/21/2014
Physio-chemical composition of GER defined as supra-UES and infra-UES

A

B

Intra-UES

Supra-UES

Intra-UES

Supra-UES

Mixed

Liquid

Gas

AGER

NAGER


Relationship of symptoms / reflux with esophageal acid contact and bolus clearance

A

B

pH only are more likely to be associated with symptoms


Sleep interruptions and disordered breathing


Symptoms distribution (no apneas)

- Respiratory symptoms (cough, bradycardia, desaturation, grunting, gagging) increased with more proximal extent of acid
- Sensory (irritability, arching, pain) symptoms were similar
- Movement symptoms were greater with esophageal exposure

Jadcherla SR et al, Am J Gastroenterol 2008

Temporary Linking

80/527 apnea events (15.2%) were temporarily linked with GER
7% AGER
8.2% NAGER

Symptoms association


Children without Chronic lung disease

Children with Chronic lung disease


Basal and Provocative Manometry


Treatment Options

Infant

Surgical treatment

Pharmacological treatment

Non-pharmacologic therapies

1. Positioning
2. Thickening of feedings
3. Changes in formula
4. Modifications in meal frequencies

Thickening formula

Does not decrease GER indices

<table>
<thead>
<tr>
<th></th>
<th>TPF</th>
<th>PF</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total apneas</td>
<td>5 (0–21)</td>
<td>4 (0–27)</td>
<td>0.876</td>
</tr>
<tr>
<td>Central apneas</td>
<td>1.5 (0–12)</td>
<td>1 (0–21)</td>
<td>0.488</td>
</tr>
<tr>
<td>Obstructive apneas</td>
<td>0.5 (0–6)</td>
<td>0 (0–9)</td>
<td>0.096</td>
</tr>
<tr>
<td>Mixed apneas</td>
<td>1 (0–12)</td>
<td>2 (0–12)</td>
<td>0.638</td>
</tr>
<tr>
<td>Pathological apneas</td>
<td>1.5 (0–10)</td>
<td>1 (0–5)</td>
<td>0.419</td>
</tr>
</tbody>
</table>

- some benefit to parents may result in
  - reducing the number of visible vomiting episodes,
  - possibly failure to thrive

Frequent feedings

- BCT and ACT during each hour of the 3-hour feeding cycle

<table>
<thead>
<tr>
<th>Periods of Hours</th>
<th>BCT, s</th>
<th>ACT, s</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26.2±30.0 (18.7, 34.3)</td>
<td>31.4±7.0 (0.7, 4.4)</td>
<td>0.9</td>
</tr>
<tr>
<td>2</td>
<td>13.3±33.0 (4.0, 21.7)</td>
<td>41.9±60.0 (0.0, 271.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>3</td>
<td>13.3±41.0 (0.0, 310)</td>
<td>39.4±70.9 (2432.4, 463.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Caloric density and feeding volume did not change reflux burden in preterm infants
- Faster flow rates and shorter durations resulted in a higher reflux burden.

Hypoallergenic formula

- Symptoms of milk protein intolerance are similar to reflux symptoms, including fussiness, regurgitation, arching, and colic
- A 2-week trial of a hypoallergenic formula has been suggested to treat symptoms of GER (NASPGHAN guidelines)

Outcome of conservative therapy in 50 infants

- 78% of the study population improved
- 25% completely resolved to normal
- Individual symptoms of regurgitation, crying, and arching improved significantly

Pharmacotherapy

- RI for pH < 4 decreased (p = .0017)
- RI for pH = (4.0–6.9) increased (p = .0022)
- The number of acidic reflux episodes > 5 minutes in duration decreased (p = .0009)

no significant differences between treatment groups in the number of gastrointestinal and cardiorespiratory events temporally associated with acidic reflux
no significant differences between treatment groups in the number of gastrointestinal and cardiorespiratory events temporally associated with acidic reflux

Orenstein et al; J Pediatr 2009; 154:514-20

- Randomized, doubleblind, placebo-controlled study
- 162 infants with symptomatic GERD
- No differences between lansoprazole and placebo
- In percentage of feedings with crying episodes or duration of crying episodes averaged across feedings
1. The ideal dosage?
2. The effect on children older than 32 weeks’ gestation?
3. The effect on acid and nonacid reflux?

**Transpyloric feedings may safely reduce episodes of apnea and bradycardia in preterm infants with suspected gastroesophageal reflux.**

![Graph showing the effects of transpyloric feedings on apnea and bradycardia](image)

**Fundoplication**

- N=1142
- Reduction in reflux related hospitalizations when the surgery was performed in younger compared with older children.

![Graph showing timing of fundoplication and hospitalizations](image)

**Conclusion (1)**

- GER is commonly diagnosed in the NICU, and in most of the cases, is a self-limited physiologic process
- Maturation of reflux protective mechanisms should be considered in evaluating for GER in the NICU
- Non-pharmacologic measures should be the first line therapy for GER
- A role for acid suppression exists in infants with evidence of esophagitis or with gastrointestinal tract bleeding

**Conclusion (2)**

- Acid suppression therapy increases the burden of non-acid reflux and is associated with increased risk of NEC and infections
- If indicated, acid suppression therapy should be:
  - continued only with clear benefit,
  - monitored closely, and
  - discontinued empirically in consideration of maturational changes

**Conclusion (3)**

- Anti-reflux treatment should thus be individualized carefully in each patient to reduce the widespread use of acid suppression medications unless clear evidence of pathologic GER exists