What's Up With Infant Gastroesophageal Reflux?
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Objectives

- To briefly review the epidemiology and mechanisms of GER and GERD
- To discuss some potential complications of GERD in infants.
- To review management approaches for common symptoms purported to result from GER in infants.

Epidemiology of Infant GER

Mechanisms of GER

**Mechanisms of GER**
- Transient LES relaxation
- ↑ Intra-abdominal pressure
- Reduced esophageal capacitance
- ↓ Gastric compliance
- Delayed gastric emptying

**Mechanisms of Esophageal Complications**
- Impaired esophageal clearance
- Defective tissue resistance
- Noxious composition of refluxate

**Mechanisms of Airway Complications**
- Vagal reflexes
- Impaired airway protection

**Mechanisms of GER**
- LES sphincter
- Specialized smooth muscle
Mechanisms of GER

- LES sphincter
  - Specialized smooth muscle
  - Crural diaphragm

Mechanisms of GER in the infant

- Esophagus short, limited capacity
  - Equivalent to: 3 liters

Hiatus Hernia

- Loss of:
  - Crural Diaphragm
  - Intra-abdominal esophagus

Mechanisms of GER in the infant

- Inadequate gastric accommodation

Prone position and Gravity = Regurgitation

Air-liquid interface

Liquid at LES
“GER is a normal physiologic process causing few or no symptoms.”

“GER Disease (GERD) is present when the reflux of gastric contents causes troublesome symptoms and/or complications.”

When to worry?

Are there symptoms or signs suggestive of a Non-GER Diagnosis?

- Recurrent vomiting or regurgitation

- History and physical exam

- Are there warning signals?

- Bilious or forceful vomiting
- Hematemesis or hematochezia
- Diarrhea
- Abdominal tenderness or distention
- Onset of vomiting after 6 months of life
- Atopic history (eczema, allergic rhinitis)
- Fever, lethargy, hepatosplenomegaly
- Macrocephaly, microcephaly, seizures

Adapted from Rudolph et al., J Pediatr Gastroenterol Nutr 2001;32:S1

Complications of GER

- Growth failure
- Esophageal symptoms
- Pain/Irritability?
- Feeding Refusal?
- Hematemesis
- Anemia
- Apnea or ALTE
- Wheezing/Asthma
- Recurrent pneumonia
- Upper airway symptoms

Diagnosis & Management of Infant GERD

“Based upon expert opinion, a history and physical examination that excludes warning signs is generally adequate to make a diagnosis of uncomplicated GER in infants.”

Management

- In the infant with uncomplicated regurgitation, parental education, reassurance and anticipatory guidance are recommended. (Level C)

- In addition, thickening of formula can be considered. (Level A) (“Long term nutritional safety and allergenicity uncertain”)

- In general no other intervention is necessary. If symptoms worsen or do not resolve by 12 to 18 months of age or “warning signs” develop, referral to a pediatric gastroenterologist is recommended (Level B)

- There is no evidence that anti-secretory or promotility agents improve physiologic infant regurgitation.

- Since regurgitation is sometimes the sole manifestation of cow’s milk protein allergy in healthy looking infants, a two-week trial of protein hydrolysate or amino acid based formula, or a trial of milk-free diet for the breast feeding mother is appropriate.

- Prone positioning is not recommended because of its association with SIDS.
Are there signs of possible GERD?

Complications of GER
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Are there warning signals?

Recurrent vomiting
History and physical exam
Are there signs of possible GERD?
GERD

Are symptoms reliable for diagnosis of GERD in infants?

Classic criteria
- Spitting up
- Crying, Irritability
- Back arching
- Feeding refusal or stopping feeds after starting

GERD Diagnosis
In adults, GERD diagnosis is based upon the patient’s description of “bothersome symptoms” or a “typical reflux syndrome”, characterized by reports of:
- Regurgitation
- Heartburn - substernal, burning chest pain behind the breastbone

Pukey is a 4 mo old male infant that spits up 4 times per day. He cries about 2 hours each day with back arching.

Is Pukey’s irritability due to GERD?

1. Yes
2. No

Is Pukey’s irritability due to GERD?

Total minutes of crying per day in normal infants

<table>
<thead>
<tr>
<th>Age (mo)</th>
<th>1-3</th>
<th>4-6</th>
<th>7-9</th>
<th>10-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crying time (min)</td>
<td>121 +/- 105</td>
<td>59 +/- 67</td>
<td>72 +/- 101</td>
<td>54 +/- 79</td>
</tr>
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</table>


James-Roberts and Hall, J Child Psychol Psychiat 1991;52:951
Causes of Infant Irritability

- CNS abnormality
- Subdural hematoma
- Non-accidental trauma
- Gastrointestinal
- Constipation?
- Cow’s milk protein intolerance?
- Gastroesophageal reflux?
- Torsioned ovary or hernia
- Cardiac disease
- Infection
- Meningitis
- Otitis media
- Urinary tract infection
- Viral illness
- Non-CNS Trauma
- Corneal abrasion
- Foreign body in eye
- Bone fracture
- Hair tourniquet syndrome
- Hunger or neglect

Pukey is a 4 mo old male infant that spits up 4 times per day. He cries about 2 hours each day with back arching.

Is Pukey’s irritability due to GERD? Maybe?

Should we treat with a PPI?

- Yes
- No
- Maybe

Infant irritability and omeprazole therapy

- Double-blind placebo controlled crossover trial
- 64 infants with microscopic esophagitis or + esophageal pH study
- Age: 3-12 months
- In the treatment group Reflux Index decreased from 9.9 to 1.0%
- Cry/fuss time decreased in both groups over 4 wks (267 min/24hr to 188 min/24hrs)
- No difference between Rx and placebo groups

Infant irritability and omeprazole therapy

- Double-blind placebo controlled with PPI Rx for 4 weeks (n=81/group)

- Subjects: Infants 28d to 12mo-
- Dx with GERD based on IGER symptom based questionnaire of typical reflux symptoms:
  - spitting up, crying, fussing, irritability, stopping feeding, feeding refusal, back arching

Orenstein et al Clinical Trial Synopsis P-GI05-109, NCT# 00324974

<table>
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<tr>
<th>Symptom within 1 hour after feeding</th>
<th>Lanzoprazole (n=81)</th>
<th>Placebo (n=81)</th>
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<tr>
<td>Crying, Fussing or Irritable</td>
<td>-19.9% (21.1)</td>
<td>-19.9% (22.8)</td>
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<td>Spitting up/vomiting</td>
<td>-14.1% (24.4)</td>
<td>-11.4% (17.3)</td>
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<td>Stopping Feeding after starting</td>
<td>-6.8% (19.8)</td>
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<td>Arching of back</td>
<td>-19.8% (31.8)</td>
<td>-18.0% (32.1)</td>
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<td>Feeding refusal</td>
<td>-13.8% (33.5)</td>
<td>-10.1% (24.2)</td>
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# Adverse events
- Mostly respiratory
  - 12.3% (p=0.03)

The available evidence does not support empiric acid-suppressive therapy for treatment of infants with irritability.

- If irritability persists with no explanation other than suspected GERD the practitioner may:
  - Continue anticipatory guidance and parent training.
  - Consider a trial of hypoallergenic formula
  - Consider esophageal impedance/pH monitoring to document symptom association with episodes of GER.
  - Consider EGD to r/o Candida or other esophagitis
  - Consider time-limited trial of PPI (2 wks) balancing risks with potential benefits and recognizing that improvement may be due to spontaneous resolution

Potential risks of PPI therapy

- Side effects including headache, diarrhea, constipation, or nausea attributable to PPIs occur in up to 14% of adult
- Increased risk of community acquired pneumonia and acute gastroenteritis in children and adults treated with PPI
- Increased risk of candidemia and NEC in premature infants treated with acid-reducing therapy

The available evidence does not support empiric acid-suppressive therapy for treatment of infants with irritability.

Classic criteria

- Spitting up
- Crying, irritability
- Back arching
- Feeding refusal or stopping feeds after starting
Feeding Refusal & Infant GER?


- 20 infants, age 5-7 mo with >95%tile acid exposure on 24 hour pH monitoring vs 20 controls
- Infants evaluated for feeding issues while on therapy (cisapride and H2 antagonists)
- Infants with GER were more likely to report swallowing problems, vomiting and respiratory symptoms, crying with feeds and more formula changes
- Infants with GER had lower energy intakes than controls despite being on therapy

16/20 judged to have moderate to severe oral motor dysfunction while on therapy

- 80% of control infants but only 16% of GERD infants could hold a spoon with feeding
- Infants with GERD are more likely to have other developmental delays that cause feeding difficulties.

% of patients

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Orenstein et al. Clinical Trial Synopsis P-GI05-109, NCT# 00324974

“GERD by itself is not a common cause of childhood odynophagia or infant feeding difficulties”

- Evaluation of infants & children with feeding difficulties or dysphagia should include
  - History & PE
  - Clinical observation of symptoms/feeding
  - Radiographic contrast study (VFSS and/or esophagram)
  - Endoscopy with biopsy if no other etiology is found.
- Empiric therapy is not recommended except in older children able to report symptoms of typical GERD

Classic criteria

- Spitting up
- Crying, irritability
- Back arching
- Feeding refusal or stopping feeds after starting

Thus, no symptom or cluster of symptoms has been shown to reliably predict complications of reflux or to predict those infants likely to respond to therapy.

Airway Protective Mechanisms

- **ESOPHAGEAL DISTENTION**
  - Large volume
  - Small volume
  - UES contracts

0.15 s
- Vocal reflexes
- Vocal cords close
- Central area occurs
- UES relaxes

0.3 s
- Refluxate enters pharynx

0.6 s
- Swallowing clears pharynx

1.0 s
- Respiration resumes
Laryngeal chemoreflex

Apnea occurs in infants with laryngeal stimulation with H\(_2\)O. This can be central and/or obstructive.

In older infant the same stimulus causes cough

Swallow clears pharynx

Does Non-acidic GER cause apnea?

GER has been associated with episodes of obstructive or mixed apnea episodes that occur while the infant is awake, supine and within one hour of a feeding.

Does GER Cause Apnea in Infants?

Chest Wall Movement

Nasal Air Flow

Esophageal pH

GER has been associated with episodes of obstructive or mixed apnea episodes that occur while the infant is awake, supine and within one hour of a feeding.

Does GER cause apnea?

Acid GER Non-Acid GER

Apnea

No statistically significant correlations between apnea and the frequency or duration of GER

Regression analyses showed a significant association between apnea and GER in 4 of 25 subjects.

Apnea & GER in the NICU

- 29-37 wks infants with at least 2 episodes of apnea (>20 seconds), bradycardia (<100 beats per minute), and/or hypoxemia (oxygen saturation < 80%) over a 2-hour period
- 524 GER episodes; 2039 apneas; 188 desats; 44 bradycardias
- No difference in the frequency of apnea episodes during GER epochs vs non-GER epochs
- No clear relationship between apnea and GER could be established.


ALTE's can also be caused by:
- Cardiac disorders- arrythmia, aberrant cardiac vessel
- CNS disease- seizure, tumor, bleed
- Infectious disorders- meningitis, sepsis
- Airway obstruction- Foreign body, Aberrant innominate artery, Laryngo-tracheomalacia
- Intentional suffocation

The available evidence suggests that in the vast majority of infants, GER is not related to pathologic apnea or to ALTE, although a clear temporal relationship based on history, observation or testing occurs in individual infants.

- Impedance-pH recording in combination with polysomnographic recording is recommended to demonstrate a relationship of GER and apnea.
- There is no data to demonstrate that pharmacological treatment is effective for GER-related apnea
  - Non-acid and acid GER are associated with apneic episodes so volume is likely the critical issue.
- Since apnea generally resolves spontaneously as the infant matures, surgical therapy is not recommended.

The best approach to diagnosis and management is not always certain but current practice patterns need reassessment.

Conclusions

- GER is common in infants
- Differentiating GER from GERD is challenging and cannot be based upon "typical" symptoms
- GERD is relatively uncommon and is likely overdiagnosed and overtreated based upon symptoms (irritability, feeding difficulties, apnea) not shown to respond to GERD therapy
- PPI therapy has potential risks altering the risk/benefit ratio of empiric treatment

The best approach to diagnosis and management is not always certain but current practice patterns need reassessment.