Diagnosis & Management of Gastroesophageal Reflux Disease in Pediatric Patients
Learning Objectives

- To understand the physiology and natural history related to GERD in pediatric patients and which patients are at increased risk for GERD
- To review the signs and symptoms related to GERD in pediatric patients
- To describe the variety of diagnostic approaches to GERD in children and what diagnostic test is/are optimal
- To explain the various treatment approaches, including medical and surgical, related pediatric patients with GERD
- To characterize the possible relationships between GERD and various extraesophageal diseases including the etiology, diagnosis and management aspects
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Disclosure Slide

• Support for the Grand Rounds Series was provided by AstraZeneca and Takeda North America Pharmaceuticals, Inc.
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• Drs. Gold, Rosen and Czinn have nothing to disclose.
• Speaker Disclosure to be added here
Program Components

• Physiology and Natural History
• Diagnosis
• Management
  – Management – Pharmacological Therapies
  – Management – Surgical Therapy
• Extraesophageal
  – Recurrent Pneumonia
  – Apnea/ALTE
  – Asthma
  – Laryngeal
• Management Algorithms
• Summary
PHYSIOLOGY & NATURAL HISTORY
The Antireflux Barrier

- The lower esophageal sphincter
- The crural diaphragm
- The phrenoesophageal ligament

Pathogenic Factors in GERD

Primary Mechanisms of GERD
- Transient LES relaxation
- Impaired esophageal clearance

Secondary Mechanisms of GERD
- Intra-abdominal pressure
- Decreased gastric compliance
- Delayed gastric emptying
- Reduced esophageal capacitance

Mechanisms of Esophageal Complications
- Defective tissue resistance
- Noxious composition of refluxate

Mechanisms of Airway Complications (Extra Esophageal Manifestations)
- Vagal reflexes
- Impaired airway protection
Airway Protective Mechanisms

- **ESOPHAGEAL DISTENTION**
  - Small volume: UES contracts
  - Large volume: Vagal reflexes
    - Vocal cords close
    - Central apnea occurs
    - UES relaxes

- Refluxate enters pharynx
  - 0.15 s
  - 0.3 s
  - 0.6 s
  - 1.0 s

- Swallowing clears pharynx

- Respiration resumes

Natural History of GER in Children Up to Two Years of Age

41% of infants age 3 to 4 months spit up most of their feedings

< 5% of infants age 13 to 14 months spit up most of their feedings

Prevalence of Regurgitation in Infancy

GERD Symptom Prevalence in Pre-Teens who had Reflux in the First Year of Life

RR, 2.3  
(95% CI, 1.3–4.0)

At Least 1 Symptom

RR, 2.7  
(95% CI, 1.4–5.5)

Vomiting

RR, 4.6  
(95% CI, 1.5–13.8)

Heartburn

RR, 4.7  
(95% CI, 1.6–14.0)

Acid Regurgitation

RR, relative risk; CI, confidence interval.

Estimated Incidence Rates of GERD in Children and Adolescents from 2000-2005

Adults With GERD have Childhood Reflux-Related Symptoms

- Spit-Up as Infant
- Abdominal Pain
- Heartburn/Chest Pain
- Dysphagia
- Underweight
- Asthma

* p<0.05
+ p<0.001

Premature and Small for Gestational Age (SGA) Infants May Be at Increased Risk of Adult Esophageal Cancer

Standardized incidence ratios for esophageal adenocarcinoma (95% CI)

- Preterm Infants: 6.55 (1.35–19.1)
- SGA Infants: 11.5
- Preterm and SGA Infants: 7.27 (1.98–18.6)

Relationship Between Presenting Symptoms, Esophagitis Severity, and Patient Age

- Significant differences among ages 1–5 years compared with ages 6–17 years with erosive GERD were found to include:
  - Greater severity in cough
  - Lesser severity in heartburn
  - Greater prevalence and severity in anorexia/feed refusal
  - Greater severity in regurgitation/vomiting

Esophageal Manifestations of GERD: Global Consensus Definitions

Esophageal

Symptoms purported to be due to GERD*
- Infant or younger child (0–8 years), or older without cognitive ability to reliably report symptoms
  - Excessive regurgitation
  - Feeding refusal/anorexia
  - Unexplained crying
  - Choking/gagging/coughing
  - Sleep disturbance
  - Abdominal pain

Symptomatic syndromes
- Older child or adolescent with cognitive ability to reliably report symptoms
  - Typical reflux syndrome

Syndromes with esophageal injury
- Reflux esophagitis
- Reflux stricture
- Barrett’s esophagus
- Adenocarcinoma

* Where other causes have been ruled out (e.g. food allergy, especially in infants)

Extraesophageal Associations of GERD: Global Consensus Definitions

- Extraesophageal

  - Definite associations
    - Sandifer’s syndrome
    - Dental erosion

  - Possible associations
    - Bronchopulmonary
      - Asthma
      - Pulmonary fibrosis
      - Bronchopulmonary dysplasia
    - Laryngotracheal and pharyngeal
      - Chronic cough
      - Chronic laryngitis
      - Hoarseness
      - Pharyngitis
    - Rhinological and otological
      - Sinusitis
      - Serous otitis media
  - Infants
    - Pathological apnea
    - Bradycardia
    - Apparent life-threatening events

Correlation of Symptoms and Injury

In infants, frequency and severity of symptoms are not reliable to predict the presence or severity of esophagitis.

GERD-Related Complications

- Erosive esophagitis
- Stricture
- Barrett’s esophagus
- Adenocarcinoma
Barrett’s Esophagus - Etiology

- BE results from a metaplastic change in where squamous epithelium is replaced by columnar epithelium
- The exact mechanisms underlying these changes remain an area of controversy
- Esophageal mucosal injury from acid or bile reflux is thought to be critical to the development of BE
- It is not known whether BE is a hereditary condition. Some studies suggest that the condition is more prevalent in first-degree relatives of patients with BE


Who is at Risk for Severe GERD?

- Cystic fibrosis
- Esophageal atresia
- Neurologic impairment
- Hiatal Hernia
- Obesity
- Family history of GERD; GERD related complications
Mechanism for GERD in Patients with Esophageal Atresia

- Narrowing at anastomosis or distal peptic strictures preventing reflux clearance
- Dysmotility of distal esophagus
  - Delayed acid clearance
  - Delayed food clearance
- Hiatal hernia created during repair
Clinical Symptoms vs. Endoscopic Findings in Children with Esophageal Atresia

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Endoscopic results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal (n=26)</td>
</tr>
<tr>
<td>Regurgitation/clinical GER [n (%)]</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Heartburn [n (%)]</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Dysphagia [n (%)]</td>
<td>10 (38)</td>
</tr>
<tr>
<td>Odynophagia [n (%)]</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Food Impaction [n (%)]</td>
<td>10 (38)</td>
</tr>
<tr>
<td>Cough at meals [n (%)]</td>
<td>6 (23)</td>
</tr>
<tr>
<td>Asymptomatic [n (%)]</td>
<td>11 (42)</td>
</tr>
</tbody>
</table>

- No significant difference for any symptom comparison
- Symptomology is NOT predictive of abnormal endoscopy in esophageal atresia patients.
- Endoscopy should be considered regardless of symptomatology

Esophageal Atresia

- Predisposed to reflux because
  - abnormal motility distal to repair prevents adequate acid clearance
  - hiatal hernia created during the repair changing the position of the LES and diaphragm
- Difficult to determine the extent to which reflux, or retained food in esophagus, is causing symptoms
- Long term risk for esophageal cancer unknown

GERD and Genetics

• Increased familial concordance
  - GERD symptoms
  - Hiatal hernia
  - Erosive esophagitis
  - Barrett’s esophagus
  - Esophageal adenocarcinoma

• Putative GERD-related genes...are there any?
  - 13q14 locus excluded for infantile esophagitis phenotype
  - Chromosome 9 locus preliminarily proposed for infantile esophagitis
  - Transient receptor potential channel vanilloid subfamily member-1 (TRPV1) contributes to symptoms in NERD and erosive esophagitis

Reflux Esophagitis is Not More Prevalent in Obese Children

- In a retrospective chart review of 230 children who underwent EGD with biopsies
  - 29.1% had BMI percentiles above the 85th percentile for age and gender
  - Prevalence of reflux esophagitis in the overweight group did not differ significantly from that in the normal weight group

Patel et al. J Obes. 2010; Published on-line May 5.
Moderately to Severely Obese Children are More Likely to have GERD

- Population-based, cross sectional review of 690,321 patients 2–19 years of age
- A diagnosis of GERD was found in 1.5% of boys and 1.8% of girls

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Odds Ratio (95% CI) for those moderately obese</th>
<th>Odds Ratio (95% CI) for those severely obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-11</td>
<td>1.16 (1.02-1.32)</td>
<td>1.32 (1.13-1.56)</td>
</tr>
<tr>
<td>12-19</td>
<td>1.16 (1.07-1.25)</td>
<td>1.40 (1.28-1.52)</td>
</tr>
</tbody>
</table>

- Obesity was not related to GERD in children 2-5 years of age
- There is an increased risk of GERD in moderately to severely obese children 6-19 years of age

Testing For *Helicobacter pylori* Is Not Recommended In Patients With GERD

- The primary goal for clinical investigation of gastrointestinal symptoms is to determine the underlying cause of the symptoms and not solely the presence of *H. pylori* infection.
- Abdominal pain consistent with diagnostic criteria of functional disease should not be investigated (i.e. diagnostic testing) for *H. pylori*, unless:
  - upper endoscopy is performed during the diagnostic work up in search for organic disease.
- Recurrent abdominal pain is not an indication to test for *H. pylori* infection.
- *H. pylori* testing is not required in patients with newly diagnosed gastroesophageal reflux disease.
  - *H. pylori* testing may be considered before long-term PPI therapy.

Jones et al. *Can J Gastroenterol.* 2005:19 (7);399-408.
DIAGNOSIS

- Differential Diagnosis
- Symptoms And Signs Associated With GERD
- Testing
# Differential Diagnosis of Vomiting in Infants & Children

<table>
<thead>
<tr>
<th>Metabolic / Endocrine</th>
<th>Toxic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Allergic</td>
</tr>
<tr>
<td>Gastrointestinal Obstruction</td>
<td>Gastrointestinal disorders</td>
</tr>
<tr>
<td>Infectious</td>
<td>Others</td>
</tr>
</tbody>
</table>

GERD Masqueraders

Pyloric Stenosis

Malrotation

Achalasia

Warning Signs Suggestive of a Non-GERD Diagnosis

Approach to the Infant with Recurrent Regurgitation and Vomiting

- History and physical exam
  - Are there warning signals

<table>
<thead>
<tr>
<th>Bilious vomiting</th>
<th>Nocturnal vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistently forceful vomiting</td>
<td>Onset of vomiting after 6 months of life</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>Vomiting undigested food</td>
</tr>
<tr>
<td>Gastrointestinal bleeding: hematemesis or hematochezia</td>
<td>Documented or suspected genetic/metabolic syndrome</td>
</tr>
<tr>
<td>Bulging fontanelle</td>
<td>Macro/microcephaly</td>
</tr>
<tr>
<td>Fever</td>
<td>Failure to thrive</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Constipation</td>
</tr>
</tbody>
</table>
## Symptoms & Signs that May Be Associated with GERD

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent regurgitation with/without vomiting</td>
<td>Esophagitis</td>
</tr>
<tr>
<td>Weight loss or poor weight gain</td>
<td>Esophageal stricture</td>
</tr>
<tr>
<td>Irritability in infants</td>
<td>Barrett’s esophagus</td>
</tr>
<tr>
<td>Ruminative behaviour</td>
<td>Laryngeal/pharyngeal inflammation</td>
</tr>
<tr>
<td>Heartburn or chest pain</td>
<td>Recurrent pneumonia</td>
</tr>
<tr>
<td>Hematemesis</td>
<td>Anemia</td>
</tr>
<tr>
<td>Dysphagia, odynophagia</td>
<td>Dental erosion</td>
</tr>
<tr>
<td>Wheezing</td>
<td>Feeding refusal</td>
</tr>
<tr>
<td>Stridor</td>
<td>Dystonic neck posturing (Sandifers Syndrome)</td>
</tr>
<tr>
<td>Cough</td>
<td>Apnea spells</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>Apparent life-threatening events</td>
</tr>
</tbody>
</table>

## History in a Child with Suspected GERD

<table>
<thead>
<tr>
<th>Feeding &amp; Dietary History</th>
<th>Pattern of Vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount and frequency (overfeeding)</td>
<td>Frequency and amount</td>
</tr>
<tr>
<td>Preparation of formula</td>
<td>Pain</td>
</tr>
<tr>
<td>Recent changes in feeding type or technique</td>
<td>Forceful</td>
</tr>
<tr>
<td>Positioning during feeding</td>
<td>Blood or bile</td>
</tr>
<tr>
<td>Burping</td>
<td>Associated fever, lethargy, diarrhea</td>
</tr>
<tr>
<td>Behavior during feeding (choking, gagging, cough, arching, discomfort, refusal)</td>
<td>Digested vs. undigested food</td>
</tr>
<tr>
<td>Food impactions</td>
<td>Sleep history, nocturnal symptoms</td>
</tr>
<tr>
<td>Intolerance to types of formulas or food</td>
<td></td>
</tr>
</tbody>
</table>
## Review of Systems and Past History

<table>
<thead>
<tr>
<th>Medical History</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity</td>
<td>Eczema, diarrhea</td>
</tr>
<tr>
<td>Growth and development</td>
<td>Dental erosions</td>
</tr>
<tr>
<td>Past surgery, hospitalizations</td>
<td>Previous weight gain</td>
</tr>
<tr>
<td>Newborn screen results</td>
<td>Symptoms of hoarseness, fussiness, hiccups</td>
</tr>
<tr>
<td>Recurrent illnesses, especially croup, pneumonia, asthma, otitis media, sinusitis</td>
<td>Celiac disease</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>Other chronic condition</td>
</tr>
<tr>
<td>Cough</td>
<td></td>
</tr>
</tbody>
</table>
Other Important Factors in a Child with Suspected GERD

<table>
<thead>
<tr>
<th>Family Medical History</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal Dilations</td>
<td>Current and past</td>
</tr>
<tr>
<td>Esophageal cancer/Barrett’s</td>
<td>Use of OTC antacids, H₂RAs and PPIs</td>
</tr>
<tr>
<td>Food allergies including hypoallergenic formulas</td>
<td>Medications affecting motility (e.g. anticholinergics, opioids, antibiotics, cancer chemotherapy, vincristine)</td>
</tr>
<tr>
<td>Esophageal surgeries</td>
<td></td>
</tr>
<tr>
<td>Thyroid disease</td>
<td></td>
</tr>
<tr>
<td>Celiac disease</td>
<td></td>
</tr>
<tr>
<td>Functional dyspepsia</td>
<td></td>
</tr>
</tbody>
</table>

Signs of Complicated GERD

- Recurrent vomiting
  - History and physical exam
    - Are there warning signals?
      - Are there signs of complicated GERD?
        - Poor weight gain
        - Excessive crying or irritability
        - Anemia; iron deficiency
        - Dysphagia, odynophagia
        - Feeding problems
        - Respiratory problems, including:
          - Wheezing
          - Stridor
          - Recurrent pneumonia
          - Choking
          - Respiratory problems

GERD in Neurologically Impaired Populations

- Increased frequency and severity of GERD among infants and children with neurological impairment
  - muscle coordination problems, dysfunction of the enteric nervous system impacting on gastric emptying, and medications
- Increased incidence and prevalence of GERD in neurologically impaired children is multifactorial
  - increased risk of aspiration pneumonia, unexplained irritability, body posturing and arching, overt or occult bleeding.
- Clinical diagnosis is hampered due to poor communication with patient
- Treatment should always include lifestyle changes tailored to the unique risk factors of the patient
- Long-term PPI is effective for symptom control and maintenance of remissions of esophagitis
- Antireflux surgery may not benefit this patient group due to high morbidity and failure rates

GERD in Neurologically Impaired Children: Signs and Symptoms

- Vomiting
- Unexplained irritability
- Uncoordinated swallow; oral-pharyngeal dysfunction
- Coughing between meals
- Malnutrition
- Arching
- Feeding refusal
- Recurrent pneumonia (primary or secondary)
- Dental erosions
- Upper gastrointestinal bleeding

## Reflux Manifestations in Neurologically Impaired Populations

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Reflux (GER) Manifestation</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain damage (cerebral palsy or tetraplegia)</td>
<td>Moderately severe to severe GER <em>(by 24 hr pH monitoring &amp; manometry)</em></td>
<td>10/32 (32%)</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>Recurrent vomiting Confirmed GER <em>(by barium and/or acid reflux test)</em></td>
<td>20/136 (15%)</td>
</tr>
<tr>
<td>Vomiting patients with neurodevelopmental delay and/or cerebral palsy</td>
<td>Failure to thrive</td>
<td>15/20 (75%)</td>
</tr>
<tr>
<td></td>
<td>Respiratory symptoms</td>
<td>31/50 (62%)</td>
</tr>
<tr>
<td></td>
<td>Oropharyngeal incoordination</td>
<td>23/50 (62%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16/50 (32%)</td>
</tr>
</tbody>
</table>

Rumination is Also Common in Neurologically Impaired Children

- **Definition:**
  - Repetitive regurgitation of gastric contents into the oropharynx

- **Occurs early after meals (post-prandial):**
  - persists for 1 – 2 hours

- **Observed in distinct populations:**
  - Infants
  - Individuals with developmental disabilities, neurological/psychiatric impairment
  - Adolescents and young adults with/without psychiatric disorders (eg, depression)

- **Hallmark:**
  - gastric contents appear in the oropharynx without retching or nausea

Testing for GERD

- Is there a single test for GERD?
- What question does each test answer?
- How reproducible or reliable is the test?
- Does it guide our management?
- Do the results improve outcomes?
## Esophageal pH Monitoring

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detects episodes of acid reflux</td>
<td>Cannot detect non-acidic reflux which is a particular problem in the post-prandial period when most reflux occurs</td>
</tr>
<tr>
<td>Determines temporal association between acid GER and symptoms</td>
<td>Cannot differentiate swallowed contents from refluxed contents</td>
</tr>
<tr>
<td>Assesses adequacy of treatment in unresponsive patients</td>
<td>Insensitive to weakly acid and non-acid reflux events</td>
</tr>
<tr>
<td>Assesses adequacy of H2RA or PPI dosage in unresponsive patients</td>
<td>Severity of pathologic acid reflux does not correlate consistently with symptom severity of demonstrable complications</td>
</tr>
<tr>
<td>Normal values exist for pediatrics</td>
<td>The majority of pH testing involves stopping medication prior to testing which some patients cannot</td>
</tr>
</tbody>
</table>
Physiological Reflux in Children and Adults is Distinctly Different by pH metry in Normal Subjects

<table>
<thead>
<tr>
<th></th>
<th>Infants (N=509)</th>
<th>Children (N=48)</th>
<th>Adults (N=432)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of daily reflux episodes</td>
<td>73</td>
<td>25</td>
<td>45</td>
</tr>
<tr>
<td>No. of reflux episodes ≥ 5 min</td>
<td>9.7</td>
<td>6.8</td>
<td>3.2</td>
</tr>
<tr>
<td>Reflux index (% of time pH &lt; 4)</td>
<td>11.7%</td>
<td>5.4%</td>
<td>6%</td>
</tr>
</tbody>
</table>
Wireless 24 Hour or Prolonged pH Monitoring

- **Miniature pH capsule (size of gelcap) is attached to esophagus**
  - Capsule measures pH in esophagus and transmits information to a pager-sized receiver worn on belt or waistband
  - Test data is uploaded to a computer and analyzed

- **Advantages**
  - More physiologic because it allows for more normal activity
  - Allows for prolonged studies; 48 hrs or more
  - Can be performed in patients that cannot tolerate catheters

- **Disadvantages**
  - Requires heavy sedation or anesthesia; invasive
  - Cannot be performed in very young children
  - Costly
  - Chest pain
  - Potential for bowel obstruction or need for endoscopic removal
  - Different normal values compared to pH probe
  - Requires cessation of acid suppression medications
Measuring Reflux by Multi-Channel Intraluminal Impedance

- Multi-channel Intraluminal
  - Impedance (MII) is a catheter-based method for measuring reflux
- It is a pH-independent method
- Measures change in resistance to electrical current flow between two sensors
- Seven sensors throughout the esophagus
- One distal pH sensor ± one proximal pH sensor
- Three sizes of catheters: infant, pediatric, adult
Advantages and Disadvantages of Multi-Channel Intraluminal Impedance

**Advantages**
- Detects non-acidic GER episodes which is ideal for post prandial reflux
- Differentiates reflux from swallows
- Able to accurately assess full column reflux
- Sensitivity of pH-MII comparable to the pH probe in untreated patients and surpasses pH probe in treated patients.

**Limitations**
- Normal values in pediatric age groups not yet defined
- Analysis of tracings time-consuming
- How the results change management still unclear


Reflux and Transient Lower Esophageal Sphincter Relaxations

Tracings provided by Center for Motility and Functional Gastrointestinal Disorders, Children's Hospital Boston
## Esophageal pH Levels May Determine the Type of Reflux

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid reflux</td>
<td>Refluxed gastric contents with a pH &lt; 4 that can either reduce the pH within the esophagus to &lt; 4 or occur when intraesophageal pH is already &lt; 4</td>
</tr>
<tr>
<td>Weakly acidic reflux</td>
<td>Reflux events that result in an esophageal pH level between 4 and 7</td>
</tr>
<tr>
<td>Weakly alkaline reflux (nonacid)</td>
<td>Reflux episodes during which the lowest esophageal pH level does not drop below 7</td>
</tr>
</tbody>
</table>
Non-Acid Reflux in Children

Non-acid reflux episodes recorded by impedance in 14 investigations involving children

- Sifrim (n = 22) 40
- Rosen (n = 28) 45
- Mousa (n = 25) 49
- Wenzl (n = 22) 69
- Del Buono (n = 20) 89
- Corvaglia (n = 5) 78
- Wenzl (n = 14) 55
- Condino (n = 24) 51
- Condino (n = 34) 53
- Lopez-Alonso (n = 21) 73
- Lopez-Alonso (n = 7) 46
- Del Buono (n = 16) 56
- Mattioli (> 1 yr) (n = 50) 49
- Mattioli (< 1 yr) (n = 50) 53

Percent of nonacid reflux episodes recorded (relative to total number of reflux episodes recorded)

Advantages and Disadvantages of Esophagogastroduodenoscopy (EGD)

**Advantages**
- Enables visualization and biopsy of esophageal epithelium
- Determines presence of esophagitis and/or GERD-related complications
- Discriminates between different types of esophagitis including reflux, infectious and allergic esophagitis

**Disadvantages**
- Need for sedation or anesthesia
- Poor correlation between endoscopic appearance and histopathology
- Relationship between esophagitis and extraesophageal symptoms is not clear
- Cost?

Advantages and Disadvantages of Histology

**Insufficient Data Exist For Recommending Histology As A Tool To Diagnose Or To Exclude GERD In Children**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enables evaluation of microscopic anatomy</td>
<td>Sampling error because of the patchy distribution of inflammatory changes</td>
</tr>
<tr>
<td>To rule out other conditions in the differential diagnosis (eosinophilic esophagitis, Crohn’s Disease, Barrett’s esophagus, infection)</td>
<td>Lack of standardization of biopsy locations, techniques for mounting, orientation and cutting, choice of fixative, and interpretation of morphometric parameters,</td>
</tr>
<tr>
<td></td>
<td>Eosinophilia, elongation of papillae, basal hyperplasia, and dilated intercellular spaces are neither sensitive nor specific for reflux esophagitis</td>
</tr>
</tbody>
</table>

Histologic Features of Esophageal Disease

- Hyperplasia of basal cell layer and elongation of rete pegs are not specific for reflux esophagitis, also found in eosinophilic esophagitis, Crohn’s disease, infections an asymptomatic adults.

- Eosinophils are found in GERD, eosinophilic esophagitis, Crohn’s disease.
Advantages and Disadvantages of Upper Gastrointestinal Radiography

Advantages
- Useful for detecting anatomic abnormalities such as malrotation, strictures, and achalasia

Disadvantages
- Cannot discriminate between physiologic and nonphysiologic GER episodes
Advantages and Disadvantages of Scintigraphy: Gastric Emptying Scans and Milk Scans

**Advantages**
- Detects acidic and non-acidic GER
- Evaluates gastric emptying
- May demonstrate aspiration
- Can assess liquid or solid emptying
- Can assist with esophageal transit

**Limitations**
- Lack of standardized techniques
- Absence of age-specific normative data
- Period of observation limited to early postprandial period
Biomarkers in Bronchoscopy Fluid or Saliva

Lipid Laden Macrophage Index (LLMI)
- Elevated in a variety of pulmonary diseases
- Inconsistent relationship between the amount of gastroesophageal reflux and LLMI
- No relationship between full column reflux by pH-MII and LLMI

Pepsin
- Found in neonates and children with pulmonary disease
- Presence in the lungs correlated with proximal reflux by pH probe
- Specificity > Sensitivity for detected reflux
- Unclear if its presence predicts prognosis

Bile
- Found in children and adults with pulmonary disease
- More sensitive than pepsin
- May predict a worse prognosis in lung transplant patients but of unclear significance in other disease
- Correlates with weakly acidic (pH 4-7) reflux as measured by pH-MII

Aspiration From Swallowing or GER?

Lipid-Laden Macrophages

New Technologies

- To better correlate reflux with symptoms, new tools are being designed:
  - Oropharyngeal probes
  - Breath testing
  - Cough catheters
  - Cough microphone
  - New lung biomarkers

MANAGEMENT

- Positioning and Feeding
- Pharmacologic Therapy
- Testing
Conservative Measures of GERD Management in Children & Adolescents

- A paucity of randomized controlled trials are available in children or adolescents which evaluate efficacy of conservative measures for GERD treatment.

- **Dietary modification**
  - Weight loss in the case of overweight or obese
  - Avoid caffeine, tomato, spicy and citrus containing foods, deep-fried or fatty foods, chocolate
  - No food/meal less than 1 hour prior to sleep
  - Smaller, more frequent meals

- **Positioning changes**
  - Raising the head of the bed
  - Left lateral decubitus sleeping position

- **Avoidance of passive (2nd hand) cigarette/tobacco smoke**

Positioning Therapy for Infants

- Decreased acid reflux in flat prone position vs. flat supine position
- Prone position is acceptable if the infant is observed and awake, particularly in the postprandial period
- Prone position during sleep can only be considered if risk of death from GERD outweighs the risk for SIDS
- Prone position may be beneficial for children older than 1 year of age as the risk for SIDS is negligible
- Side-lying is not recommended as it is an unstable position from which the infant may slip into the prone position

Left Lateral Position May Lead to Reduced Reflux

- Studies of manometry and impedance have shown:
  - the number of transient LES relaxations increases in the right lateral position (RLP)
  - the number of reflux events increase in the RLP

- These effects are reversed when the child is turned to the left lateral position (LLP) which may be beneficial for reflux

- Gastric emptying is faster in the right lateral position but this benefit is not outweighed by the increased TLESRs

Effect of Thickening Milk Formula Feedings with Rice Cereal

- Caloric Density (cal/cc)
- Emesis (episodes/90 min)
- Sleep Time (min asleep/90 min)
- Crying Time (min crying/90 min)

Management

Pharmacological Therapies
Goals of Pharmacotherapy

- Control symptoms
- Promote healing
- Prevent complications
- Improve health-related quality of life
- Avoid adverse effects of treatment
Available Pharmacotherapy

- Antacids
- Histamine-2 receptor antagonists
- Proton pump inhibitors
- Prokinetic agents
- Surface agents
- GABA-B agonists
Inhibition of Acid Secretion in the Gastric Parietal Cell

Adapted from Sanders SW, Clin Therapeutics 18, 2-34. Copyright 1996 by Excerpta Medica Inc.
Effect of H₂RAs on Healing of Esophagitis

N = 32 children with esophagitis treated with cimetidine 30-40 mg/kg/d or placebo for 12 weeks

- Cimetidine: 71% Esophagitis Healing
- Placebo: 20%

Significant symptom improvement with cimetidine, not placebo

N = 26 children with esophagitis treated with nizatidine 10 mg/kg/d or placebo for 8 weeks

- Nizatidine: 69% Esophagitis Healing
- Placebo: 15%

“Vomiting” reduced in both treatment arms; significant improvement in other GERD symptoms only with nizatidine

## Available H$_2$RAs and PPIs

<table>
<thead>
<tr>
<th>H$_2$ Receptor Antagonists</th>
<th>Proton Pump Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>Dexlansoprazole</td>
</tr>
<tr>
<td>Famotidine</td>
<td>Esomeprazole</td>
</tr>
<tr>
<td>Nizatidine</td>
<td>Lansoprazole</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Omeprazole</td>
</tr>
<tr>
<td></td>
<td>Pantoprazole</td>
</tr>
<tr>
<td></td>
<td>Rabeprazole</td>
</tr>
<tr>
<td></td>
<td>Zegerid</td>
</tr>
</tbody>
</table>

For the most current treatment dosage information please consult the respective product information.
Infants, GERD and Proton Pump Inhibitors: Caution in Use and More Research Needed

- Approximately 50% of PPI prescriptions are written by general pediatricians
- Approximately 50% of PPI prescriptions administered by pediatric gastroenterologists and other subspecialists (Otolaryngology, Pulmonology)
- Less than 10% of patients undergo a diagnostic test prior to initiation of therapy
- Approximately 33% of infants and neonates are given PPIs as the first-line prescription

## Knowledge, Attitudes and Practice Styles Survey of Members of the American Academy of Pediatrics

1245 responders (82% primary care; 18% subspecialists)

<table>
<thead>
<tr>
<th>Testing practice</th>
<th>Responders (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat (PPI or H₂RA) before testing</td>
<td>82</td>
</tr>
<tr>
<td>Order diagnostic testing for GERD in routine practice</td>
<td>66</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Start testing in:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>54</td>
</tr>
<tr>
<td>Infants &gt; 1 month of age</td>
<td>38</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Common tests ordered:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Barium esophagram</td>
<td>45</td>
</tr>
<tr>
<td>Esophageal pH monitoring</td>
<td>37</td>
</tr>
</tbody>
</table>

Conservative Therapy for Symptoms Suggestive of GERD in Infants

- Consenting parents of 50 infants who had abnormal infant gastroesophageal reflux (defined by the I-GERQ-R) were taught conservative therapy measures
  - Feeding modifications, positioning, tobacco smoke avoidance
- Resulting I-GERQ-R scores after two weeks:
  - 78% of the study population improved
  - 24% completely resolved to normal
  - Individual symptoms of regurgitation, crying and arching improved significantly
- Two weeks of conservative therapy resulted in successful resolution of GERD-related symptoms in cohort of infants in the primary care setting

Evidence-Based Treatment Recommendations for Children with GER

• In the infant with recurrent regurgitation, a thorough history and physical examination with attention to warning signs is generally sufficient to allow the clinician to establish a diagnosis of uncomplicated GER [Quality of Evidence: C]

• In the infant with uncomplicated regurgitation, parental education, reassurance and anticipatory guidance are recommended [Quality of Evidence: C]

• Thickening of formula can be considered in addition to parental education, reassurance and anticipatory guidance. [Quality of Evidence: A]

• 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 [Quality of Evidence: A]

Treatment: Role of Acid Suppression

• In otherwise normal infants with unexplained crying, irritability, or distressed behavior, there is no evidence to support acid suppression [Quality of Evidence: A]

• If you indeed need to prescribe a PPI to an infant for medical reasons consider using the “smallest, most effective dose”;
  – Once per day vs. twice per day
  – Weaning after the planned course of therapy is completed

Long-term Proton Pump Inhibitor Use: Safe and Well Tolerated

- Retrospective analysis of 113 children (age range: 0.1 – 17.6 years; median age 4.5 years)
- Received at least 1 year of continuous PPI treatment
  - Increase in serum gastrin
    - No significant correlation found with PPI dose, elevation or frequency, or demographic parameters of age or race
  - No significant change in biochemical (i.e. laboratory), histologic, and endoscopic findings from the onset of PPI treatment.
  - Normal B12 levels in patients where data were available
- Conclusion: long-term PPI therapy appears to be safe and well tolerated in children

Proton Pump Inhibitor Use and Risk of Fracture

- Meta analysis, largely using adult data, were performed to identify an association between PPI use and risk of fracture
  - A modest association was found between PPI use and an increased risk of hip and vertebral fractures.
  - Observational studies cannot clarify whether the observed epidemiologic association is a causal effect or a result of unmeasured/residual confounding
- Randomized controlled studies are required to confirm or refute these results
- Skeletal evaluation should be considered for patients who are taking PPIs and also at risk for osteoporotic fracture
- Current NASPGHAN and AGA guidelines do not recommend blood tests or a DEXA scan at this time

Proton Pump Inhibitor Use and Infections

- There are limited pediatric data, particularly population-based;
  - Most conclusions regarding PPI risk in children arise from retrospective adult studies
- Children exposed to PPIs therapy seem to be at higher risk for the development of *Clostridium difficile*-associated disease
- Use of a proton pump inhibitor or histamine(2) receptor antagonist may be associated with an increased risk of both community- and hospital-acquired pneumonia
- Small intestinal bacterial overgrowth occurs significantly more frequently among long-term PPI users than patients with IBS or control subjects

Proton Pump Inhibitor Use: Other Considerations

- There are case reports of low magnesium in patients taking PPI therapy
- Healthcare professionals should consider obtaining serum magnesium levels prior to initiation of prescription PPI treatment in patients expected to:
  - be on these drugs for long periods of time
  - patients who take PPIs with medications such as digoxin, diuretics or drugs that may cause hypomagnesemia
-Patients taking cardiac medications may be at particular risk
Mechanism of Proton Pump Inhibition

Adapted from Sanders SW, Clin Therapeutics 18, 2-34.
Copyright 1996 by Excerpta Medica Inc.
Optimal Timing of PPI Dose

- Single PPI dose: Administer 1 half-hour before breakfast
- If second PPI dose: Administer 1 half-hour before evening meal

Differential Diagnosis of Esophagitis

- Gastroesophageal reflux
- Eosinophilic esophagitis
- Infections (Canadida albicans, Herpes simplex, Cytomegalovirus)
- Crohn’s disease
- Vomiting, bulimia
- Pill induced
- Graft-versus-host disease
- Caustic ingestion
- Postsclerotherapy/banding
- Radiation/chemotherapy
- Bullous skin diseases
- Lymphoma

Esophagitis - Management

- A PPI for 3 months is recommended as initial therapy
- Increase the PPI dose at 4 weeks if symptom control is not adequate
- In most cases efficacy can be monitored by extent of symptom relief without routine endoscopic follow-up

- Most patients require a once daily dose of PPI to relieve symptoms and heal esophagitis

Esophagitis: Ongoing Management

- Endoscopic monitoring may be useful in patients with
  - Atypical signs or symptoms
  - Persistent symptoms on therapy
  - Higher grades of damage at diagnosis
- Trial of dose reduction or withdrawal after 3-6 months on treatment
- PPIs should not be stopped abruptly but may need to be tapered
- Recurrence after repeated trials of PPI withdrawal usually indicates chronic-relapsing GERD that require long-term PPI treatment or antireflux surgery

No Difference Between Pantoprazole and Placebo in Symptom Change in Infants 1-11 Months of Age

OL: 3 week open label Treatment Phase – pantoprazole for both groups
DB: 4 week double blind treatment phase – pantoprazole or placebo

Randomized, Controlled Trial of Omeprazole and Placebo on GER and Acidity in Preterm Infants

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Omeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastric pH:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% time pH &lt;4 (+SEM)</td>
<td>53.8 (6.8)</td>
<td>13.9 (5.1)**</td>
</tr>
<tr>
<td><strong>Esophageal pH:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% time pH &lt;4 (+SEM)</td>
<td>19 (4.5)</td>
<td>4.9 (3.4)**</td>
</tr>
<tr>
<td><strong>Number of Acid Reflux Episodes:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number</td>
<td>119.4 (20.9)</td>
<td>59.6 (26.7)*</td>
</tr>
<tr>
<td>Number &gt; 5 minutes</td>
<td>8.0 (2.1)</td>
<td>3.0 (2.0)**</td>
</tr>
<tr>
<td><strong>Duration of Acid Reflux Episodes:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longest (min)</td>
<td>48.6 (10.1)</td>
<td>16.3 (8.0)**</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01, ***P<0.0005

PPIs Do Not Improve Symptoms in Infants

- Omeprazole showed no improvement in cry-fuss time over a 24 hour period as compared to placebo in a randomized, controlled trial.

- Lansoprazole showed no improvement in crying, back arching, wheezing or regurgitation as compared to placebo in a randomized, controlled trial.

- In preterm infants and term neonates esomeprazole produces no change in bolus reflux characteristics despite significant acid suppression.

Randomized, Controlled Trial of Omeprazole and Placebo for Crying

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Combined*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Omeprazole (n=15)</strong></td>
<td>246 ± 105</td>
<td>203 ± 113</td>
<td>179 ± 129</td>
<td>191 ± 120</td>
</tr>
<tr>
<td><strong>Placebo (n=15)</strong></td>
<td>287 ± 132</td>
<td>204 ± 87</td>
<td>198 ± 115</td>
<td>201 ± 100</td>
</tr>
<tr>
<td><strong>Total (n=30)</strong></td>
<td>267 ± 119†⁺</td>
<td>203 ± 99†⁺</td>
<td>188 ± 121†⁺</td>
<td></td>
</tr>
</tbody>
</table>

*Mean of the combined data from Periods 1 and 2
† Baseline vs. Period 1, *P* = .040
‡ Baseline vs. Period 2, *P* = .008
Esomeprazole Infant Indication

- Esomeprazole (Nexium® Oral Suspension) is FDA-approved for treatment of Erosive Esophagitis due to acid-mediated GERD in patients 1 month to ≤ 12 months of age.

- Dosing recommendations are as follows:
  - Weight 3 kg to 5 kg
    - 2.5 mg Once Daily (QD) for up to 6 weeks
  - Weight >5 kg to 7.5 kg
    - 5 mg Once Daily (QD) for up to 6 weeks
  - Weight >7.5 kg to 12 kg
    - 10 mg Once Daily (QD) for up to 6 weeks

Esomeprazole Improves GERD Symptoms in Children 1-11 Years of Age

![Graph showing the improvement of GERD symptoms in children with esomeprazole]

- **Children < 20 kg**
  - Baseline: Esomeprazole 5 mg (0.3-0.6 mg/kg) (n=26)
  - Final Visit: Esomeprazole 10 mg (0.6-1.0 mg/kg) (n=23)

- **Children > 20 kg**
  - Baseline: Esomeprazole 10 mg (0.2-0.5 mg/kg) (n=31)
  - Final Visit: Esomeprazole 20 mg (0.3-1.0 mg/kg) (n=29)

*Significant difference from baseline.*

Erosive Esophagitis Healing Rates of H2RAs and PPIs in Children

Pantoprazole Provides Resolution of GERD Symptoms in Children 5-11 Years of Age

Esomeprazole Improves GERD Symptoms in Adolescents 12-17 Years of Age

Esomeprazole 20 mg qd (n = 73)

Esomeprazole 40 mg qd (n = 72)

Histologic, Endoscopic and Symptom Scores Remain Resolved in Children Three Months after Omeprazole Discontinuation

Treatment with Erythromycin

- Low dose erythromycin is a motilin receptor agonist which improves antral contractility and gastric emptying.
- Adults studies show a benefit by improving gastric emptying and the symptoms of gastroparesis.
- Two neonatal randomized, controlled studies:
  - 5 mg/kg/dose Q8 did not improve reflux burden by pH probe or time to full feeds.
  - 12.5 mg/kg/dose Q6 improved time to full feeds but reflux burden not assessed.

Treatment with Metoclopramide

- Metoclopramide is a 5HT4 agonist and dopamine antagonist
- It increases esophageal, fundic, and antral contractions
- It may reduce acid reflux burden as measured by pH probe but the effect is not consistent
- No change in bradycardic events in neonates randomized to metoclopramide versus placebo
- Side effects include dystonic reactions and tardive dyskinesia
- Adult and pediatric guidelines strongly state that the risks of metoclopramide outweigh the benefits.
- FDA implemented a Black Box warning in 2009 regarding long-term and high dose use.

Baclofen Reduces Transient Lower Esophageal Sphincter Relaxations and Acid Reflux

Baclofen Reduces Transient Lower Esophageal Sphincter Relaxations and Acid Reflux

- Total and postprandial episodes of reflux decreased
- Number of prolonged acid refluxes decreased
- No change in the percent time intraesophageal pH<4

Management with Transpyloric Feeds

- Comparable success to fundoplication in preventing aspiration pneumonias
- May be beneficial in the neonatal population to prevent apnea and bradycardia
- Reflux burden is reduced with transpyloric feeding but not completely eliminated
- Tube migration and blockage, the need for continuous feeding, and radiation exposure with tube changes may limit long term use

Barrett’s Esophagus: Definitions

- **US definition**
  - Displacement of the squamocolumnar junction proximal to the gastroesophageal junction proximal to the gastroesophageal junction with histological evidence of specialized intestinal metaplasia on biopsy specimens

- **British**
  - Endoscopically apparent area above the esophagogastric junction that is suggestive of Barrett esophagus (salmon-colored mucosa) which is supported by the finding of columnar lined esophagus on histology
  - **Note:** areas of intestinal metaplasia are not a requirement

- **Prague classification**
  - Prague C – circumferential; length of the circumferential segment
  - Prague M – maximal extent; maximal length including tongues

Barrett’s Esophagus: Pathogenesis

- Esophageal mesenchyme
  - Proinflammatory factors (acid, bile)
  - Increased levels of BMP4
    - Stem-cell activation in basal layer of esophageal epithelium
    - Development of columnar epithelium
      - Activation of gene transcription
        - CDX2 activation
        - Specialized columnar epithelium
      - CDX2 not activated
        - Nonspecialized columnar epithelium

Bone morphogenetic protein 4 (TGFb) cellular differentiation, migration, proliferation
CDX2 – homeobox gene: differentiation of gastrointestinal cells

Barrett’s Esophagus: Epidemiology

Only 1 population based study...
- 6731 patients underwent upper endoscopy in 12 pediatric facilities
- 17 patients had suspected BE (prevalence, 2.5 per 1,000)
  - Intestinal metaplasia was reported in 9 of these patients (53%)
  - Older age (odds ratio [OR] 1.13, 95% confidence interval [CI] 1.02-1.35) and hiatus hernia (OR 4.62, 95% CI 1.03-20.66) were independently associated with suspected BE

Key Points
- Endoscopically suspected BE is rare (<0.25%) in children and adolescents
- Older age and the presence of hiatus hernia are possible risk factors for BE in this group
- Limitations: Lack of standardization for identifying and recording endoscopic landmarks

Barrett’s Esophagus: Prevalence and Diagnosis

- Prevalence of BE in children is less than that of adults; overall epidemiology in pediatric patients is unclear
- Columnar metaplasia was reported in 5% of children with severe-chronic GERD
- Accuracy of diagnosis has important implications for longevity and surveillance.
  - If esophagogastric landmarks are obscured, consider a high-dose PPI for 12 weeks to allow better visualization
- Multiple biopsies should be taken to characterize the BE and to rule out dysplasia

Barrett’s Esophagus: Management

- Dysplasia is managed in accordance with adult guidelines.
- If dysplasia is absent, a follow-up endoscopy every 3 to 5 years until 20 years of age, is recommended.
- Symptoms are often a poor guide to adequacy of treatment.
- Standard management is with long-term PPI or antireflux surgery however, it is unclear whether progression of dysplasia is slowed by acid control.

Neurologically Impaired Children: Management

- These patients are often resistant to standard medical treatment
  - Thicken liquids
  - Acid suppression therapy
  - Gastrostomy or gastro-jejunostomy feeds

- Surgical options
  - Fundoplication associated with high risk of complications and reoperation
    - Dysphagia
    - Aspiration
  - Esophagogastric disconnection

GERD in Neurologically Impaired Populations: Management

- Long-term PPI is effective and often necessary for symptom control and maintenance of remissions of esophagitis
- Feeding often carried out by gastrostomy or gastro-jejunostomy tube
- Esophageal-gastric disassociation may benefit a very select few number of neurologically impaired patients
  - Associated with complications and mortality
  - Only small single center studies, no long-term studies exist
- Antireflux surgery may not benefit this patient group due to high morbidity and failure rates
  - Careful selection of appropriate surgical candidates is critical

GER in Neurologically Impaired Populations: Management Cont’d

- A study conducted in Hong Kong demonstrated that PPIs significantly reduced vomiting episodes in neurologically impaired children with GER

<table>
<thead>
<tr>
<th>Duration (days)</th>
<th>Baseline* (days)</th>
<th>Proton Pump Inhibitors* (days)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (days)</td>
<td>62 (28-356)</td>
<td>81 (42-157)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Vomiting index†</td>
<td>0.4 (0.26-0.63)</td>
<td>0.2 (0.06-0.26)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Gastrointestinal bleeding index†</td>
<td>0.014 (0-0.026)</td>
<td>0 (0-0.05)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Pneumonia index†</td>
<td>0 (0-0.04)</td>
<td>0 (0-0.04)</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

* The range is expressed in brackets
† Episode of event per day

Summary: Medical Management

• H₂RAs produce relief of symptoms and mucosal healing.

• PPIs are superior to H₂RAs in relieving symptoms and healing esophagitis

• There is insufficient support to justify the routine use of metoclopramide, erythromycin, bethanechol, or domperidone for GERD.

• Antireflux surgery should be considered only in children with GERD and failure of optimized medical therapy, or long-term dependence on medical therapy where compliance or patient preference preclude ongoing use, or life-threatening complications.

Who is a Candidate for Antireflux Surgery?

A child who:

- Fails medical therapy due to GERD
- Is dependent on aggressive or prolonged medical therapy
- Is significantly non-adherent with medical therapy
- Has persistent asthma or recurrent pneumonia due to GERD
- Has life threatening complications of GERD

Principles of Antireflux Surgery

- Restore intra-abdominal segment of esophagus
- Approximate diaphragmatic Crurae
- Reduce hiatal hernia when present
- Wrap fundus around LES to reinforce antireflux barrier
Antireflux Surgery
Antireflux Surgery: Effect on GER Mechanisms

- Increases
  - The LES baseline pressure
  - The residual LES pressure
  - The rate of gastric emptying
  - The length of the esophagus that is intra-abdominal
- Accentuates the angle of His
- Decreases
  - The number of TLSERs and nadir pressure
  - Compliance
- Reduces a hiatal hernia, if present

Rates for Reoperation in Children: Laproscopic vs. Open Nissen Fundoplication

KAPLAN–MEIER CURVES FOR LNF AND ONF

- N = 456; Mean follow-up, 36.2 months (SD, 10.9 months)
- Laproscopic Nissen fundoplication: n = 306; open Nissen: n = 150
- Overall reoperation, 12.1%; LNF, 14.1%; ONF, 8% (not statistically significant)
- Risk factors: Prematurity, chronic respiratory disease

# Antireflux Surgery: Outcomes in Children

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success rate (complete relief of symptoms)</td>
<td>57 – 92%</td>
</tr>
<tr>
<td>Mortality related to operation</td>
<td>0 – 5%</td>
</tr>
<tr>
<td>Overall complication rate</td>
<td>2 – 45%</td>
</tr>
<tr>
<td>Dumping syndrome</td>
<td>NA</td>
</tr>
<tr>
<td>Gas bloat syndrome</td>
<td>2 – 8%</td>
</tr>
<tr>
<td>Small-bowel obstruction</td>
<td>1 – 11%</td>
</tr>
<tr>
<td>Wrap failure</td>
<td>1 – 13%</td>
</tr>
<tr>
<td>Continued medication</td>
<td>85%</td>
</tr>
<tr>
<td>Reoperation rate</td>
<td>3 – 19%</td>
</tr>
</tbody>
</table>

Extraesophageal Associations of GERD: Global Consensus Definitions

Extraesophageal

Definite associations
- Sandifer’s syndrome
- Dental erosion

Possible associations

Bronchopulmonary
- Asthma
- Pulmonary fibrosis
- Bronchopulmonary dysplasia

Laryngotracheal and pharyngeal
- Chronic cough
- Chronic laryngitis
- Hoarseness
- Pharyngitis

Rhinological and otological
- Sinusitis
- Serous otitis media

Infants
- Pathological apnea
- Bradycardia
- Apparent life-threatening events

Sherman et al. *Am J Gastroenterol.* 2009;104:1278-95
GERD and Dental Erosions

- GERD may cause dental erosions in children
- Some studies link GERD with a higher prevalence of dental erosions while others do not
- A recent review found that children with GERD are at an increased risk of dental erosions
- Unclear how acid suppression changes the natural history of GERD or appropriate duration of treatment

Sandifer’s Syndrome

- Is a specific manifestation of pediatric GERD
- Abnormal posturing
  - Head tilt
  - Torticollis
  - Arching of the back
- Must be differentiated from
  - Seizures
  - Infantile spasms
  - Dystonia
- May be a vagally mediated reflex response to esophageal acid exposure
- Resolves with antireflux therapy

Extraesophageal Manifestations of GERD are Possible

At present, no single diagnostic test can prove or exclude extraesophageal presentations of GERD in pediatrics.

- Sinusitis
- Pulmonary fibrosis
- Pharyngitis
- Serous otitis media
- Chronic cough
- Acute life-threatening event
- Laryngitis
- Hoarseness
- Throat clearing
- Asthma
- Apnea/bradycardia
- Acute life-threatening event
- Interstitial lung disease
- Bronchiectasis
- Bronchiolitis obliterans

Respiratory

• Recurrent pneumonia
• Apnea/ALTE
• Asthma
• Laryngeal
• Nocturnal Acid Breakthrough

Respiratory: Mechanism of Responses to GER

Aspiration From Swallowing or GER?

Barium Swallow

Technetium-99m Salivagram
RECURRENT PNEUMONIA
Recurrent Pneumonia & GER: Relationship

- May be a complication of reflux, presumably as a result of failure of the airway protective mechanisms.
- No test can determine whether reflux is causative.
- Management decisions based on inconclusive diagnostic studies with no certainty regarding outcome.

Recurrent Pneumonia & GER: Management

- Combination of tests may aid in diagnosis
  - Reflux testing (pH-MII, pH probe)
  - Flexible bronchoscopy with pulmonary lavage
  - Bedside and Direct Laryngoscopy
  - Nuclear scintigraphy
  - Swallowing assessment (VSS, FEES)

- Differential diagnosis
  - Neuromuscular
  - Immune deficiency
  - H type TEF
  - Bronchiectasis
  - Ciliary diskinesia
  - Cystic fibrosis
  - Achalasia for other cause of recurrent pneumonia

Recurrent Pneumonia & GER: Management

- Antireflux surgery may be necessary in patients with severely impaired lung function
- Medical therapy with careful follow-up of pulmonary function may be considered in patients with minimum pulmonary disease
- Naso-gastric feeding trial may be used to exclude aspiration during swallowing
- Naso-jejunal therapy may help to determine the impact of reflux on symptoms, and if the patient is likely to benefit from fundoplication

Recurrent Pneumonia & GER: Fundoplication

- Elimination or significant reduction of reflux does not guarantee prevention of recurrent pneumonias
- Aspiration pneumonia and reflux related hospitalizations are not uncommon after fundoplication or initiation of transpyloric feeding
- Fundoplication and transpyloric feeding are comparable in preventing aspiration pneumonias
  - fundoplication – 15% developed pneumonia
  - gastrojejunal feeding tube – 16% developed pneumonia

Antireflux Surgery and Extraesophageal Symptoms

- Aspiration pneumonias may improve after fundoplication.
- Rates of other pneumonias after fundoplication may be unchanged or even higher than prior to fundoplication.
- Patients, who previously had not had a pneumonia, may develop them.
- Asthma improvement after fundoplication is variable depending on the case series.
- The majority of pediatric patients remain on reflux medications, even after surgery.

Apnea/ALTE
Acute Life-Threatening Event

A diagnosis of ALTE warrants consideration of causes other than gastroesophageal reflux

- Esophageal pH monitoring is useful only if performed simultaneously with measurement of respiration and chest wall movement
- The infant is more likely to respond to antireflux therapy if:
  - emesis or regurgitation is present at time of ALTE
  - infant is awake
  - obstructive apnea is present

Acute Life-Threatening Event

- Therapeutic options include:
  - Thickened feedings theoretically may decrease frequency of regurgitation and volume of reflux although this is not proven
  - Acid suppression has a limited role in ALTEs related to vomiting

- There may be some beneficial effect of transpyloric feeds on ALTE however patients with transpyloric feeds may be at risk for NEC

- In some exceptional situations, prone sleeping (with cardiorespiratory monitoring) may be recommended

- Antireflux surgery is considered only in severe cases shown clearly to be related to GER

Asthma and GER: Etiology

• An etiologic role for reflux in asthma has not been established
• Proposed mechanisms by which reflux aggravates asthma are
  - Direct production of airway inflammation
  - Airway hyperresponsiveness
  - Vagally mediated bronchial or laryngeal spasm
  - Neurally mediated inflammation
• Few studies have evaluated the impact of asthma on GERD
  - Chronic hyperinflation may reduce resting LES pressure
  - Lung hyperinflation and airflow obstruction may increase negative intrathoracic pressure
  - Oral corticosteroids promote reflux in adults

Prevalence of GER in Children with Asthma

- 60 – 80% of children with asthma have abnormal esophageal pH or pH/MII recordings
- GER symptoms are absent or mild in 44% of those with persistent asthma and abnormal esophageal pH studies
- Nocturnal wheezing appears particularly related to GERD

Asthma: Does GER Cause It?

GER ➔ Asthma

GER ➔ Asthma

GER ➔ Asthma

GER ➔ Asthma


Respiratory: Mechanism of Responses to GER

# Asthma: When to Treat for GERD

<table>
<thead>
<tr>
<th>Persistent asthma with heartburn or regurgitation</th>
<th>Treat with a PPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent asthma that is difficult to control or nocturnal-onset</td>
<td>GER is an unlikely contributor to asthma if reflux testing is negative</td>
</tr>
</tbody>
</table>
  * Rule out other causes of wheezing;  
  * Perform pH (+/- impedance) monitoring |
| Persistent asthma that is difficult to control or nocturnal-onset with abnormal pH (+/- impedance) monitoring | Trial with a PPI |

Approach to Child with Persistent Asthma

Heartburn or regurgitation

Yes → Treat with a PPI

No (or infant/child too young to report symptoms reliably)

Difficult to control? or Nocturnal-onset asthma

Yes

GER unlikely contributor to asthma

No

Rule out other causes of wheezing. Do pH (± impedance) monitoring

pH (± impedance) normal?

Yes → GER unlikely contributor to asthma

No → Trial PPI

Varying Results of Using Acid Suppression in Children with Asthma

Randomized, controlled trial
- 36 children with asthma and GERD
- Omeprazole vs. placebo
- No difference in any of the study parameters

Open label study
- 44 children with asthma and GERD
- Esomeprazole/metoclopramide vs. ranitidine
- Ranitidine patients had significantly more exacerbations

Størdal et al. Arch Dis Child. 2005 Sep;90(9):956-60.
No Effect of Omeprazole and Placebo for Asthmatic Children with GER

<table>
<thead>
<tr>
<th></th>
<th>Omeprazole ($n=18$)</th>
<th>Placebo ($n=18$)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom Score</td>
<td>-1.28 (-2.65 to 0.1)</td>
<td>-1.28 (-3.28 to 0.72)</td>
<td>1.00</td>
</tr>
<tr>
<td>PAQLQ</td>
<td>-0.62 (-0.29 to 0.95)</td>
<td>-0.50 (-0.29 to 0.70)</td>
<td>.051</td>
</tr>
<tr>
<td>$\text{FEV}_{1%} (\text{mean, median})$</td>
<td>-1.38 (0.33)</td>
<td>-2.01 (-0.50)</td>
<td>0.77</td>
</tr>
<tr>
<td>$\text{FEF}_{25-75} (\text{mean, median})$</td>
<td>-0.07 (-0.05)</td>
<td>0.04 (0.05)</td>
<td>0.12</td>
</tr>
<tr>
<td>Rescue medication ($\text{mean, median}$)</td>
<td>-1.9 (0.0)</td>
<td>-1.9 (0.5)</td>
<td>0.89</td>
</tr>
<tr>
<td>$\text{ECP baseline}$</td>
<td>25.9 (14.3 to 37.5)</td>
<td>20.2 (12.7 to 27.7)</td>
<td></td>
</tr>
<tr>
<td>$\text{ECP change}$</td>
<td>1.27 (-5.5 to 8.1)</td>
<td>1.39 (-4.3 to 7.1)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Values expressed as changes from baseline (week 0) to end of treatment (week 12) with 95% confidence intervals for mean ± 1.96 SEM) unless otherwise stated.

**PAQLQ**: Pediatric Asthma Quality of Life Questionnaire  
**ECP**: Eosinophilic Cationic Protein

Størdal et al. *Arch Dis Child*. 2005 Sep;90(9):956-60.
Asthma: Antireflux Therapy

- There are no controlled trials of fundoplication in children with extraesophageal symptoms
- Fundoplication (anti-reflux surgery) associated with significantly fewer exacerbations of asthma symptoms in children with moderate-persistent asthma and concomitant GERD in comparison with medical therapy with an H₂RA (i.e. ranitidine)
  - Asthma symptom scores improved
  - Pulmonary function, asthma medication use similar improvements for both medication and surgery

Asthma: Antireflux Therapy Cont’d

- Less asthma medication used by children with persistent moderate asthma and reflux when treated with acid suppression therapy; i.e. lansoprazole (uncontrolled, open-label study)

- Fundoplication and acid suppression plus a prokinetic employed in patients with abnormal 24 hr pH-metry resulted in:
  - Decrease in asthma medications, asthma exacerbations
  - Improvement in asthma symptom scores and pulmonary function

The Relationship Between Laryngeal Symptoms/Findings and GER

Chronic cough, chronic laryngitis, hoarseness, and asthma may be associated with GERD

- Data showing a relation between reflux and upper airway disease are weak
- Airway symptoms attributed to reflux in adults include hoarseness, chronic cough, and globus sensation
- Affected adults rarely have typical reflux symptoms
- The sensitivity of laryngoscopic findings to identify reflux disease are poor

Laryngeal: Normal vs. Erythema

Not all red in the airways = reflux!

Normal

Laryngeal Pharyngeal Reflux

Unclear if Treatment Improves Laryngeal GER-Related Symptoms

- Laryngoscopy is generally indicated to rule out anatomic abnormalities of airway protection.
- Adult studies suggest that a therapeutic trial of acid suppression must last >3 months to adequately assess efficacy.
- Clinical improvement followed by recurrence off treatment suggests an association with GER.
- Extrapolation from adult studies suggests that PPIs will not benefit most children with upper airway symptoms.
- There is insufficient evidence to recommend for, or against, the use of acid suppression therapy.

Patients with Nocturnal Acid Breakthrough (NAB) may have:

- Symptoms such as nocturnal heartburn
- May be asymptomatic
- May experience sleep disturbance

Nocturnal Acid Breakthrough: Management

- The pharmacodynamics of PPIs limit their control of nighttime acidity
- Nighttime acidity may be improved by:
  - Attention to PPI dosing schedule
  - Using higher doses of PPIs
  - Adding an H₂-RA at bedtime to an QD or BID PPI

Nocturnal Acid Breakthrough - Adult

- Multichannel intraluminal impedance-pH studies in 100 patients were reviewed
- 58 patients were studied on PPI bid; 42 patients were studied on a PPI bid + H₂RA

<table>
<thead>
<tr>
<th></th>
<th>%age with NAB</th>
<th>%age time intragastric pH &lt;4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Upright</td>
</tr>
<tr>
<td>PPI bid</td>
<td>64</td>
<td>29 +/-3</td>
</tr>
<tr>
<td>PPI bid + H₂RA qhs</td>
<td>17</td>
<td>18 +/-2.9</td>
</tr>
</tbody>
</table>

- H₂RAs may be considered as adjunct therapy when suppression of night time gastric acid is required

Nocturnal Acid Breakthrough and Sleep Disorders

- The relationship between GER, pulmonary manifestations, and sleep disorders is complex and is not understood.
- Adult studies have shown that sleep-related GER is associated with poor sleep quality. It is unclear whether these findings simply reflect common risk factors or truly indicate a cause-and-effect relationship.
- A causal connection is supported by recent studies which demonstrate improvements in sleep function in adults and adolescents following treatment of GER with acid-suppression medications.
- Further studies are needed to corroborate findings in adults which have suggested a stronger link between GER and Obstructive Sleep Apnea Syndrome (OSAS).

Nocturnal Acid Breakthrough: Infants and Children

A prospective double blind study in 18 patients between 1 and 13 years of age reported:

- NAB is common (89%) in pediatric patients treated with PPIs
- The reflux index remains normal in spite of NAB
- Symptoms and esophagitis continued to improve during therapy in spite of NAB
- There appears to be no additional benefit to supplementation with an ranitidine at bedtime.

Nocturnal Acid Breakthrough: Infants and Children

The effect of esomeprazole therapy on health outcomes in children (12-17 years of age) with GERD was assessed over 8 weeks

- All domains of the Quality of Life scale were improved
- Sleep dysfunction was significantly improved after treatment

## Nocturnal Acid Breakthrough: Children vs. Adults

<table>
<thead>
<tr>
<th></th>
<th>Adult (Farup et al)</th>
<th>Children (Molle et al)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence of nocturnal GER</strong></td>
<td>10% in a random phone survey of the population</td>
<td>8.7% in children with asthma</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Impaired esophageal clearance due to reduced swallows and saliva volume</td>
<td>Not studied</td>
</tr>
</tbody>
</table>
| **Outcome**             | - Impaired Health Related Quality of Life  
- Recumbent episodes > 5 minutes predictive of erosive GERD  
- Increased risk for severe GERD | Associated with nocturnal asthma, nocturnal cough, and other supraesophageal manifestations |


MANAGEMENT ALGORITHMS
Esophageal Manifestations of GERD: Global Consensus Definitions

Esophageal
- Symptoms purported to be due to GERD*
  - Infant or younger child (0–8 years), or older without cognitive ability to reliably report symptoms
  - Excessive regurgitation
  - Feeding refusal/anorexia
  - Unexplained crying
  - Choking/gagging/coughing
  - Sleep disturbance
  - Abdominal pain
- Symptomatic syndromes
  - Older child or adolescent with cognitive ability to reliably report symptoms
  - Typical reflux syndrome
- Syndromes with esophageal injury
  - Reflux esophagitis
  - Reflux stricture
  - Barrett’s esophagus
  - Adenocarcinoma

Extraesophageal
- Definite associations
  - Sandifer’s syndrome
  - Dental erosion
- Possible associations
  - Bronchopulmonary
    - Asthma
    - Pulmonary fibrosis
    - Bronchopulmonary dysplasia
  - Laryngotracheal and pharyngeal
    - Chronic cough
    - Chronic laryngitis
    - Hoarseness
    - Pharyngitis
  - Rhinological and otological
    - Sinusitis
    - Serous otitis media
    - Infants
      - Pathological apnea
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* Where other causes have been ruled out (e.g., food allergy, especially in infants)
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Definition of GERD in Pediatric Patients

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Sherman et al. Am J Gastroenterol 2009;104:1278-95
Approach to the Infant with Recurrent Regurgitation and Vomiting

1. History and physical exam
   - No
   - Are there warning signals?
     - Yes → Evaluate further: differential diagnosis of vomiting in infants and children
     - No → Are there signs of complicated GER disease?
       - Yes → Evaluate further: symptoms and signs that may be associated with GERD
       - No → Uncomplicated infantile GER – “Happy spitter”

2. Uncomplicated infantile GER – “Happy spitter”
   - No testing
   - Education: warning signals
   - Reassurance
   - Consider: thickened formula
   - Resolves by 18 Months of age
     - No → Consultation with Pediatric GI
       - Consider: EGD & biopsy

Approach to the Infant with Recurrent Regurgitation and Weight Loss

1. History and physical exam
   - No
   - Are there warning signals
     - Yes → Evaluate further
     - No
   - Adequate caloric intake?
     - Yes → Education, close follow-up
     - No
   - Workup for failure to thrive
     - Consider: Upper GI Series
       - No
       - Abnormal?
         - Yes → Manage accordingly
         - No
   - Dietary management
     - Protein hydrolysate/amino acid formula
     - Thickened feedings
     - Increased caloric density
       - Improved?
         - Yes → Education, close follow-up
         - No
   - Consultation with Pediatric GI
     - Consider: EGD & biopsy
Approach to the Older Child or Adolescent with Heartburn

1. History and physical exam
2. Consultation with Pediatric GI
   Consider: EGD & biopsy
   - If improves, continue:
     - Continue PPI for 8 – 12 weeks
     - Discontinue PPI
       - If relapses, observe
6. Consultation with Pediatric GI
Approach to the Child with Persistent Asthma

Heartburn or regurgitation

Yes → Treat with PPI

No (or infant/child too young to report symptoms reliably)

Difficult to control or Nocturnal-onset asthma

Yes → GER unlikely contributor to asthma

No

Rule out other causes of wheezing. Do pH (± impedance) monitoring

pH (± impedance) normal?

Yes → Treat with PPI

No → Trial PPI

Summary

- GER is common in healthy infants and usually resolves by 18 months of age
- Population-based studies of reflux symptoms in children of different age groups are insufficient and are a priority for further research
- Pediatric GERD can present with variable symptoms
- Currently available tests often do not conclusively demonstrate a relationship between GERD and specific symptoms
- Approach to GERD diagnosis and treatment depends on presenting symptoms and signs in the specific patient
- Good history and clinical judgment are important for optimal evaluation and management
Summary

• More research is needed to address optimal methods for the diagnosis and, more importantly, the treatment of GERD in otherwise healthy infant populations
  – The role of PPIs in the treatment of GER in infants is limited
• Current evidence supports use of antisecretory therapy to treat reflux-associated esophagitis in all age groups
• PPIs are superior to H₂RAs with respect to acid suppression, healing of erosive and non-erosive esophagitis and maintenance of disease resolution
• Treatment effectiveness for other GERD manifestations is not well documented
  – Since antisecretory agents reduce esophageal acid exposure, they are likely to be useful in treating GER-related respiratory disorders