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
# PROGRAM FACULTY

<table>
<thead>
<tr>
<th>Dr. Benjamin D. Gold, Chair</th>
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<tbody>
<tr>
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<th>Dr. Rachel Rosen</th>
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<tr>
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# CONTENT REVIEWER

<table>
<thead>
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Disclosure Slide

• Educational Support for the NASPGHAN FOUNDATION & NASPGHAN Reflux and GERD Grand Rounds Program was provided by AstraZeneca and Takeda North America

• Educational Support for the Diagnosis and Management of Reflux and GERD Slide Set was provided by Takeda North America

• NASPGHAN FOUNDATION & NASPGHAN do not endorse any commercial product. Any products named in this slide set are presented as part of the scientific evidence being cited and are used only to illustrate teaching points. A number of diagnostic tests and pharmacological agents used for treatment are off-label and have not been FDA-approved for use in infants, children and adolescents. Audience members are required to critically evaluate any product that they will use in clinical care.

• 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
• Summary
• Management Algorithms
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
Estimated Incidence Rates of GERD in Children and Adolescents from 2000-2005

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

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


RR, relative risk; CI, confidence interval.

- At Least 1 Symptom: RR, 2.3 (95% CI, 1.3–4.0)
- Vomiting: RR, 2.7 (95% CI, 1.4–5.5)
- Heartburn: RR, 4.6 (95% CI, 1.5–13.8)
- Acid Regurgitation: RR, 4.7 (95% CI, 1.6–14.0)

*All children vs. children with history of frequent spilling in the first year of life*
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
Who is at Risk for Severe GERD?

- Cystic fibrosis
- Esophageal atresia
- Neurologic impairment
- Hiatal Hernia
- Obesity
- Family history of GERD; GERD related complications
DIAGNOSIS

• Symptoms And Signs Associated With GERD
• Testing
## 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>Warning Signals</th>
<th>Non-GERD Diagnosis</th>
</tr>
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<tbody>
<tr>
<td>Bilious vomiting</td>
<td>Nocturnal vomiting</td>
</tr>
<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>
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<tr>
<td>Diarrhea</td>
<td>Constipation</td>
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GERD Masqueraders

- Pyloric Stenosis
- Malrotation
- Achalasia

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

Esophageal Manifestations of GERD: Global Consensus Definitions

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

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>
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<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>
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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
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

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>
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<tr>
<td>Enables evaluation of microscopic anatomy</td>
<td>Sampling error because of the patchy distribution of inflammatory changes</td>
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<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>
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<tr>
<td></td>
<td>Eosinophilia, elongation of papillae, basal hyperplasia, and dilated intercellular spaces are neither sensitive nor specific for reflux esophagitis</td>
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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
MANAGEMENT

• Positioning and Feeding
• Pharmacologic Therapy
• Testing
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

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.
# Available H$_2$RAs and PPIs

<table>
<thead>
<tr>
<th><strong>H$_2$ Receptor Antagonists</strong></th>
<th><strong>Proton Pump Inhibitors</strong></th>
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<tbody>
<tr>
<td>Cimetidine</td>
<td>Dexlansoprazole</td>
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<tr>
<td>Famotidine</td>
<td>Esomeprazole</td>
</tr>
<tr>
<td>Nizatidine</td>
<td>Lansoprazole</td>
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<tr>
<td>Ranitidine</td>
<td>Omeprazole</td>
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<td></td>
<td>Pantoprazole</td>
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<tr>
<td></td>
<td>Rabeprazole</td>
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<tr>
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<td>Zegerid</td>
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For the most current treatment dosage information please consult the respective product information.
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

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 (*Candida 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

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

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 motility agents (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.
Management

Surgical Therapy
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
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

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
MANAGEMENT ALGORITHMS
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Definite associations
- Sandifer’s syndrome
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Extraesophageal

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

- Rhinological and otological
  - Sinusitis
  - Serous otitis media

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

* Where other causes have been ruled out (e.g. food allergy, especially in infants)
Approach to the Infant with Recurrent Regurgitation and Vomiting

**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”
        - 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
       - Workup for failure to thrive
         - Consider: Upper GI Series
       - No
         - Abnormal?
           - Yes → Manage accordingly
           - No
     - No

2. Dietary management
   - Protein hydrolysate/amino acid formula
   - Thickened feedings
   - Increased caloric density

3. 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
3. If improves, continue PPI for 8 – 12 weeks.
4. If relapses, consult Pediatric GI.
5. Observation:
   - Yes: Consultation with Pediatric GI
   - No: Discontinue PPI

References:
Approach to the Child with Persistent Asthma

1. Heartburn or regurgitation
   - Yes → Treat with PPI
   - No (or infant/child too young to report symptoms reliably)
2. Difficult to control or Nocturnal-onset asthma
   - Yes → Rule out other causes of wheezing. Do pH (± impedance) monitoring
   - No → GER unlikely contributor to asthma
3. pH (± impedance) normal?
   - Yes → Treat with PPI
   - No → Trial PPI