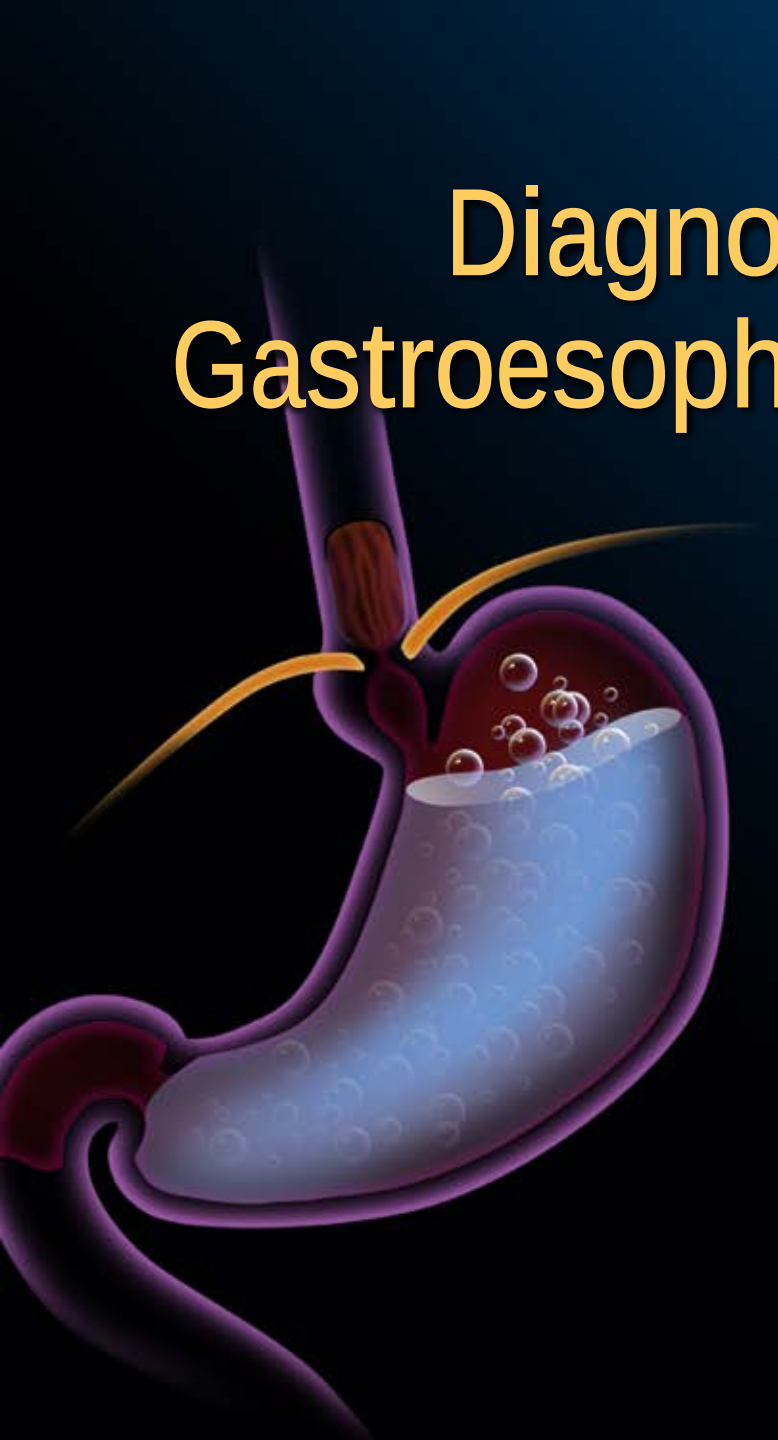
Diagnosis & Management of Gastroesophageal Reflux Disease in Pediatric Patients



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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

Dr. Benjamin D. Gold, Chair
Children's Center for Digestive Healthcare, Hepatology & Nutrition Children's Healthcare of Atlanta
Atlanta, GA

Dr. Rachel Rosen
Assistant Professor of Pediatrics, Harvard Medical School
Boston, MA

Dr. Steven J. Czinn
Professor & Chairman, Department of Pediatrics , University of Maryland School of Medicine
Baltimore, MD

CONTENT REVIEWER

Dr. Philip Sherman
Professor of Paediatrics, Microbiology and Dentistry, The Hospital for Sick Children
Toronto, ON

CME REVIEWER

Dr. Sandeep Gupta
Riley Hospital for Children Indiana University School of Medicine,
Indianapolis, IN

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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
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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
- Summary
- Management Algorithms

PHYSIOLOGY & NATURAL HISTORY

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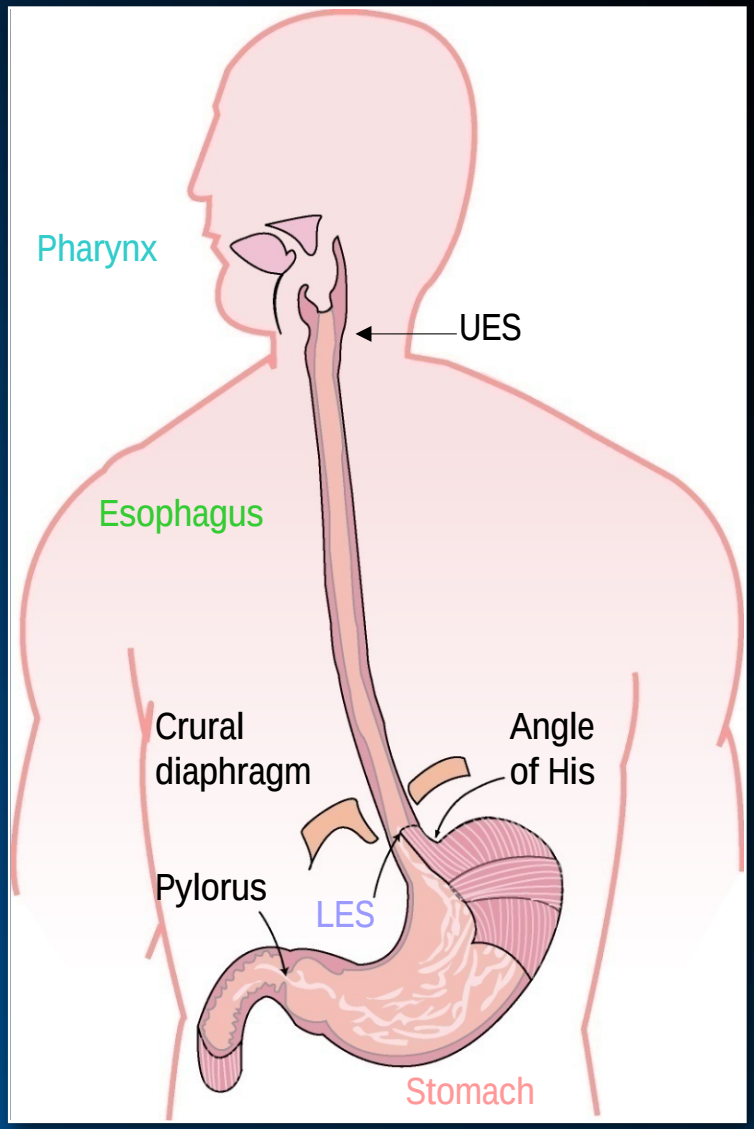
Pathogenic Factors in GERD



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

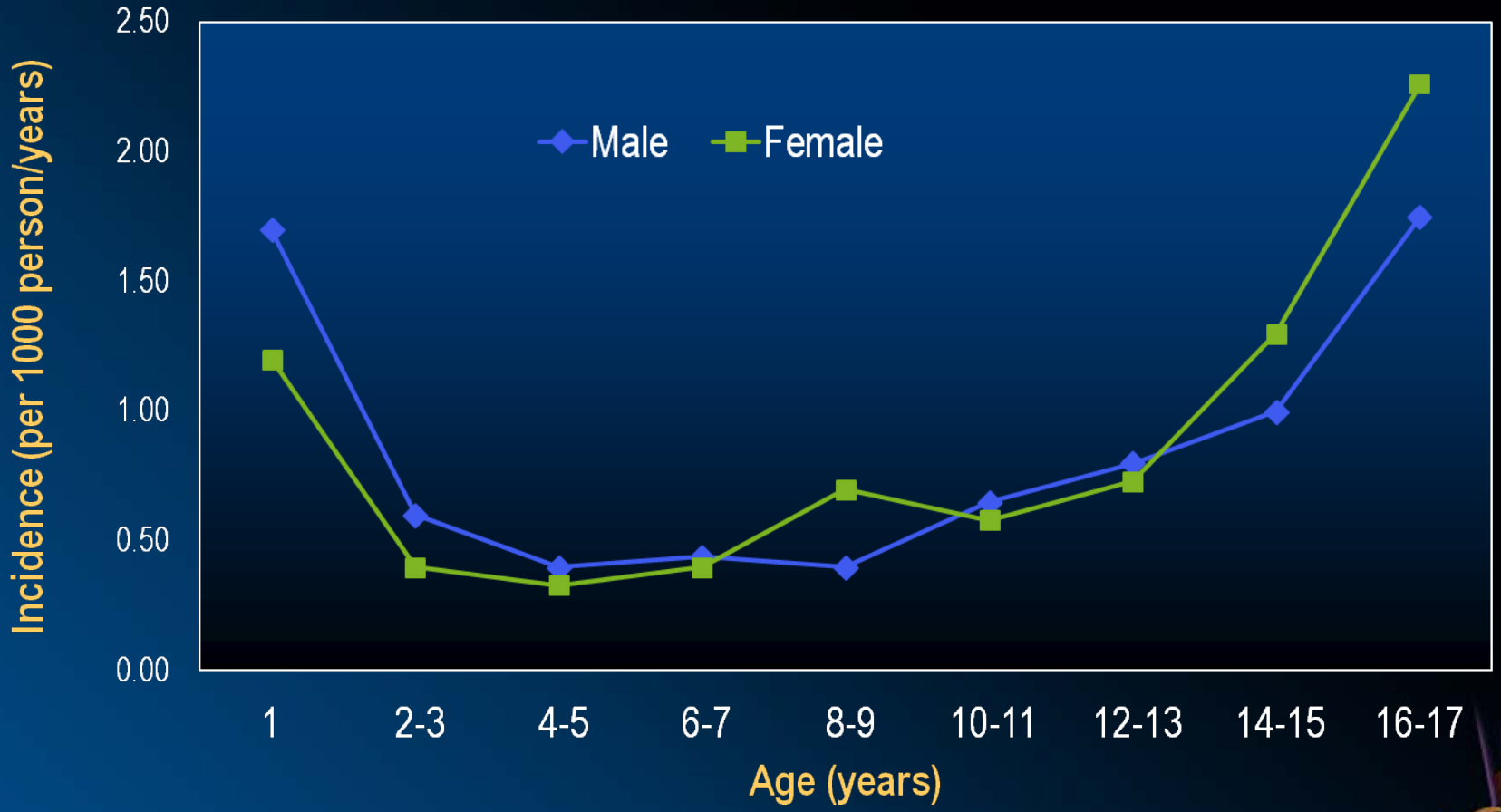
Mechanisms of Esophageal Complications

- Defective tissue resistance
- Noxious composition of refluxate

Mechanisms of Airway Complications (Extra Esophageal Manifestations)

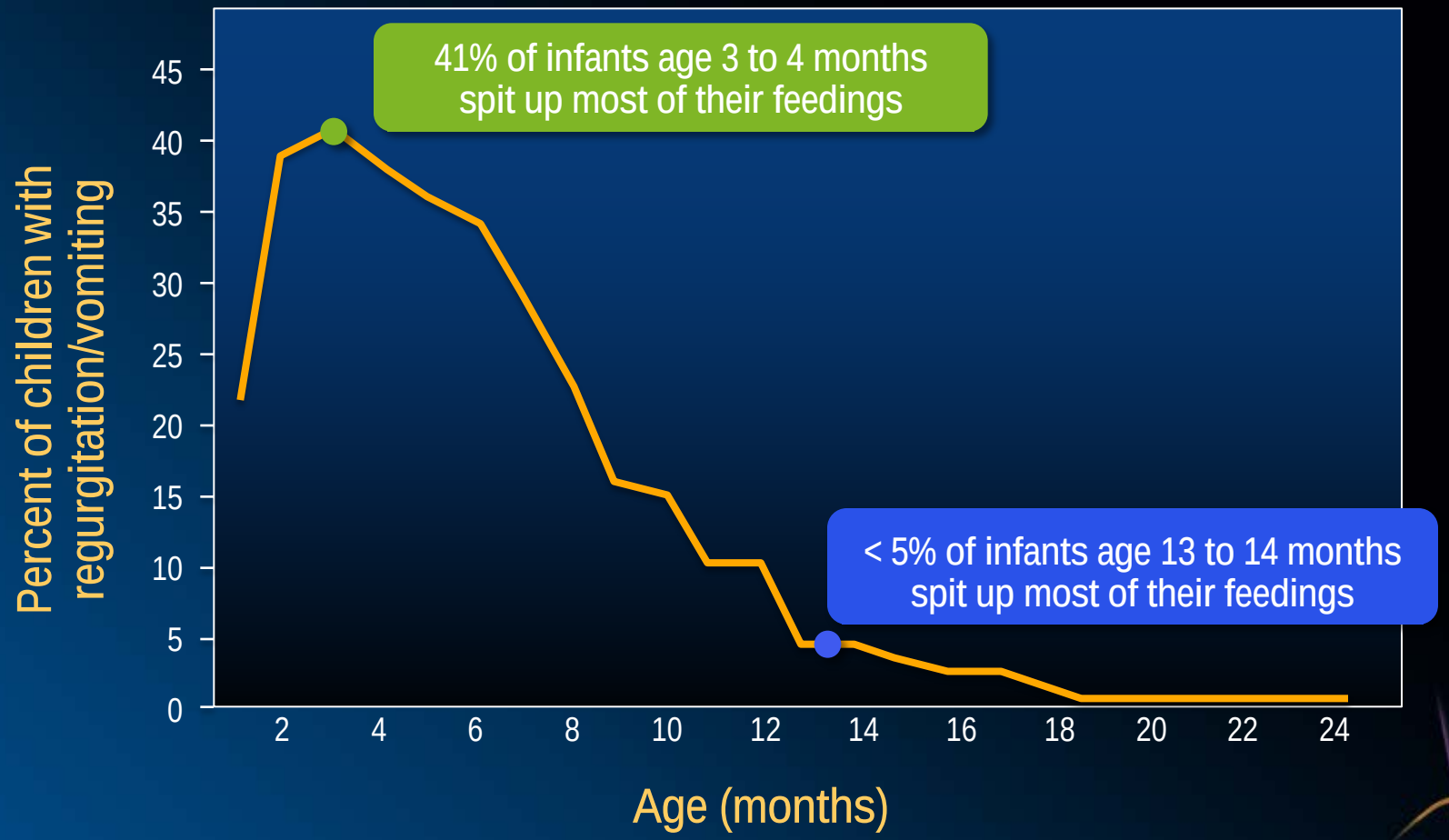
- Vagal reflexes
- Impaired airway protection

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



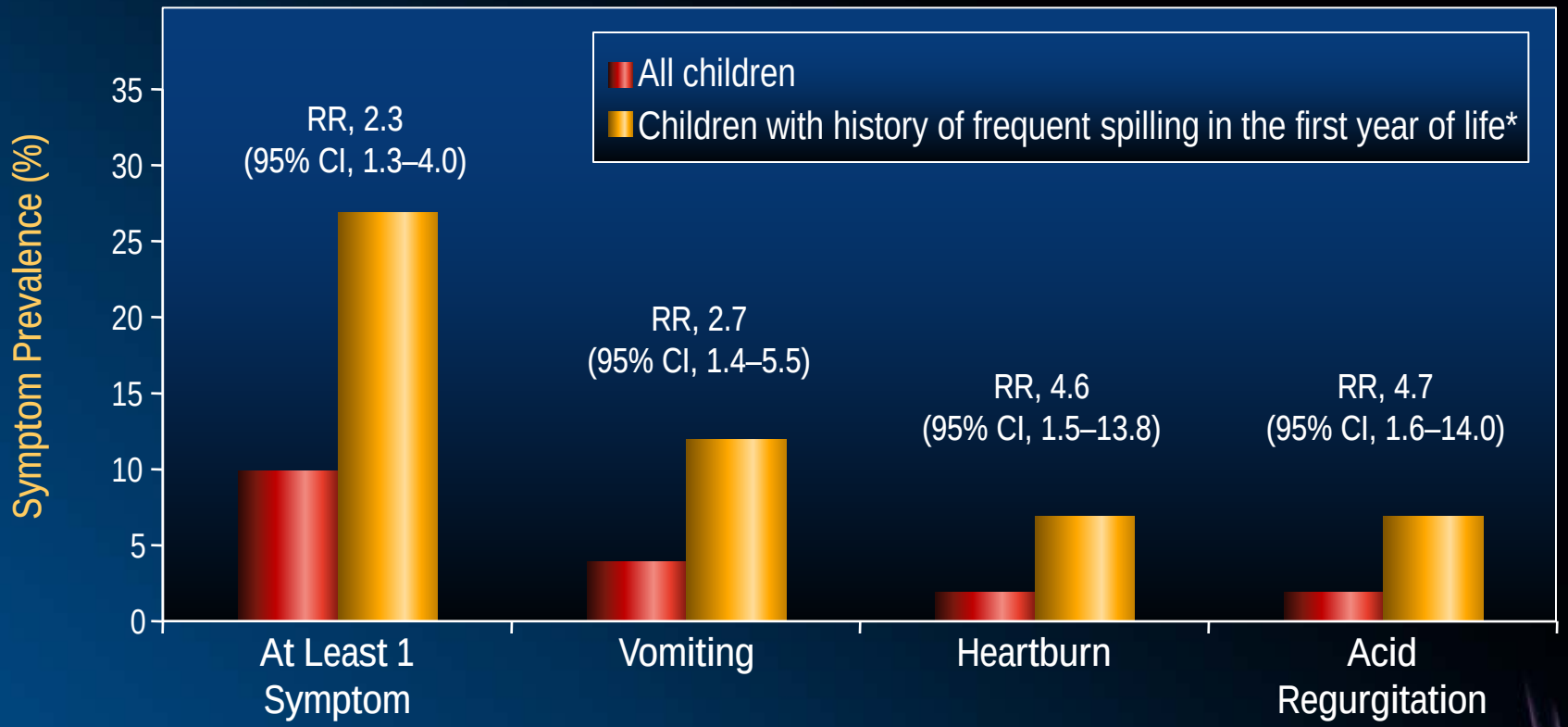
Ruigómez et al. *Scand J Gastroenterol.* 2010;45(2):139-46.

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



Martin et al. *Pediatrics*. 2002;109:1061–1067.

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



RR, relative risk; CI, confidence interval.

Martin et al. *Pediatrics*. 2002;109:1061–1067.

Correlation of Symptoms and Injury

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

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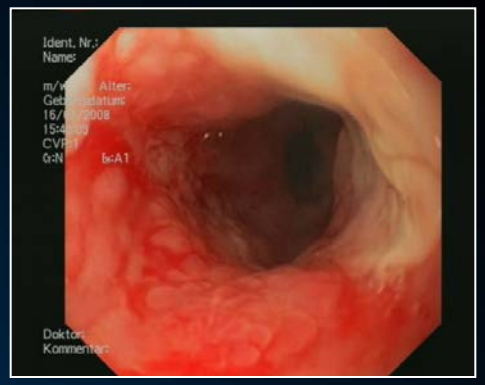

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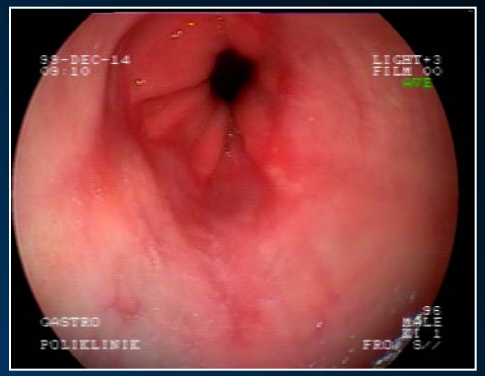

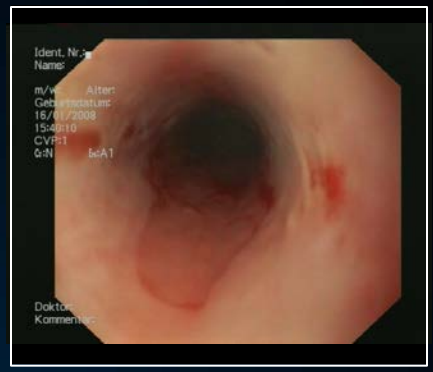

Heine et al. *J Paediatr Child Health.* 2006;42(3):134-9.
Orenstein et al. *Am J Gastroenterol.* 2006; 101(3):628-40.
Salvatore et al. *J Pediatr Gastroenterol Nutr.* 2005;40(2):210-5.

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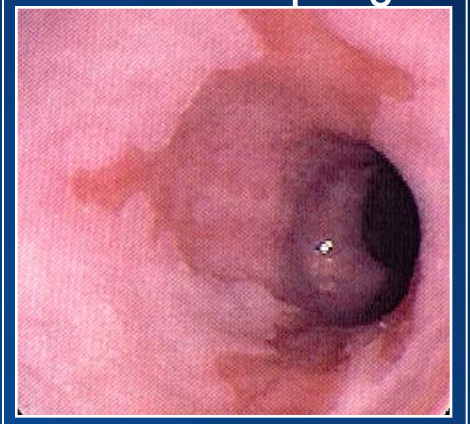
GERD-Related Complications

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*

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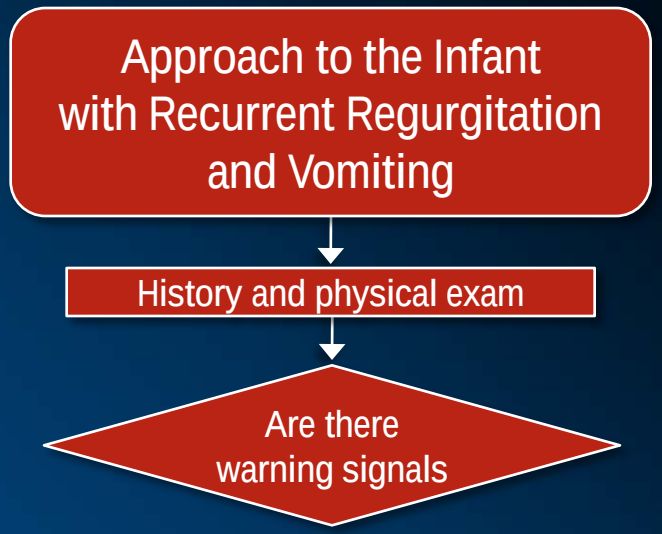
Warning Signs Suggestive of a Non-GERD Diagnosis



Bilious vomiting	Nocturnal vomiting
Consistently forceful vomiting	Onset of vomiting after 6 months of life
Hepatosplenomegaly	Vomiting undigested food
Gastrointestinal bleeding: hematemesis or hematochezia	Documented or suspected genetic/metabolic syndrome
Bulging fontanelle	Macro/microcephaly
Fever	Failure to thrive
Diarrhea	Constipation

Vandenplas et al. *J Pediatr Gastroenterol Nutr.* 2009;49:498-547.

GERD Masqueraders

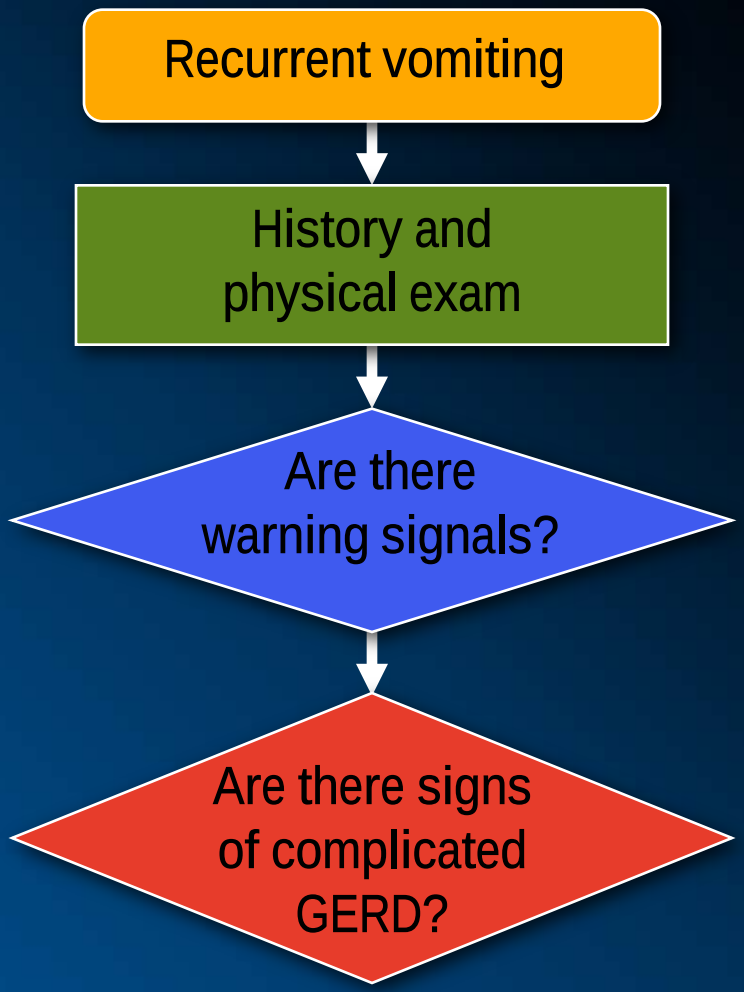
Pyloric Stenosis

Malrotation

Achalasia

Permission Granted by OESEO, " The Esophago – gastric junction,420 questions", J Libbey Publ.

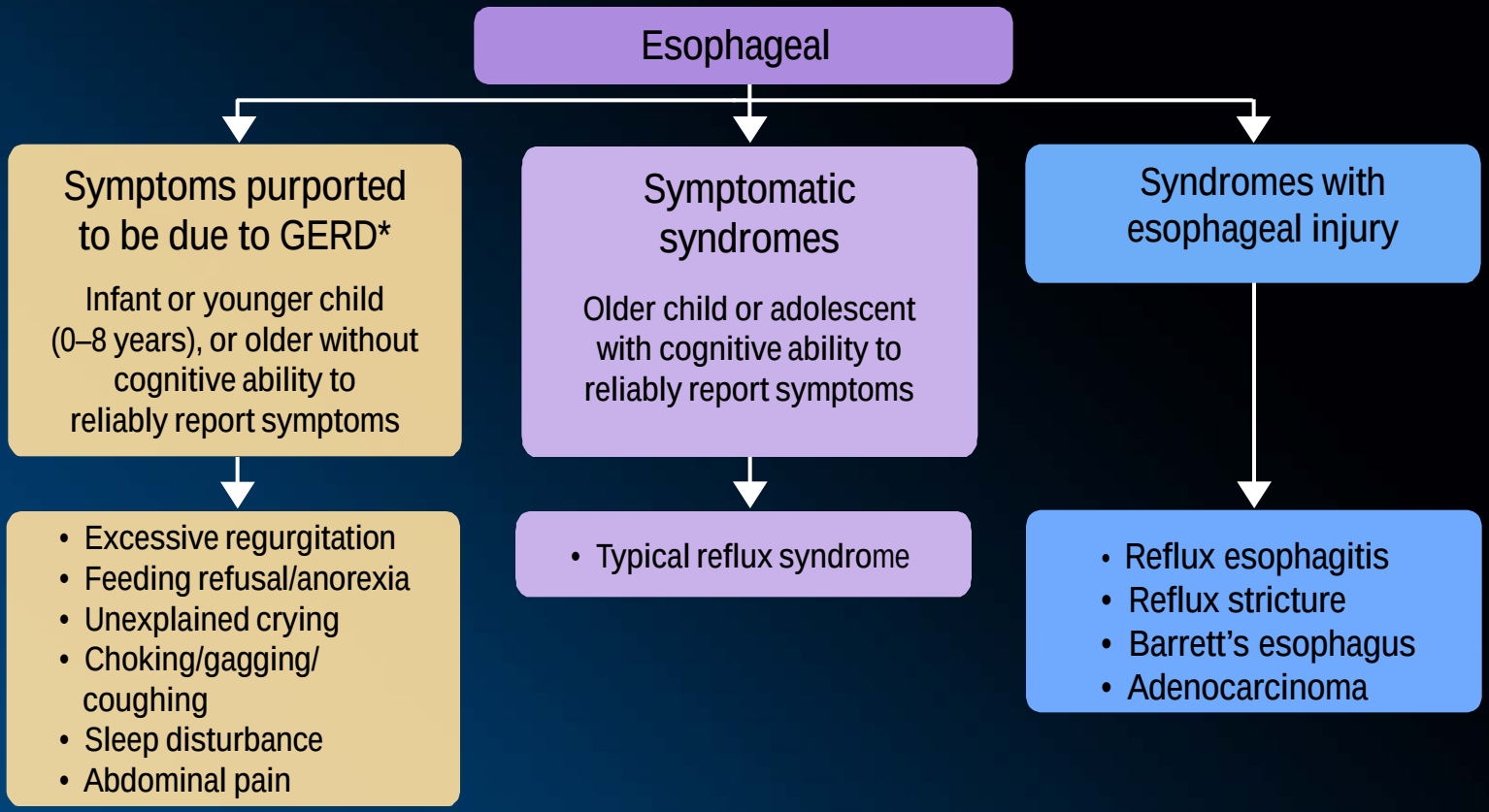
Signs of Complicated GERD



- Poor weight gain
- Excessive crying or irritability
- Anemia; iron deficiency
- Dysphagia, odynophagia
- Feeding problems
- Respiratory problems, including:
  - Wheezing
  - Stridor
  - Recurrent pneumonia
  - Choking
  - Respiratory problems

Vandenplas et al. *J Pediatr Gastroenterol Nutr.* 2009;49:498-547.

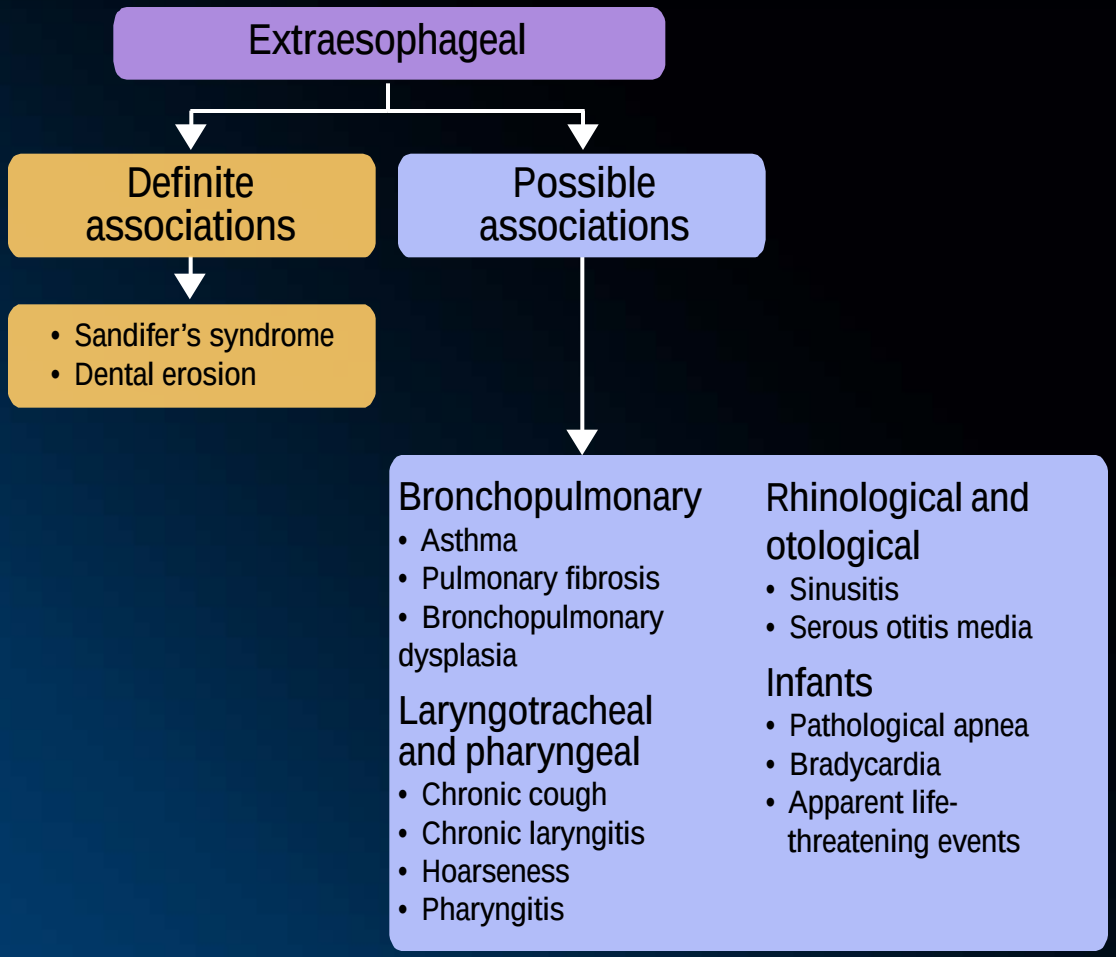
Esophageal Manifestations of GERD: Global Consensus Definitions



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

Sherman et al. *Am J Gastroenterol.* 2009;104:1278-95.

Extraesophageal Associations of GERD: Global Consensus Definitions



Sherman et al. *Am J Gastroenterol* . 2009;104:1278-95.

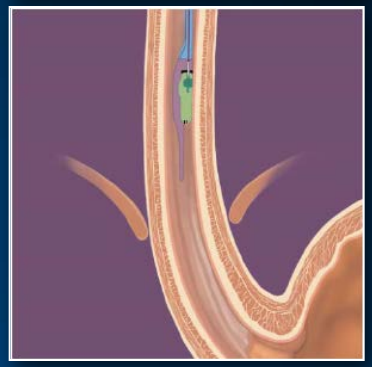
Testing for GERD

- 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

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

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

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Advantages and Disadvantages of Multi-Channel Intraluminal Impedance

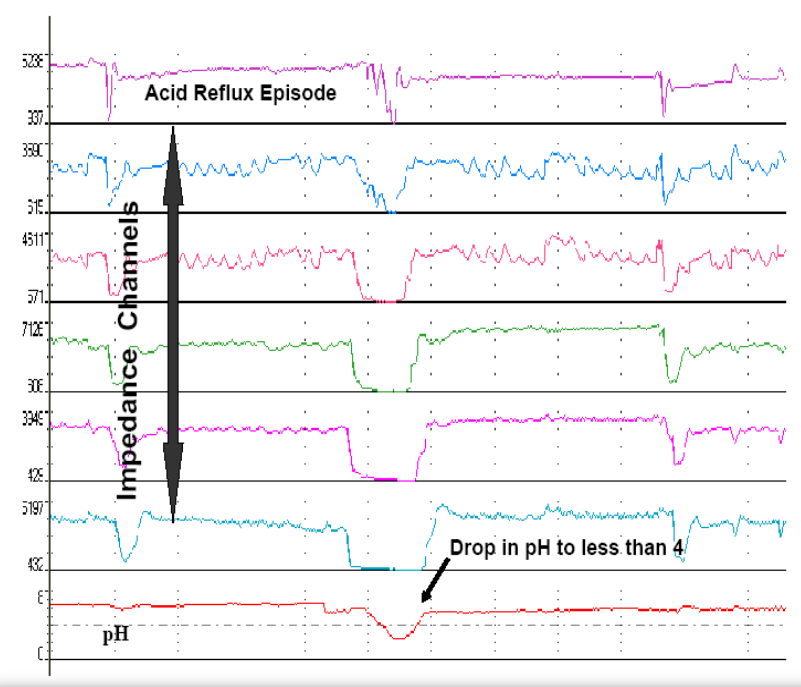


Image from Effects, Diagnosis and Management of Extra-Esophageal Reflux. Editors: Nikki Johnston and Robert J. Toohill. ©2010 Nova Science Publishers, Inc

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

Rosen R et al *J Pediatr Gastroenterol Nutr.* 2011;52:404-7.
Wenzl. *J Pediatr Gastroenterol Nutr.* 2002;34:261-8.

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

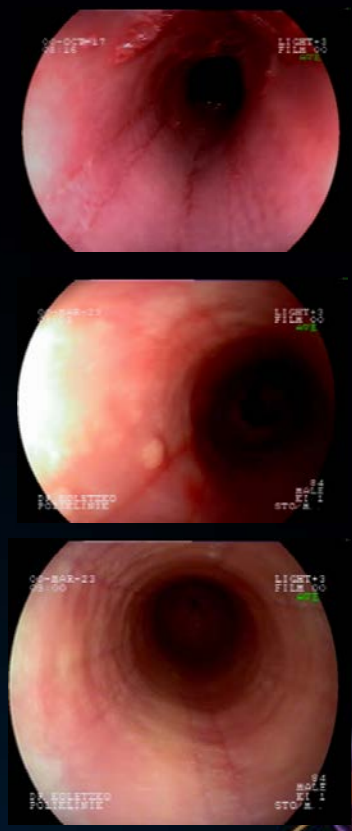
- Need for sedation or anesthesia
- Poor correlation between endoscopic appearance and histopathology
- Relationship between esophagitis and extraesophageal symptoms is not clear
- Cost?

Vandenplas et al. *J Pediatr Gastroenterol Nutr.* 2009;49:498-547.

Advantages and Disadvantages of Histology

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

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



Vandenplas et al. *J Pediatr Gastroenterol Nutr.* 2009;49:498-547.
Sherman et al. *Am J Gastroenterol.* 2009;104:1278-95.

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*

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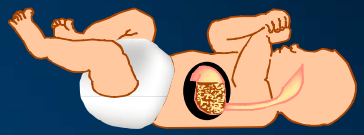
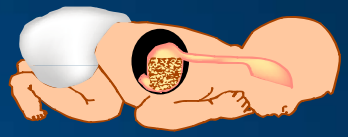
Positioning Therapy for Infants

Sitting



Supine



Prone

- 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

Jeske et al. *Anest Analg.* 2005;101:597-600.
Skadberg et al. *J Pediatr.* 1998;132:340-3.

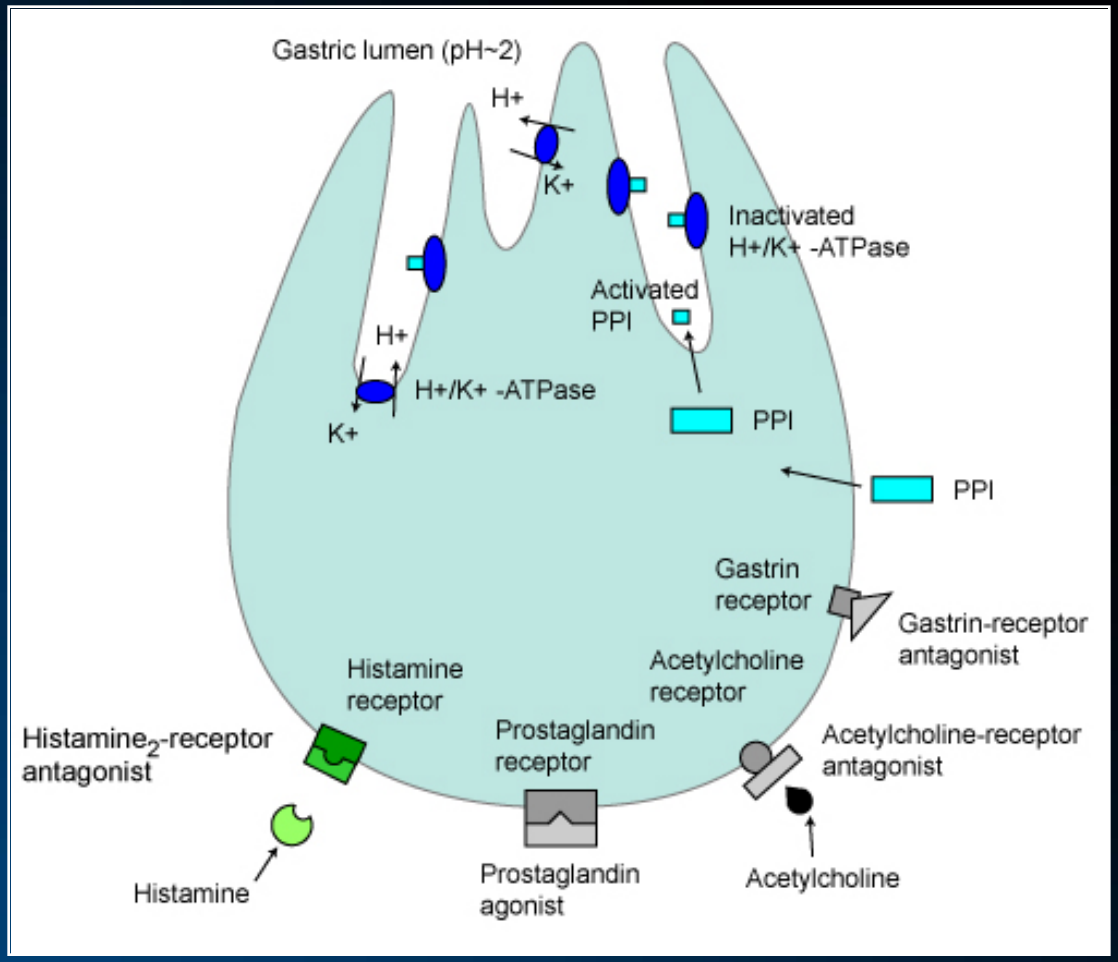
Goals of Pharmacotherapy

- 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.
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Available H_2RAs and PPIs

H_2 Receptor Antagonists
Cimetidine
Famotidine
Nizatidine
Ranitidine

For the most current treatment dosage information please consult the respective product information

Proton Pump Inhibitors
Dexlansoprazole
Esomeprazole
Lansoprazole
Omeprazole
Pantoprazole
Rabeprazole
Zegerid

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]

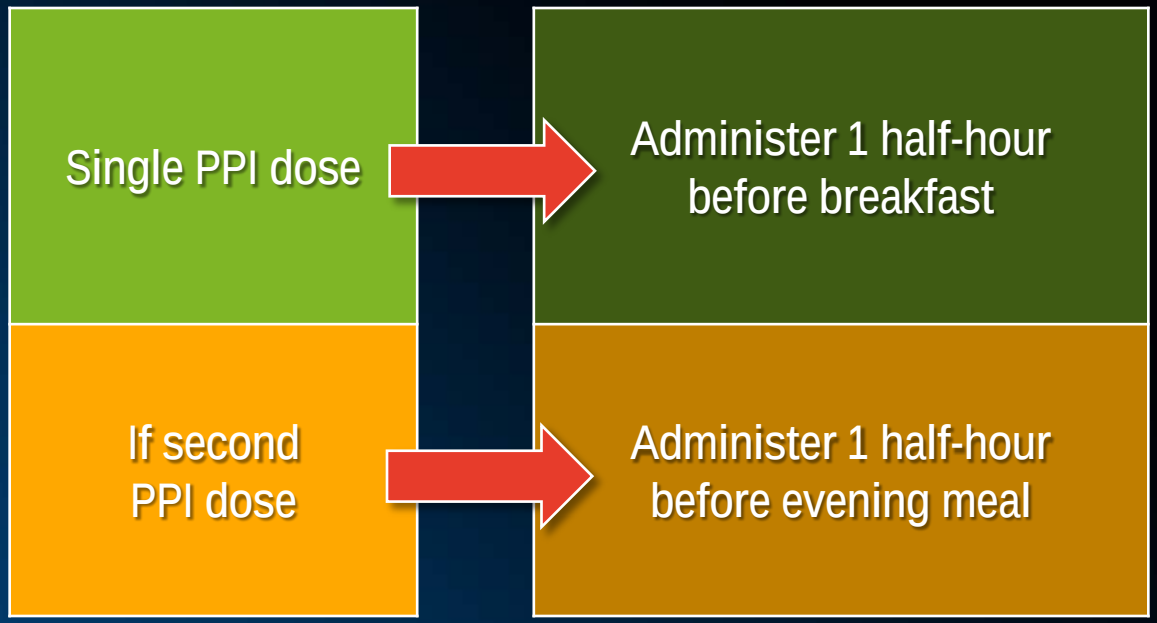
Vandenplas et al. *J Pediatr Gastroenterol Nutr.* 2009;49:498-547.

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

Vandenplas et al. *J Pediatr Gastroenterol Nutr.* 2009;49:498-547.

Optimal Timing of PPI Dose



Katz et al. *Gastrointest Surg.* 2010;14 Suppl 1:S62-6.
Chey et al. *Am J Gastroenterol.* 2005 Jun;100(6):1237-42.

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

Vandenplas et al. *J Pediatr Gastroenterol Nutr.* 2009;49:498-547.

Esophagitis - Management

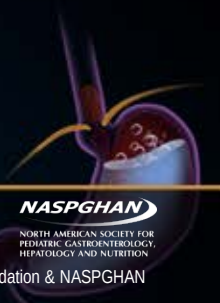
- A PPI for 3 months is recommended as initial therapy
- Increase the PPI dose at 4 weeks if symptom control is not adequate
- In most cases efficacy can be monitored by extent of symptom relief without routine endoscopic follow-up

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

Vandenplas et al. *J Pediatr Gastroenterol Nutr.* 2009;49:498-547.

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



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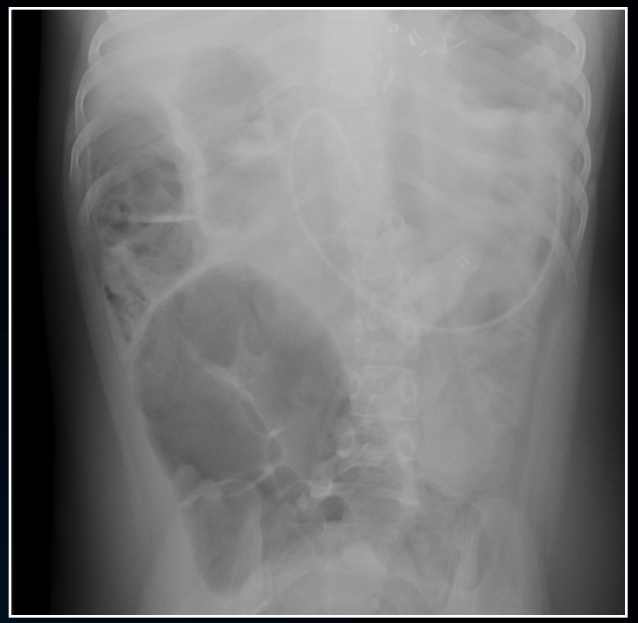
Management with Transpyloric Feeds

- 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



Rosen et al. *J Pediatr Gastroenterol Nutr.* 2011;52(5):532-5.
Mousa et al. *J Pediatr Gastroenterol Nutr.* 2011;52(2):129-139.
Malcolm. *J Perinatol.* 2009;29(5):372-5.
Srivastava. *Pediatrics.* 2009;123(1):338-45.

Summary: Medical Management

- H_2RAs produce relief of symptoms and mucosal healing.
- PPIs are superior to H_2RAs in relieving symptoms and healing esophagitis
- There is insufficient support to justify the routine use of motility agents (metoclopramide, erthromycin, 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.

Vandenplas et al. *J Pediatr Gastroenterol Nutr.* 2009;49:498-547.

Management

Surgical Therapy

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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

Kane et al. *J Pediatr Surg.* 2009;44(5):1034-40.
Kane . *Minerva Chir.* 2009;64(2):147-57.

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

Lobe. *Surg Endosc.* 2007;21(2):167-74.
Vandenplas et al. *J Pediatr Gastroenterol Nutr.* 2002;35(2):119-36.

SUMMARY

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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

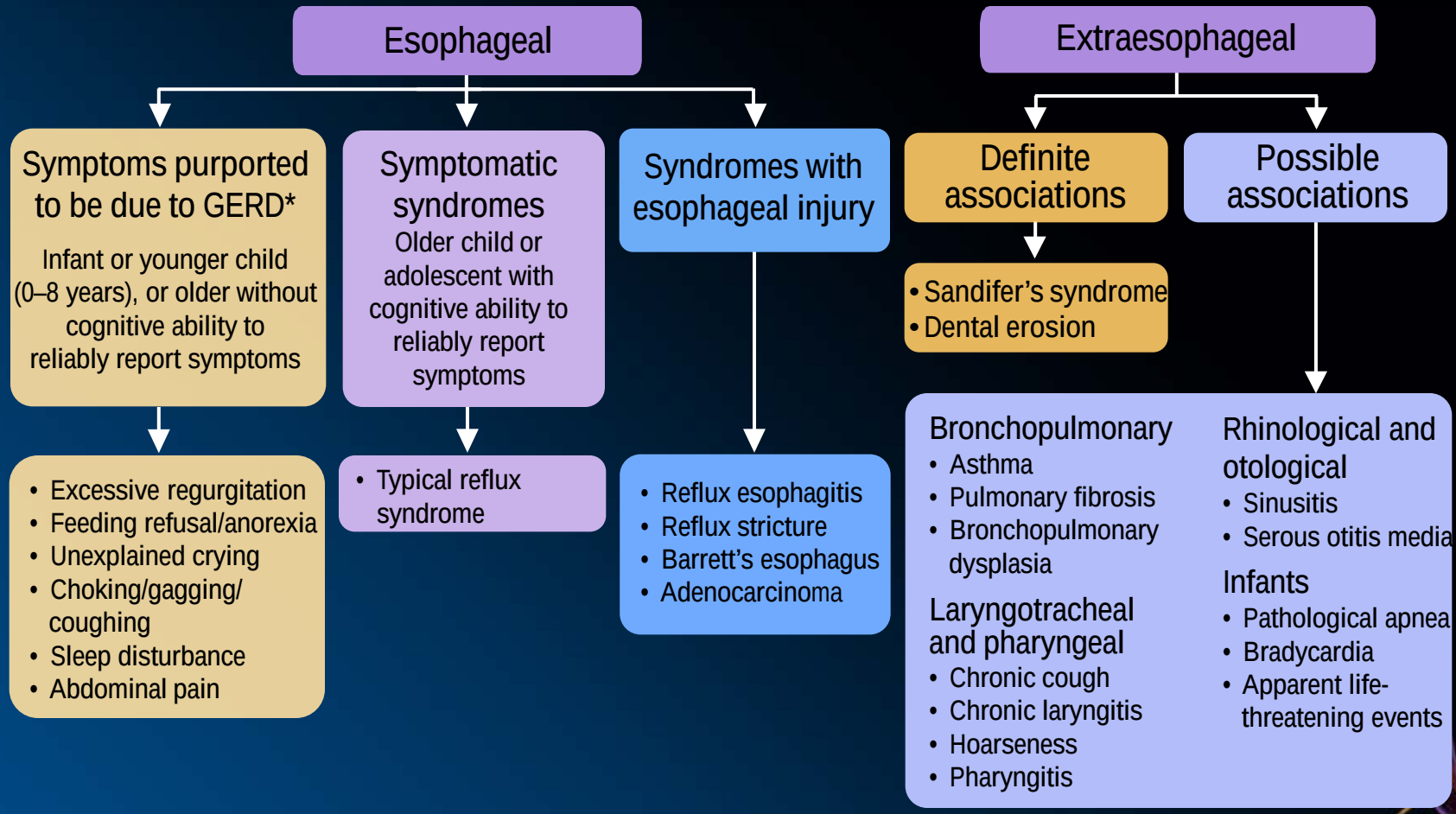
- More research is needed to address optimal methods for the diagnosis and, more importantly, the treatment of GERD in otherwise healthy infant populations
  - The role of PPIs in the treatment of GER in infants is limited
- Current evidence supports use of antisecretory therapy to treat reflux-associated esophagitis in all age groups
- PPIs are superior to H_2RAs 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

NASPGHAN FOUNDATION
For Children's Digestive Health & Nutrition

NASPGHAN
NORTH AMERICAN SOCIETY FOR PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

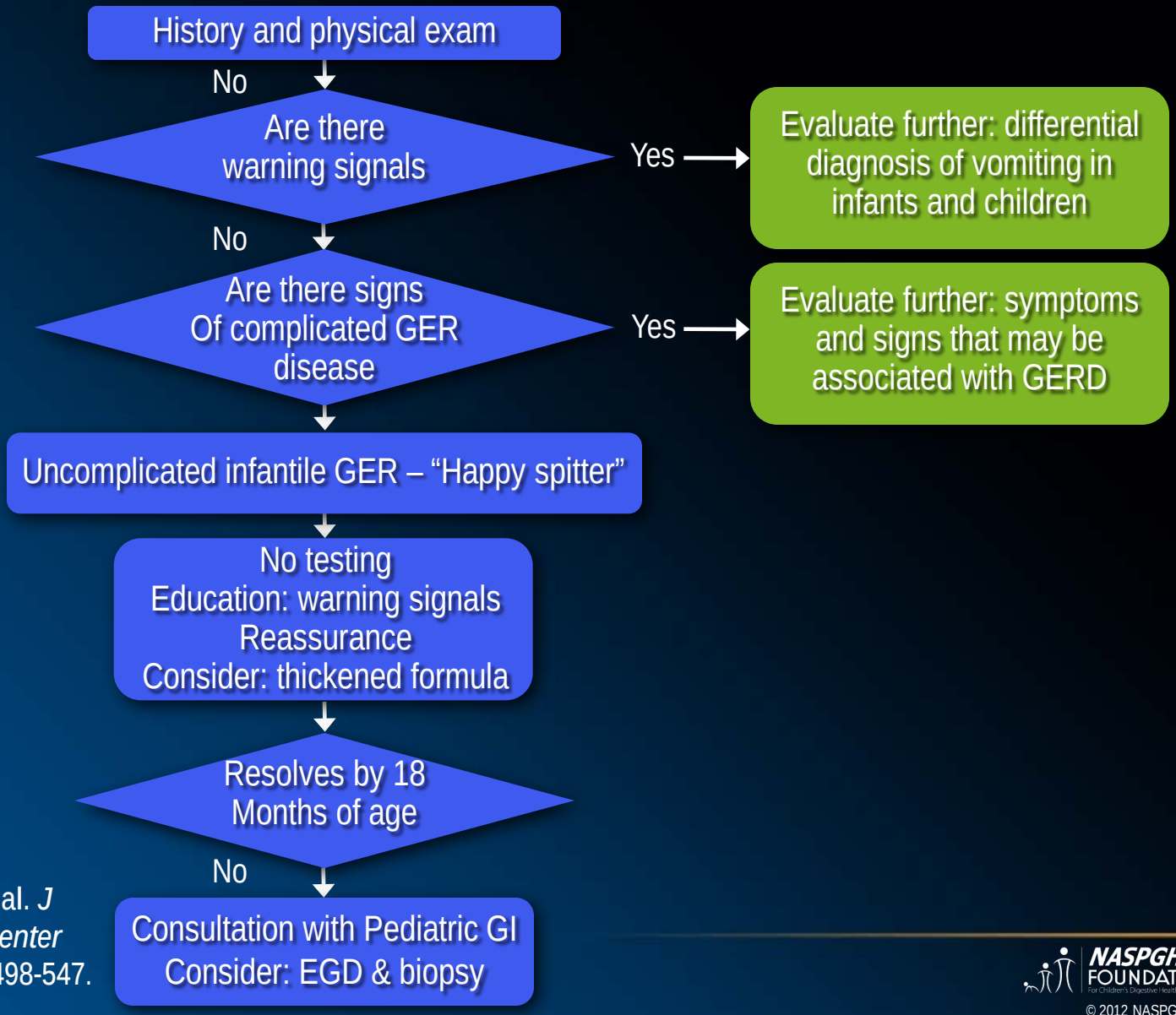
Esophageal Manifestations of GERD: Global Consensus Definitions



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

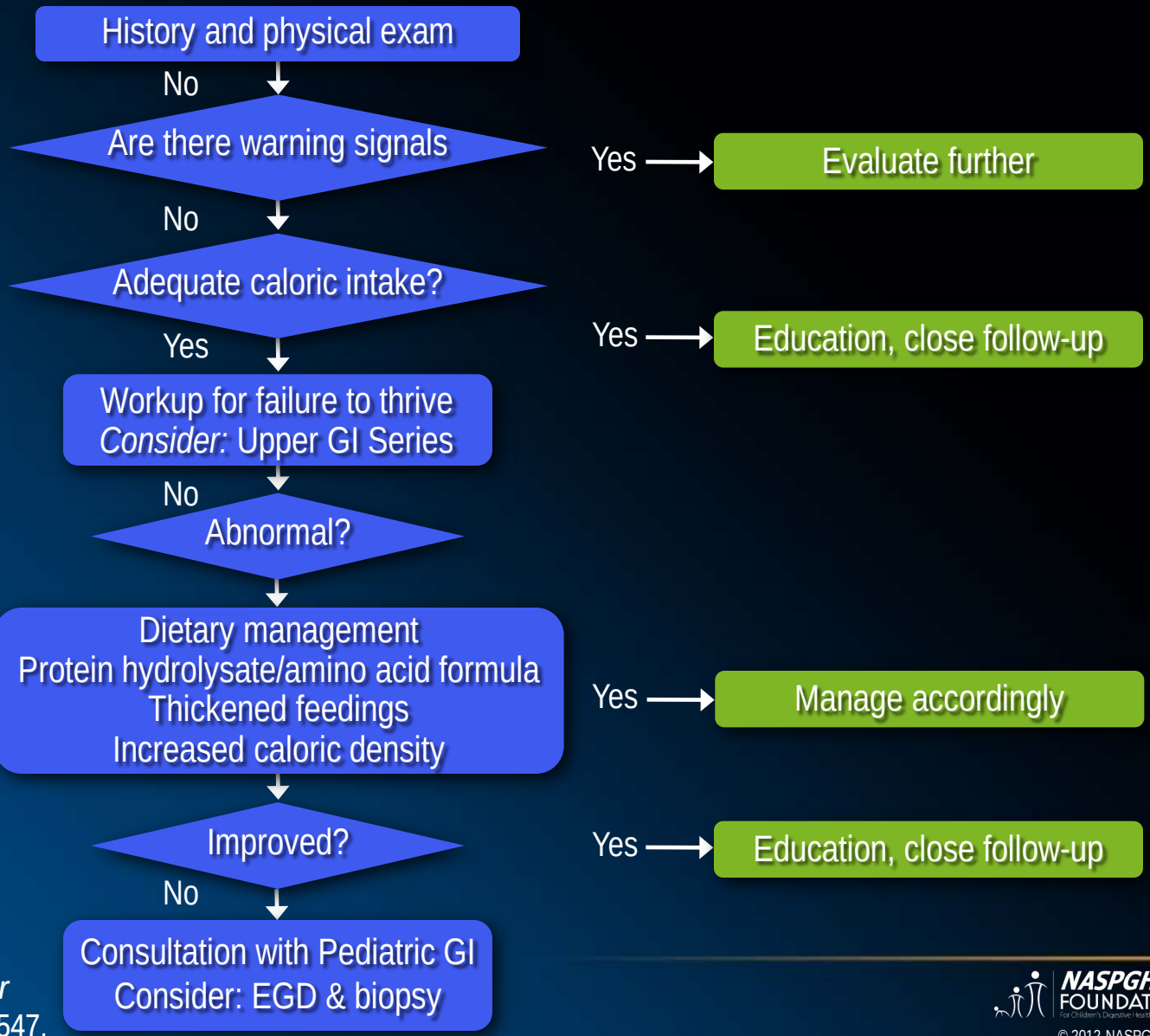
Sherman *et al. Am J Gastroenterol* 2009;104:1278-95.

Approach to the Infant with Recurrent Regurgitation and Vomiting



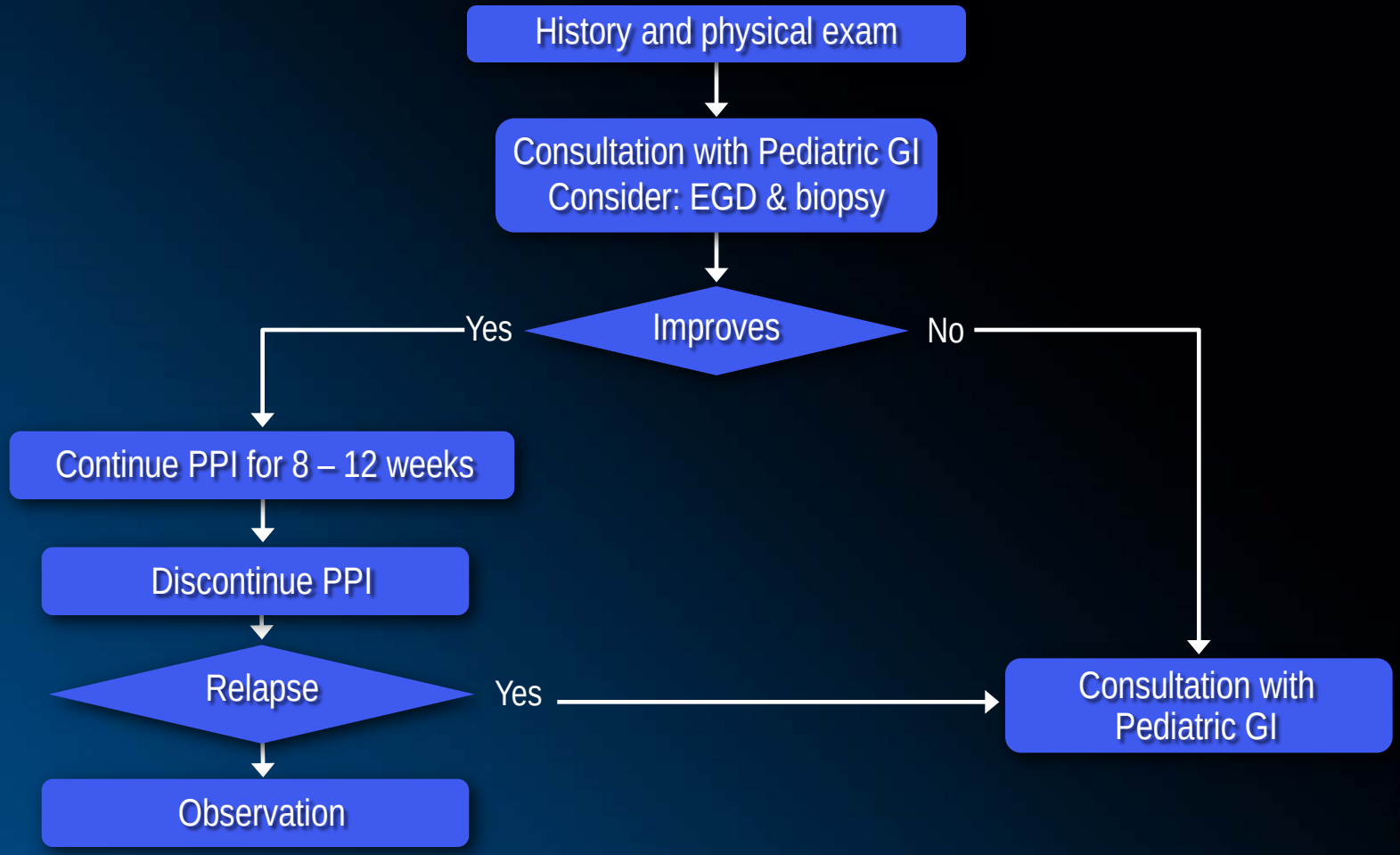
Vandenplas et al. *J Pediatr Gastroenter Nutr.* 2009;49:498-547.

Approach to the Infant with Recurrent Regurgitation and Weight Loss



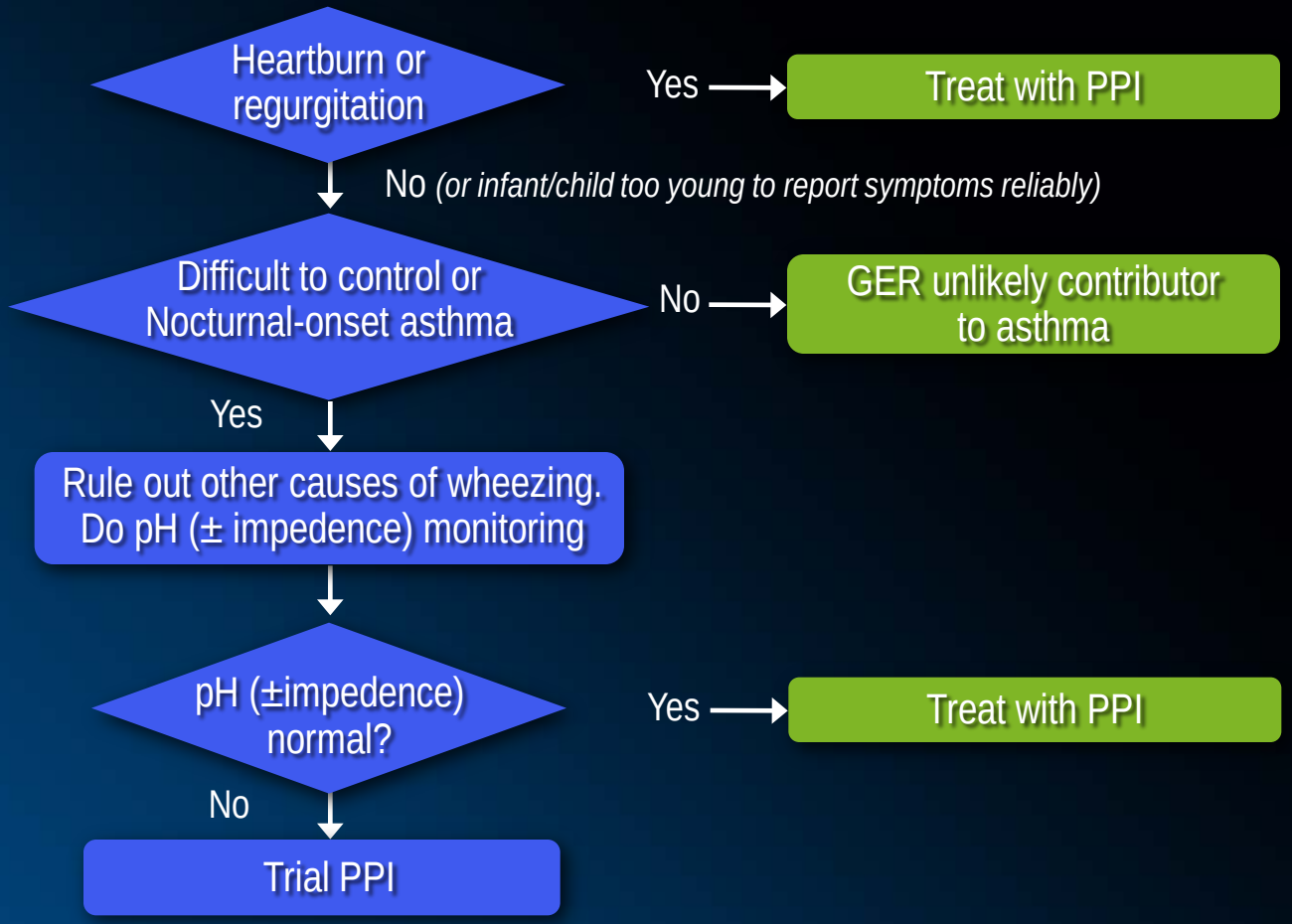
Vandenplas et al. *J Pediatr Gastroenter Nutr.* 2009;49:498-547.

Approach to the Older Child or Adolescent with Heartburn



Vandenplas et al. *J Pediatr Gastroenterol Nutr.* 2009;49:498-547.

Approach to the Child with Persistent Asthma



Vandenplas et al. *J Pediatr Gastroenter Nutr.* 2009;49:498-547.