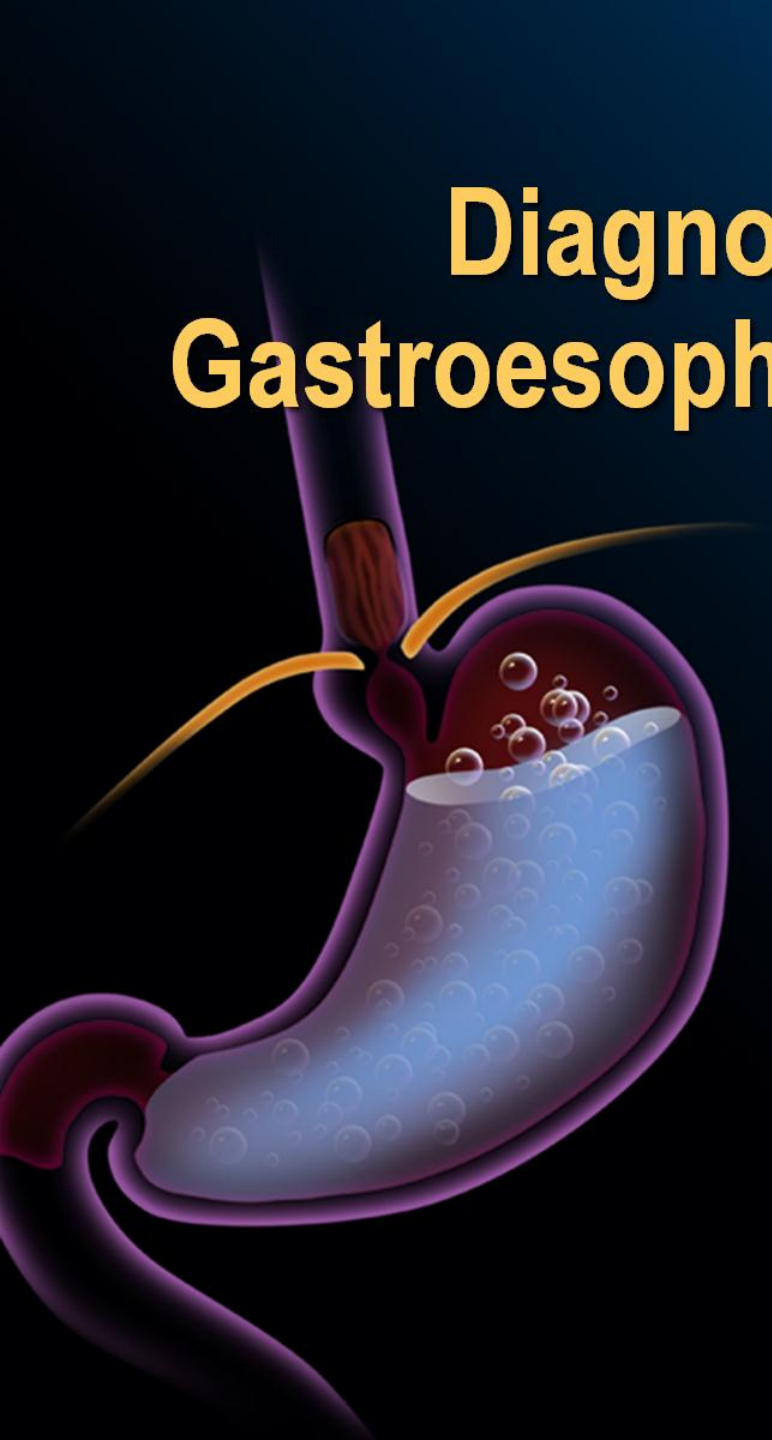
Diagnosis & Management of Gastroesophageal Reflux Disease in Pediatric Patients



NASPGHAN FOUNDATION
For Children's Digestive Health & Nutrition

NASPGHAN
NORTH AMERICAN SOCIETY FOR PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

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

Disclosure Slide

- Support for the Grand Rounds Series was provided by AstraZeneca and Takeda North America Pharmaceuticals, Inc.
- Support for the NASPGHAN FOUNDATION & NASPGHAN GERD Slide Set was provided by Takeda North America Pharmaceuticals, Inc.
- 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
- Extraesophageal
  - Recurrent Pneumonia
  - Apnea/ALTE
  - Asthma
  - Laryngeal
- Management Algorithms
- Summary

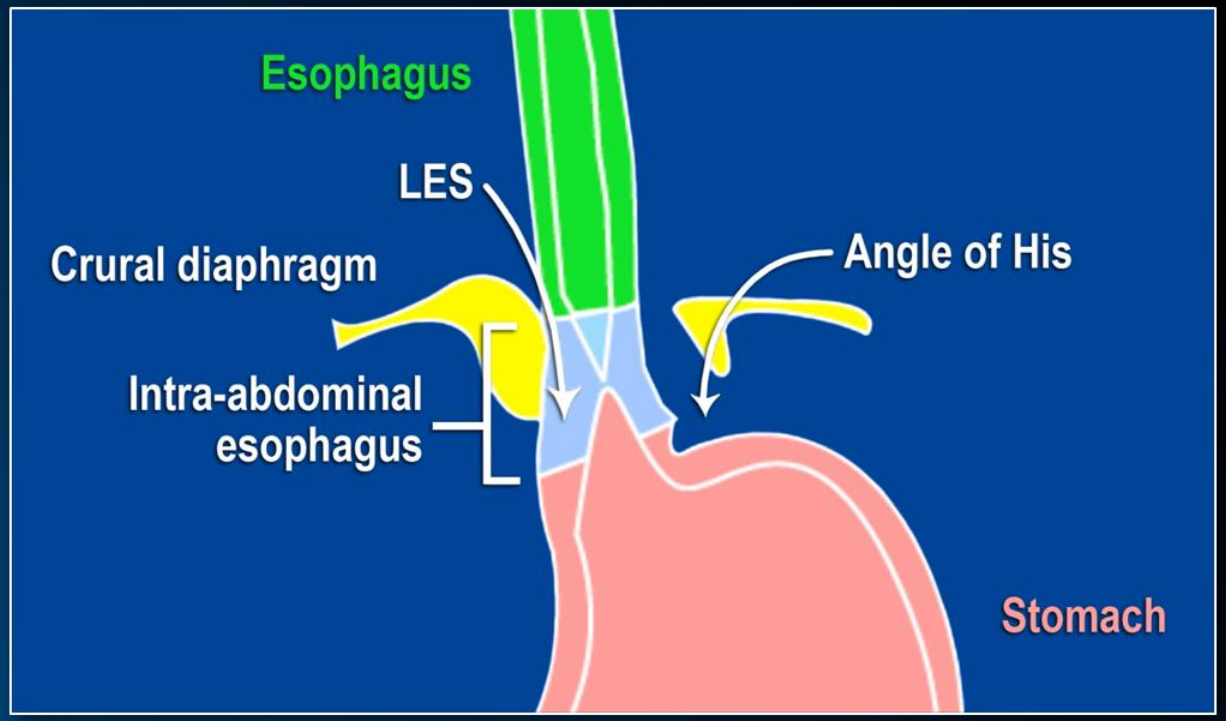
PHYSIOLOGY & NATURAL HISTORY

NASPGHAN FOUNDATION
For Children's Digestive Health & Nutrition

NASPGHAN
NORTH AMERICAN SOCIETY FOR PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

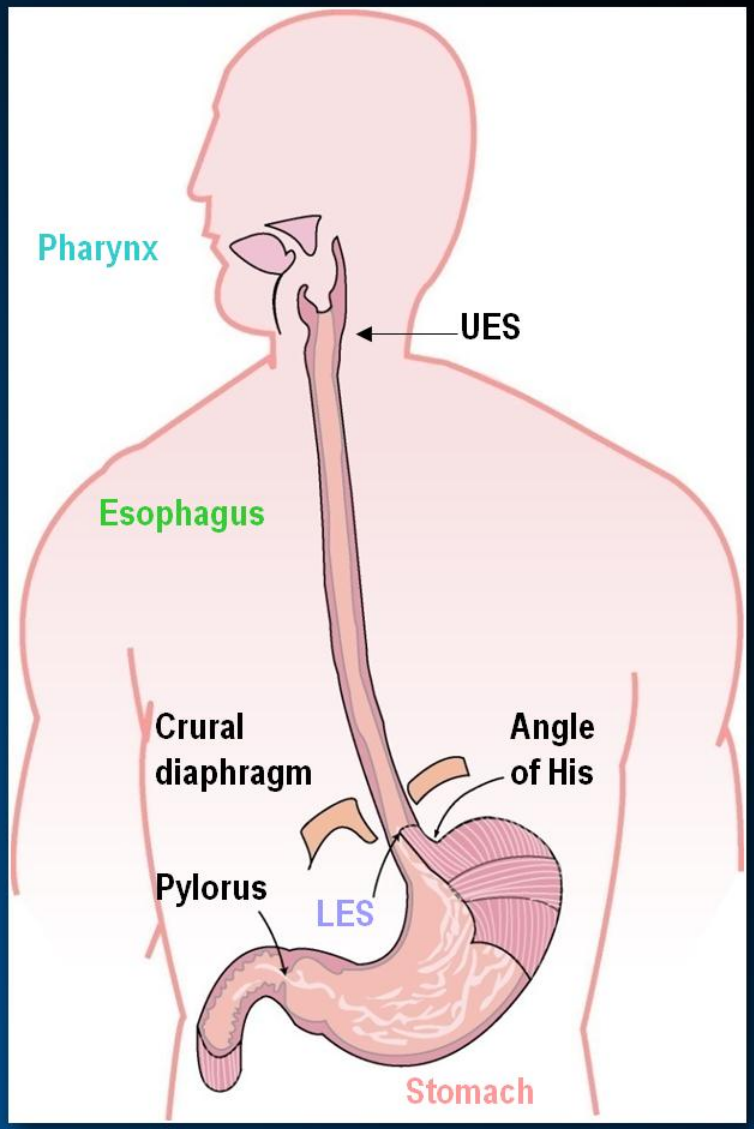
The Antireflux Barrier

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



Mittal et al. *N Engl J Med* 1997;336:924-32.
Bardaji et al. *Pediatr Surg Int* 1986;1:172-6.

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

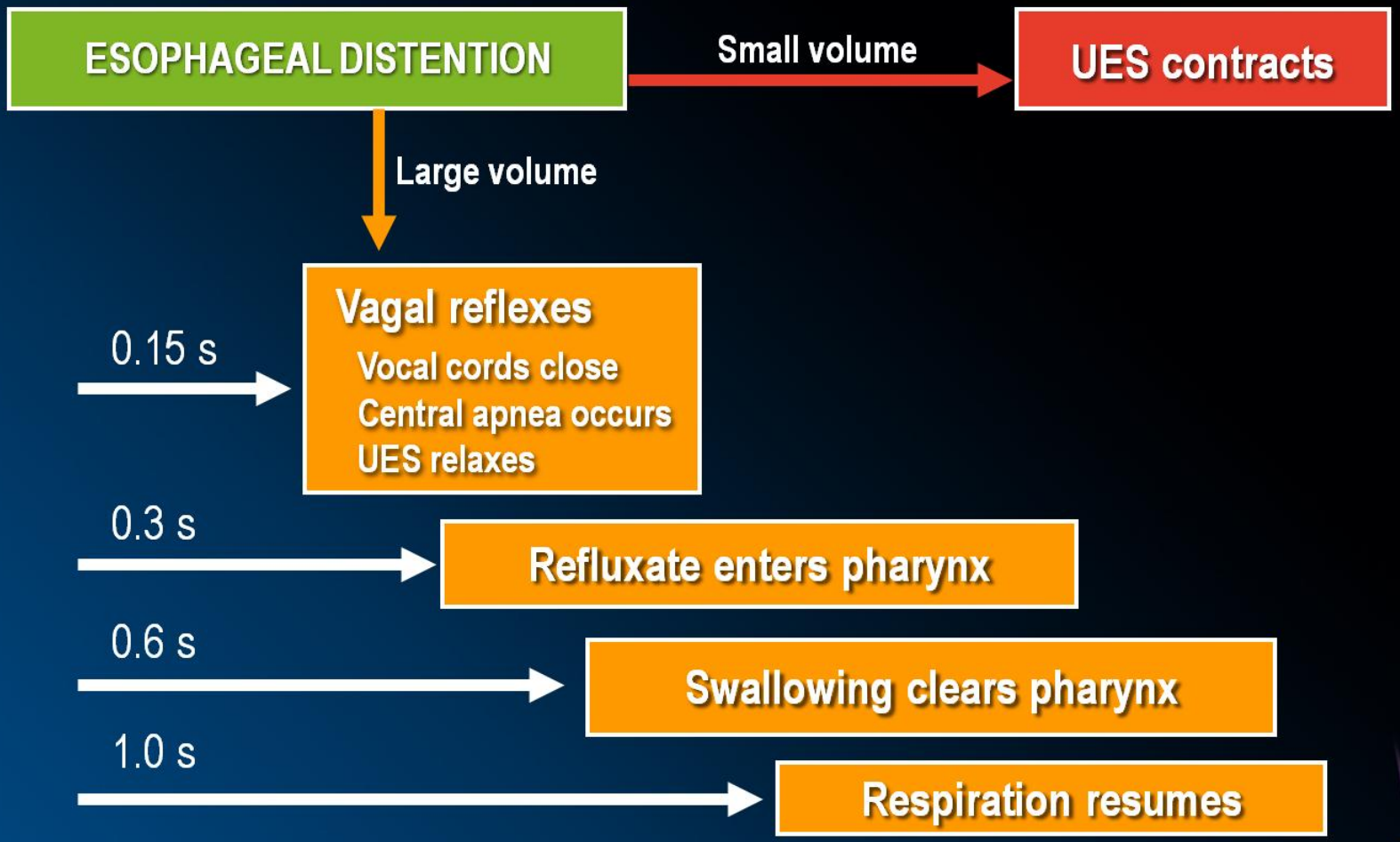
Mechanisms of Esophageal Complications

- Defective tissue resistance
- Noxious composition of refluxate

Mechanisms of Airway Complications (Extra Esophageal Manifestations)

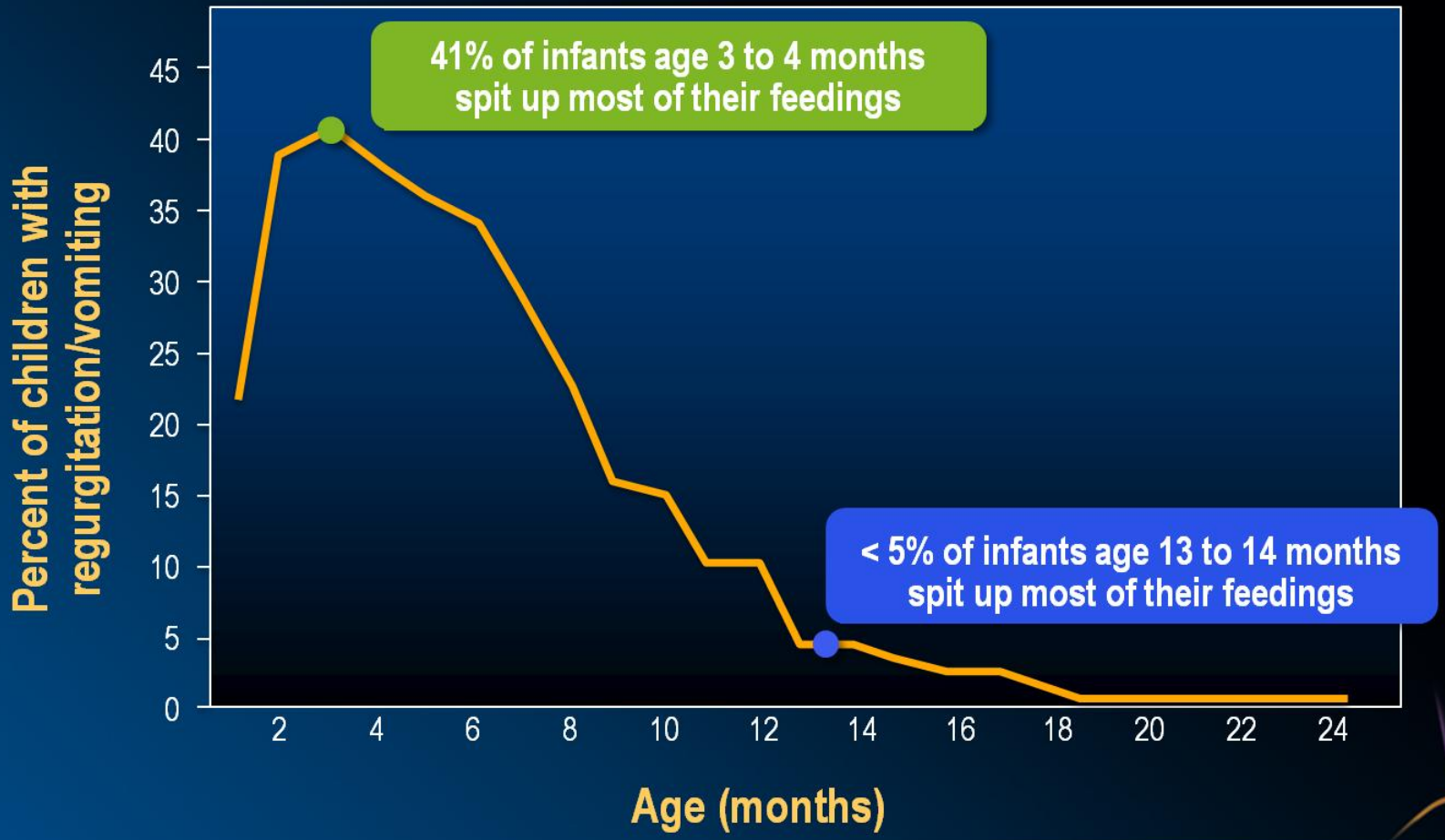
- Vagal reflexes
- Impaired airway protection

Airway Protective Mechanisms



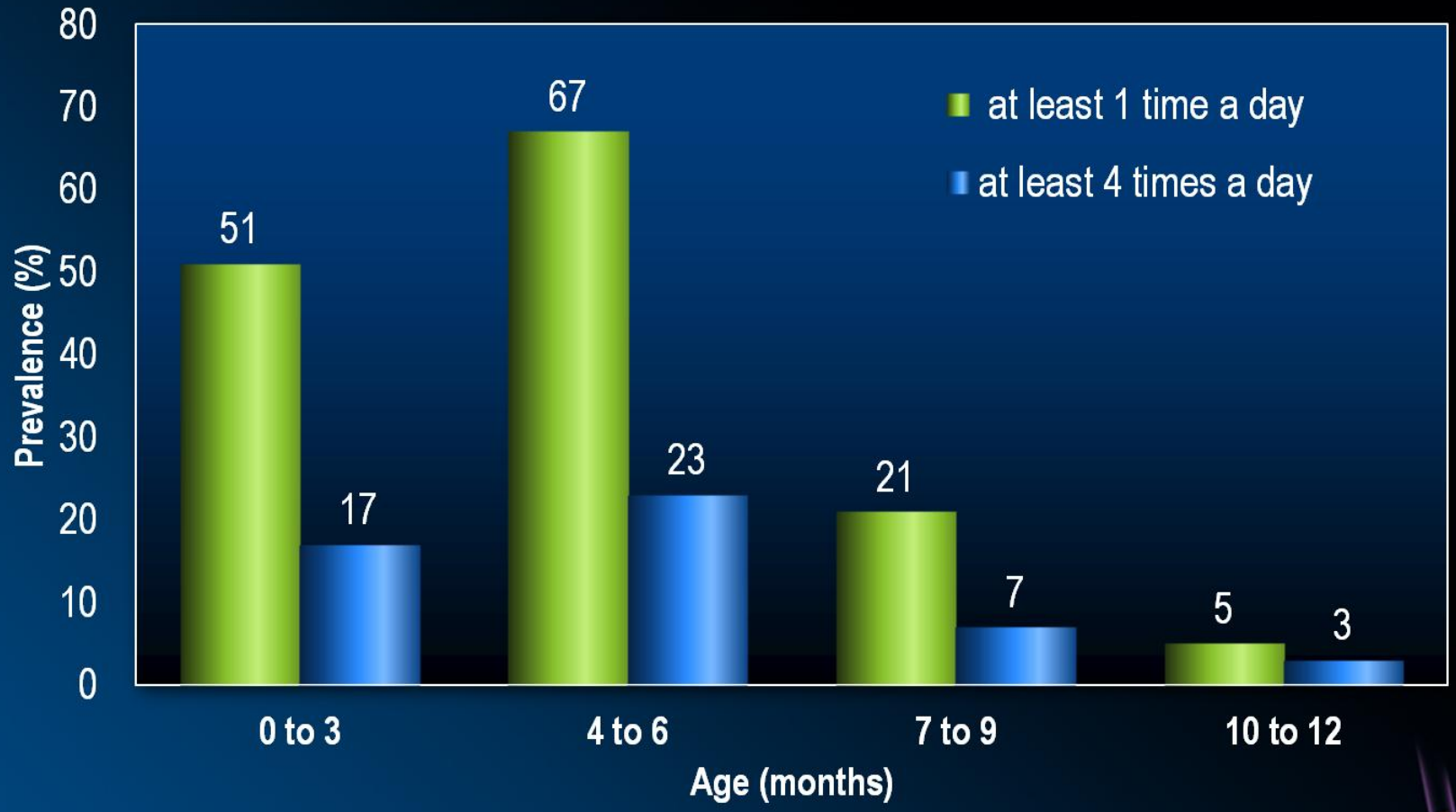
Jadcherla. *Am J Gastroenterol.* 2009;104(10):2572-82.
Jadcherla. *J Pediatr Gastroenterol Nutr.* 2009;48(2):186-92.

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



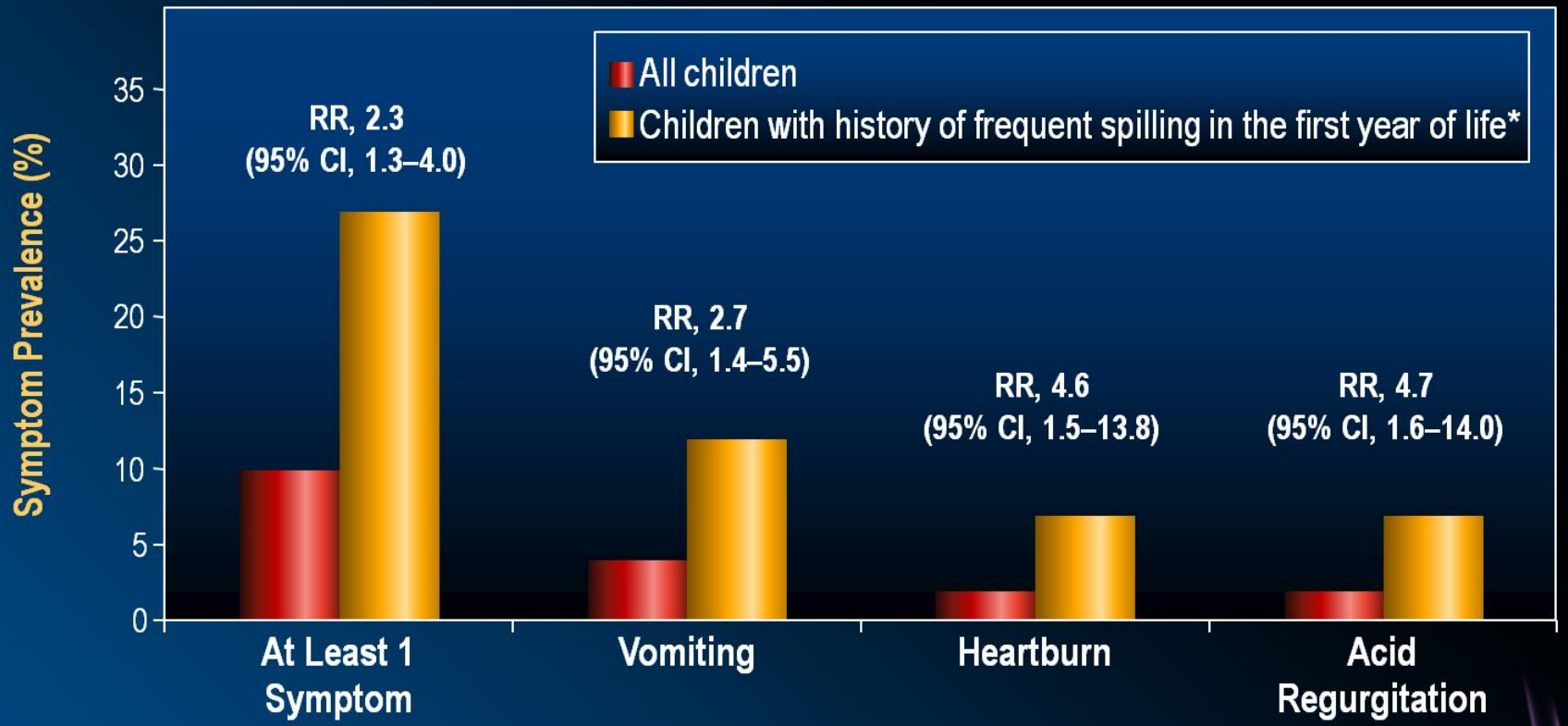
Martin et al. *Pediatrics*. 2002;109:1061–1067.

Prevalence of Regurgitation in Infancy



Nelson et al. *Arch Pediatr Adolesc Med*.1997;151:569-72.

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



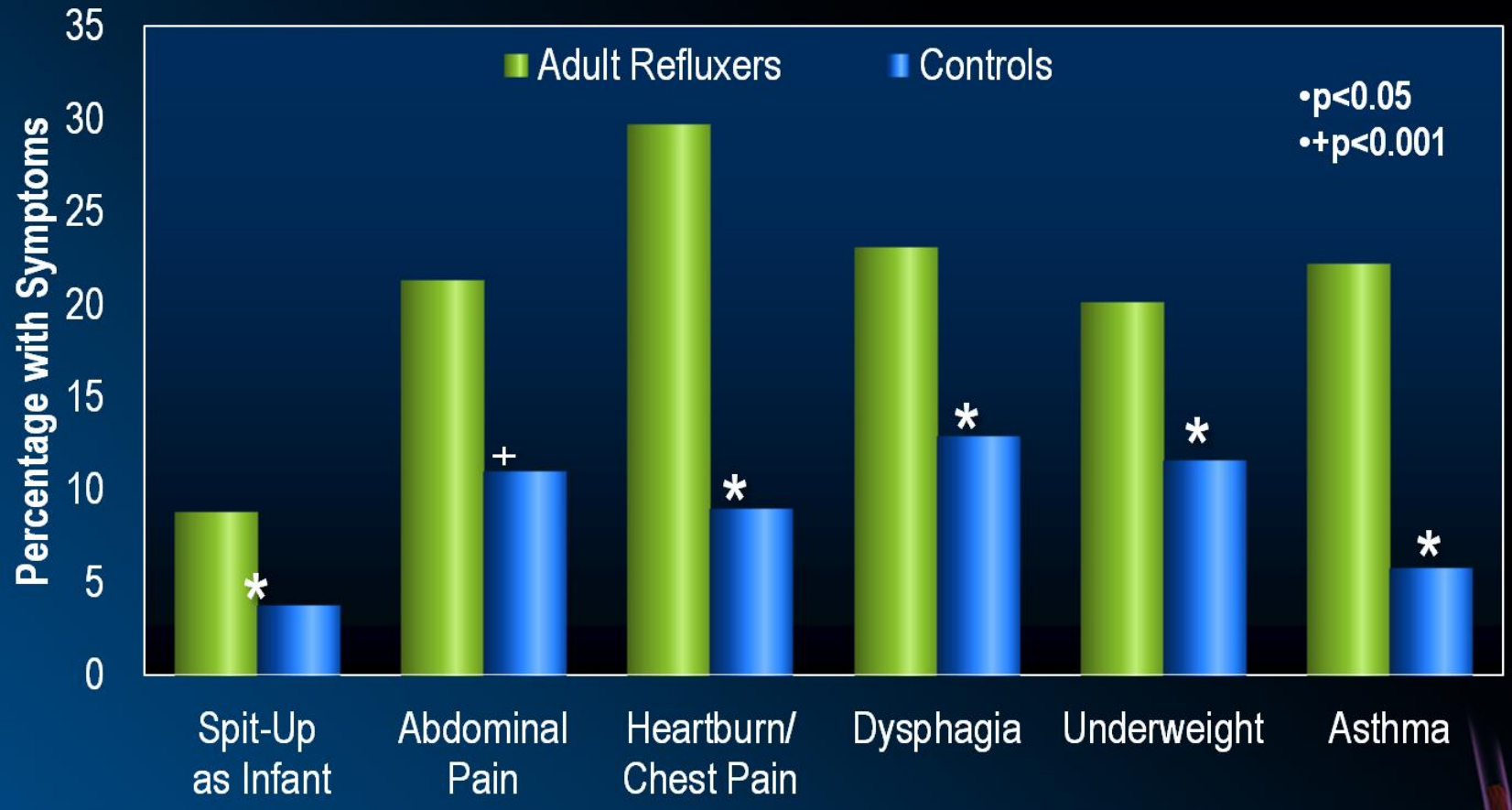
RR, relative risk; CI, confidence interval.

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

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

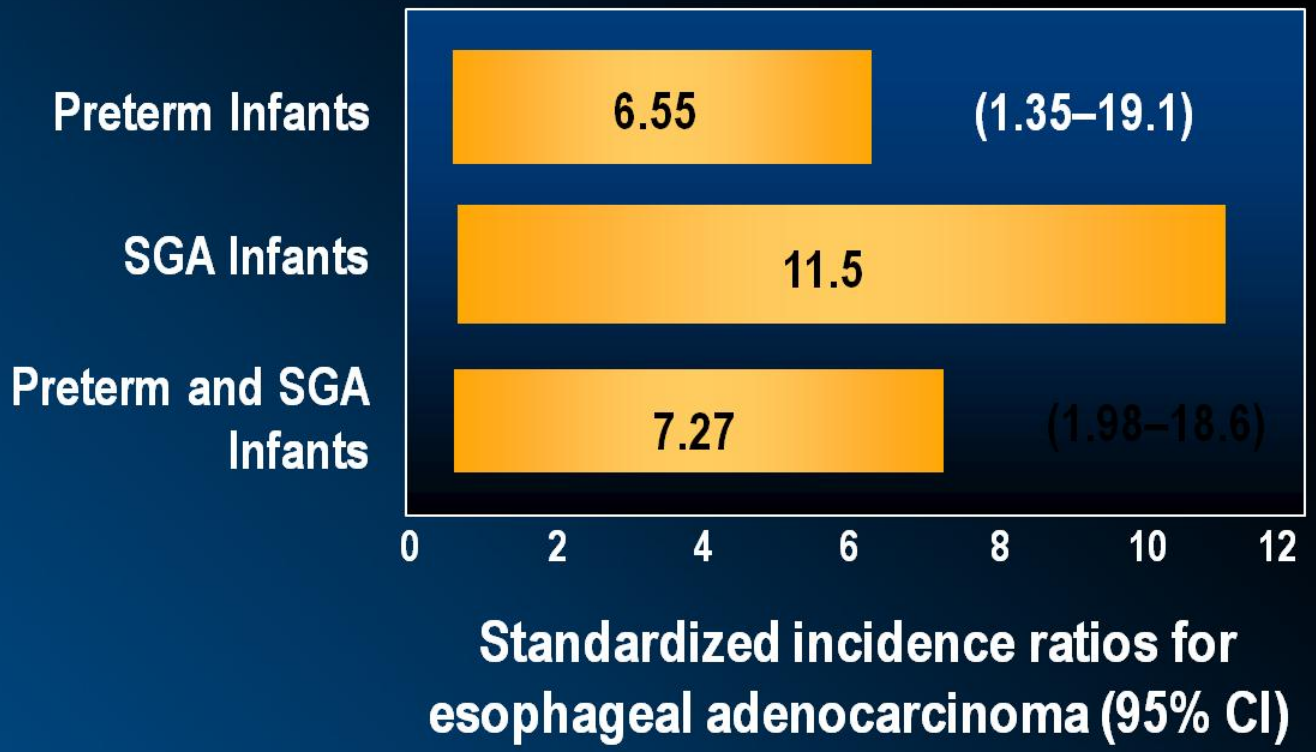
Ruigómez et al. *Scand J Gastroenterol.* 2010;45(2):139-46.

Adults With GERD have Childhood Reflux-Related Symptoms



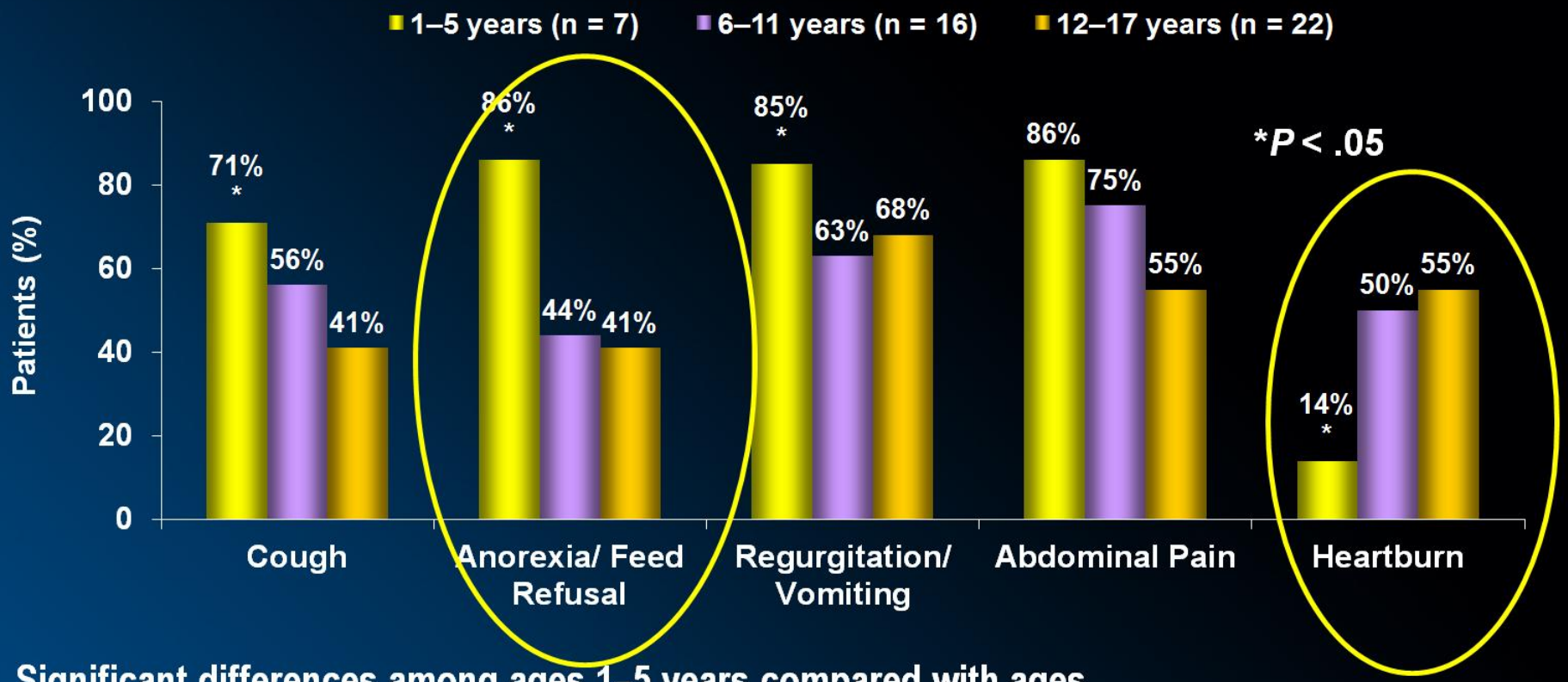
Waring et al. *J Pediatr Gastroenterol Nutr.* 2002;35:334–8.

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



Kaijser et al. *Gastroenterology* 2005;128:607–609.

Relationship Between Presenting Symptoms, Esophagitis Severity, and Patient Age



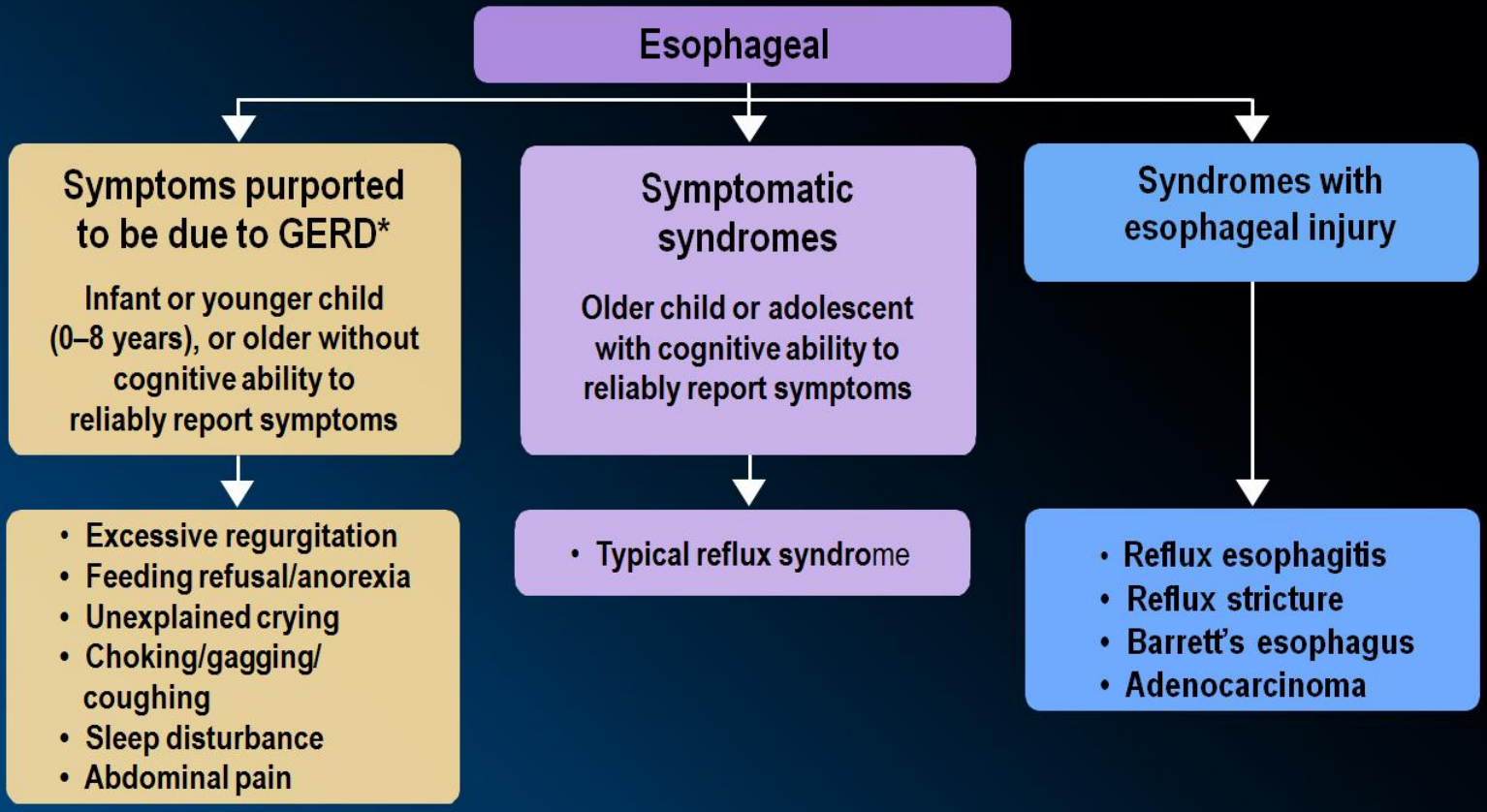
- Significant differences among ages 1–5 years compared with ages 6–17 years with erosive GERD were found to include
  - Greater severity in cough
  - Lesser severity in heartburn
- Greater prevalence and severity in anorexia/feed refusal
- Greater severity in regurgitation/vomiting

Gupta et al. *Dig Dis Sci*. 2006;51:858–63.

NASPGHAN FOUNDATION For Children's Digestive Health & Nutrition

NASPGHAN North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

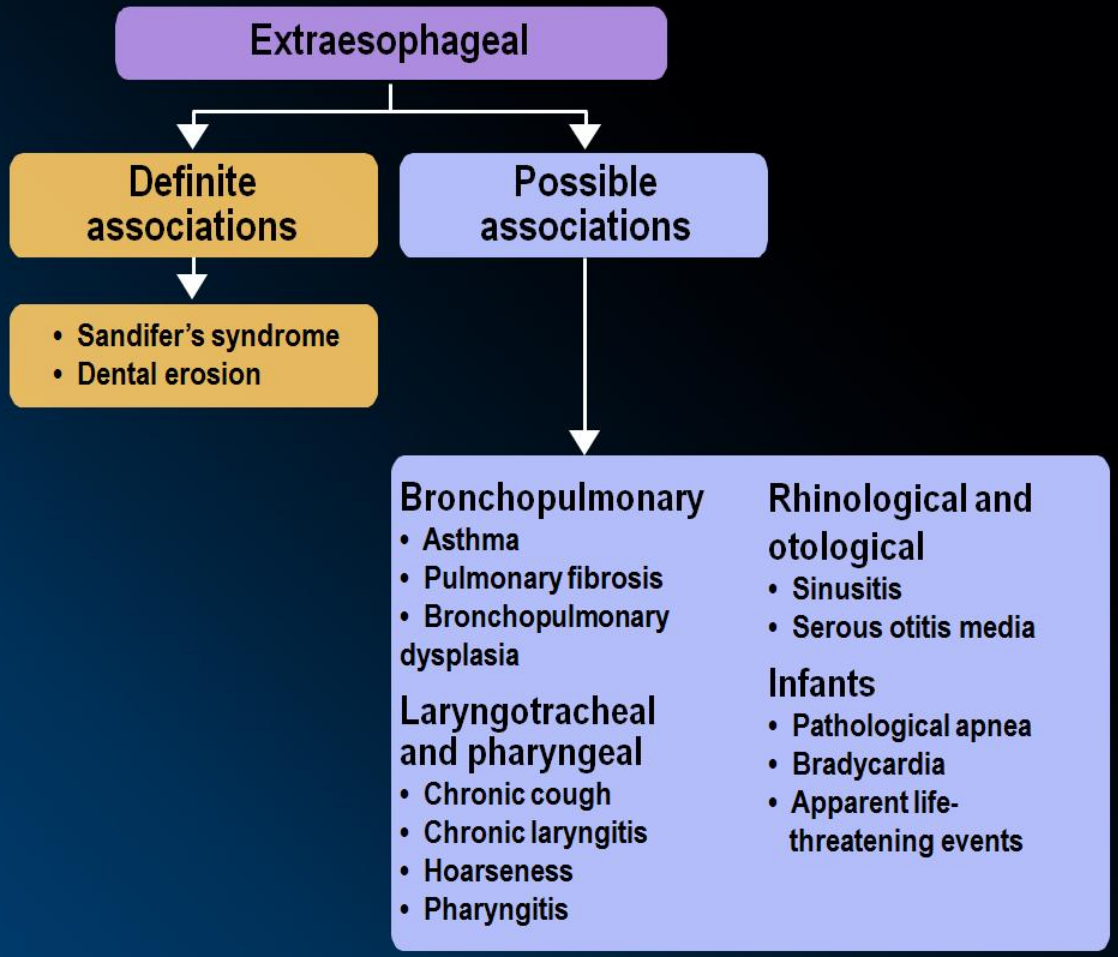
Esophageal Manifestations of GERD: Global Consensus Definitions



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

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

Extraesophageal Associations of GERD: Global Consensus Definitions

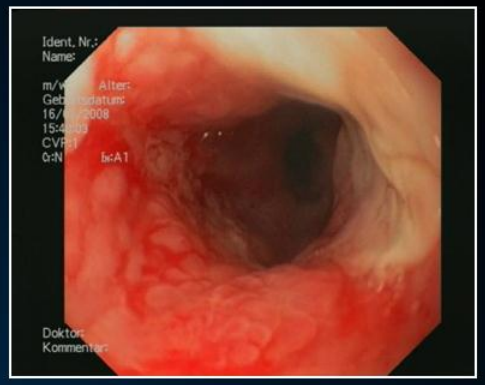


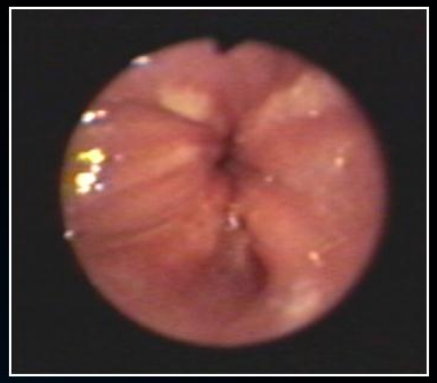
Sherman et al. *Am J Gastroenterol* . 2009;104:1278-95.

Correlation of Symptoms and Injury

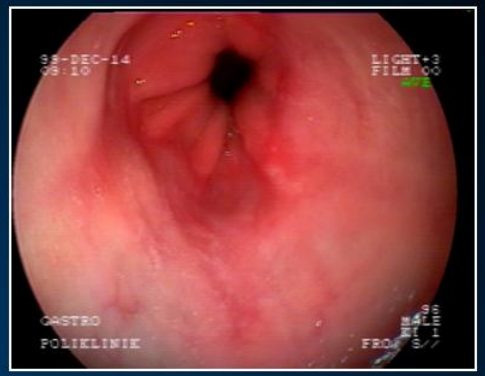
In infants, frequency and severity of symptoms are not reliable to predict the presence or severity of esophagitis.

≠





≠



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.

GERD-Related Complications

Erosive esophagitis

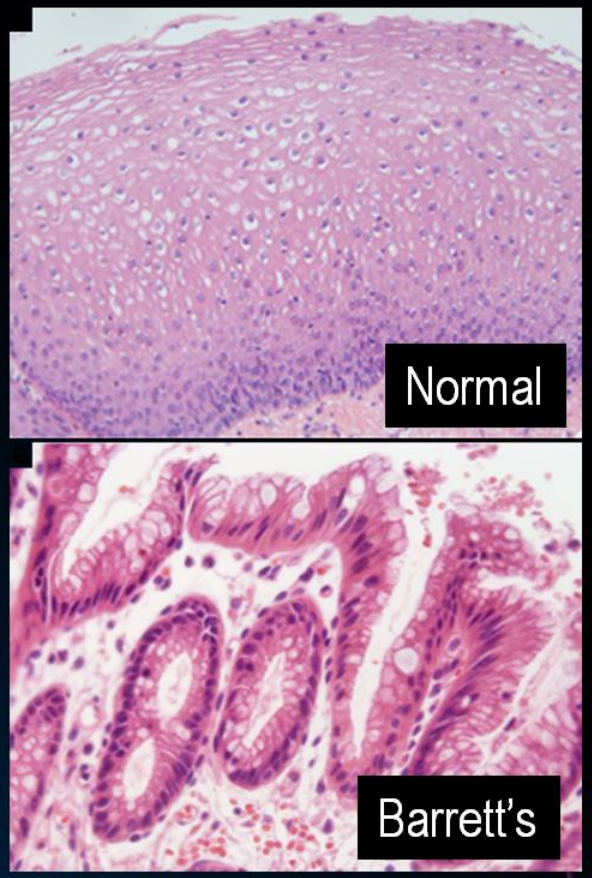
Stricture

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



http://AtlasGeneticsOncology.org/Tumors/BarrettsEsophagID5591.html by permission of the Atlas.

Badreddine et al. *Nat Rev Gastroenterol Hepatol.*2010;7:369–78.

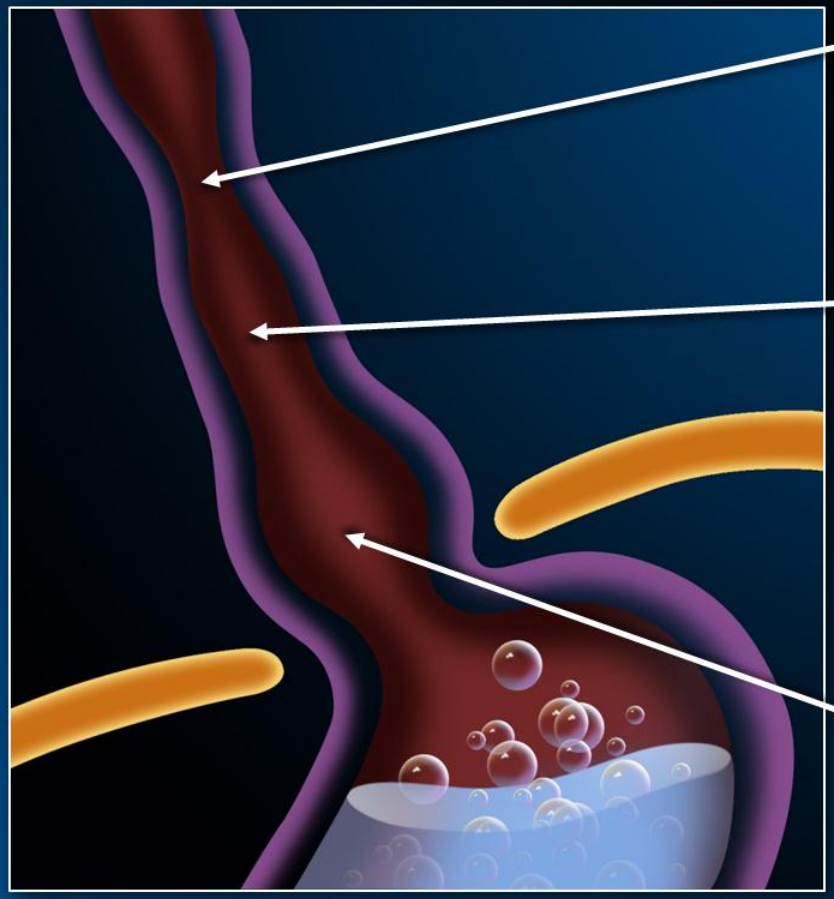
Who is at Risk for Severe GERD?

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

NASPGHAN FOUNDATION
For Children's Digestive Health & Nutrition

NASPGHAN
NORTH AMERICAN SOCIETY FOR PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

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

Symptom	Endoscopic results	
	Normal (n=26)	Abnormal n=19)
Regurgitation/clinical GER [n (%)]	4 (15)	5 (26)
Heartburn [n (%)]	2 (8)	4 (21)
Dysphagia [n (%)]	10 (38)	8 (42)
Odynophagia [n (%)]	1 (4)	0 (0)
Food Impaction [n (%)]	10 (38)	6 (32)
Cough at meals [n (%)]	6 (23)	6 (32)
Asymptomatic [n (%)]	11 (42)	6 (32)

- 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

Castilloux et al. *Can J Gastroenterol*. 2010;24(5): 312-316.

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

Sistonen SJ et al. *Pediatr Surg Int.* 2011 Sep 30. [Epub ahead of print].
Rintala RJ et al. *Pediatr Gastroenterol Nutr.* 2011;52:S35-6.
Sistonen SJ et al. *Pediatr Surg.* 2008;43:602-5.

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

Guarino et al. *Neurogastroenterol Motil.* 2010;22(7): 746-51.
Zhai et al. *J Clin Oncol,* 2010;28(14): 2445-51.
Stein et al. *Nat Rev Gastroenterol Hepatol.* 2010;7(1):8-10.
Schramm et al. *Eur J Med Genet.* 2011;54(1):9-13.

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 n 1.5% of boys and 1.8% of girls

Age (years)	Odds Ratio (95% CI) for those moderately obese	Odds Ratio (95% CI) for those severely obese
6-11	1.16 (1.02-1.32)	1.32 (1.13-1.56)
12-19	1.16 (1.07-1.25)	1.40 (1.28-1.52)

- 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

Koebnick et al. *Int J Pediatr Obes.* 2011;6(2-1):E257-63.

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

Koletzko et al. *J Pediatr Gastroenterol Nutr.* 2011;53(2):230-243.
Jones et al. *Can J Gastroenterol.* 2005:19 (7);399-408.

DIAGNOSIS

- *Differential Diagnosis*
- *Symptoms And Signs Associated With GERD*
- *Testing*

NASPGHAN FOUNDATION
For Children's Digestive Health & Nutrition

NASPGHAN
NORTH AMERICAN SOCIETY FOR PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

Differential Diagnosis of Vomiting in Infants & Children

Metabolic / Endocrine	Toxic
Renal	Cardiac
Neurologic	Allergic
Gastrointestinal Obstruction	Gastrointestinal disorders
Infectious	Others

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.

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.

Symptoms & Signs that May Be Associated with GERD

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

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

History in a Child with Suspected GERD

Feeding & Dietary History
Amount and frequency (overfeeding)
Preparation of formula
Recent changes in feeding type or technique
Positioning during feeding
Burping
Behavior during feeding (choking, gagging, cough, arching, discomfort, refusal)
Food impactions
Intolerance to types of formulas or food

Pattern of Vomiting
Frequency and amount
Pain
Forceful
Blood or bile
Associated fever, lethargy, diarrhea
Digested vs. undigested food
Sleep history, nocturnal symptoms

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

Review of Systems and Past History

Medical History	
Prematurity	Eczema, diarrhea
Growth and development	Dental erosions
Past surgery, hospitalizations	Previous weight gain
Newborn screen results	Symptoms of hoarseness, fussiness, hiccups
Recurrent illnesses, especially croup, pneumonia, asthma, otitis media, sinusitis	Celiac disease
Thyroid disease	Other chronic condition
Cough	

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

Other Important Factors in a Child with Suspected GERD

Family Medical History
Esophageal Dilations
Esophageal cancer/Barrett's
Food allergies including hypoallergenic formulas
Esophageal surgeries
Thyroid disease
Celiac disease
Functional dyspepsia

Medications
Current and past
Use of OTC antacids, H_2RAs and PPIs
Medications affecting motility (e.g. anticholinergics, opioids, antibiotics, cancer chemotherapy, vincristine)

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

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.

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

Vandenplas et al. *J Pediatr Gastroenterol Nutr.* 2009;49:498-547.
Fortunato et al. *Curr Gastroenterol Rep. 2011*;13(3):293-299.
Srivastava et al. *Pediatr Ann.* 2010;*39(4)*:225-231.
Ruigomez et al. *Scand J Gastroenterol.* 2010;45(2):139-146.

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

Vandenplas et al. *J Pediatr Gastroenterol Nutr.* 2009;49:498-547.
de Veer et al. *BMC Gastroenterol* . 2008;8: 23.

Reflux Manifestations in Neurologically Impaired Populations

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

Pensabene et al. *Brain Dev.* 2008;30(9):563-71.
Luzzani et al. *Am J Med Genet A.* 2003;119A(3):283-7.

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

Olden. *Curr Treat Options Gastroenterol.* 2001;4(4):351-58.
Chial et al. *Pediatrics* 2003;111(1):158-62.

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

NASPGHAN FOUNDATION
For Children's Digestive Health & Nutrition

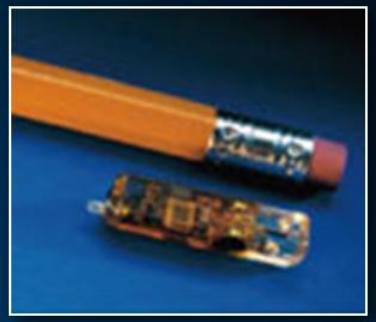
NASPGHAN
NORTH AMERICAN SOCIETY FOR PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

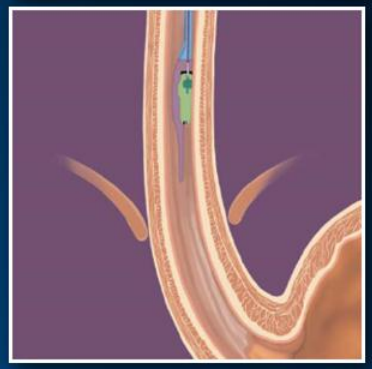
Physiological Reflux in Children and Adults is Distinctly Different by pH metry in Normal Subjects

	Infants *(N=509)*	Children *(N=48)*	Adults *(N=432)*
No. of daily reflux episodes	73	25	45
No. of reflux episodes ≥ 5 min	9.7	6.8	3.2
Reflux index (% of time pH < 4)	11.7%	5.4%	6%

Rudolph et al, *J Pediatr Gastroenterol Nutr* 2001;32:S1

Wireless 24 Hour or Prolonged pH Monitoring





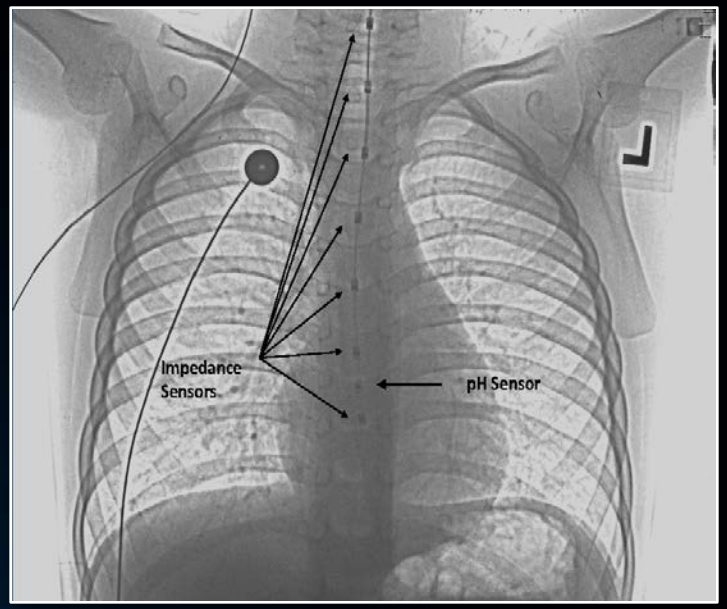
- **Miniature pH capsule (size of gelcap) is attached to esophagus**
  - Capsule measures pH in esophagus and transmits information to a pager-sized receiver worn on belt or waistband
  - Test data is uploaded to a computer and analyzed
- **Advantages**
  - More physiologic because it allows for more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

NASPGHAN FOUNDATION
For Children's Digestive Health & Nutrition

NASPGHAN
NORTH AMERICAN SOCIETY FOR PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

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

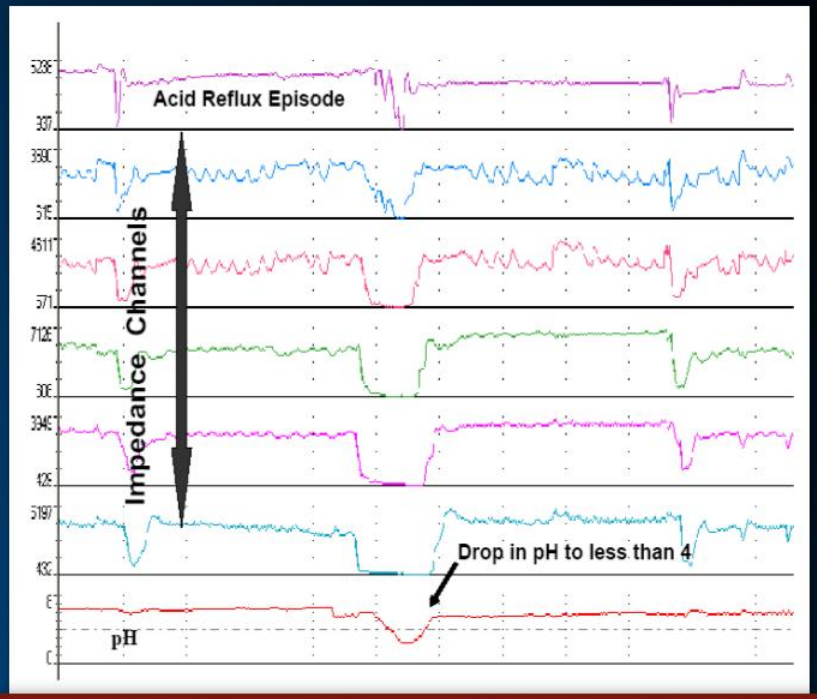


Image from Effects, Diagnosis and Management of Extra-Esophageal Reflux. Editors: Nikki Johnston and Robert J. Toohill. ©2010 Nova Science Publishers, Inc

Advantages

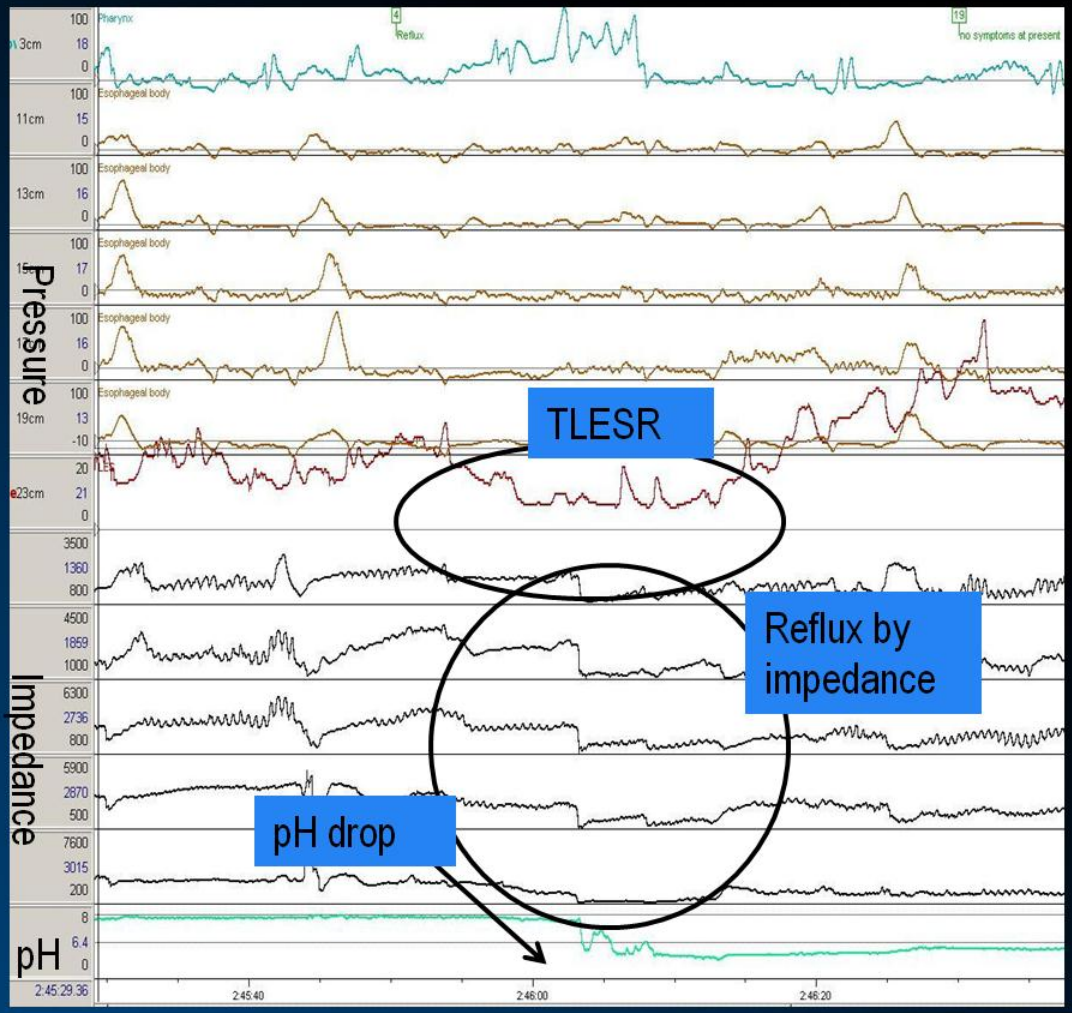
- Detects non-acidic GER episodes which is ideal for post prandial reflux
- Differentiates reflux from swallows
- Able to accurately assess full column reflux
- Sensitivity of pH-MII comparable to the pH probe in untreated patients and surpasses pH probe in treated patients.

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.

Reflux and Transient Lower Esophageal Sphincter Relaxations



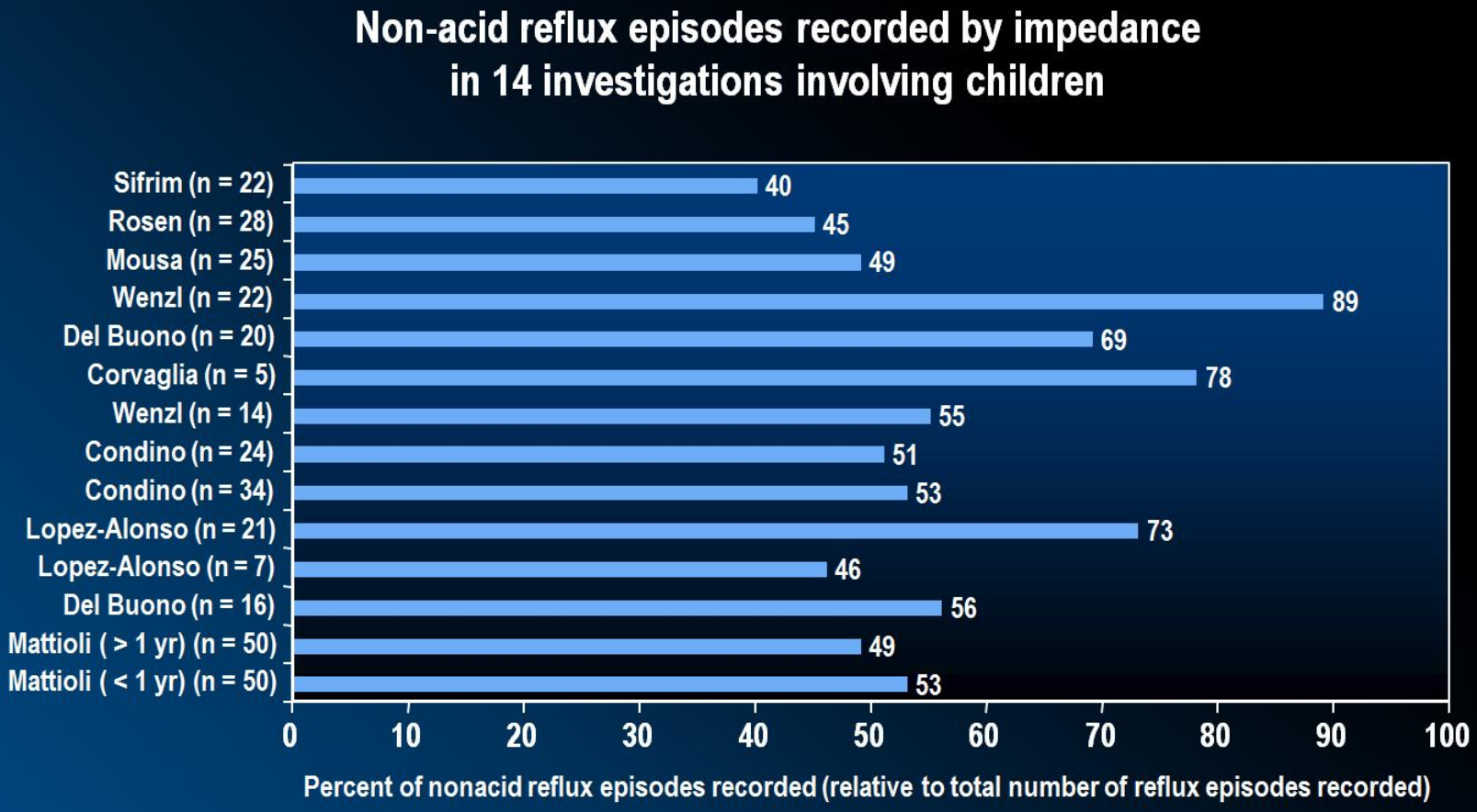
Tracings provided by Center for Motility and Functional Gastrointestinal Disorders, Children's Hospital Boston

Esophageal pH Levels May Determine the Type of Reflux

Acid reflux	Refluxed gastric contents with a pH < 4 that can either reduce the pH within the esophagus to < 4 or occur when intraesophageal pH is already < 4
Weakly acidic reflux	Reflux events that result in an esophageal pH level between 4 and 7
Weakly alkaline reflux (nonacid)	Reflux episodes during which the lowest esophageal pH level does not drop below 7

Sifrim et al. *Gut.* 2004:53:1024-31.

Non-Acid Reflux in Children



Vandenplas et al . *Acta Paediatr.* 2007;96(7):956-62.
Vela et al. *Gastroenterology*. 2001;120(7):1599-606.

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

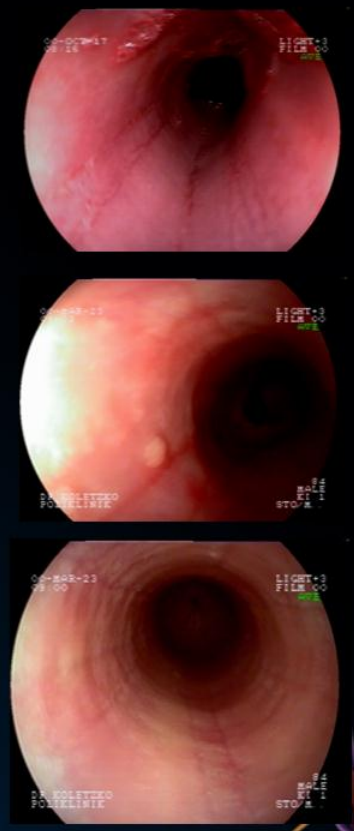
- Need for sedation or anesthesia
- Poor correlation between endoscopic appearance and histopathology
- Relationship between esophagitis and extraesophageal symptoms is not clear
- Cost?

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

Advantages and Disadvantages of Histology

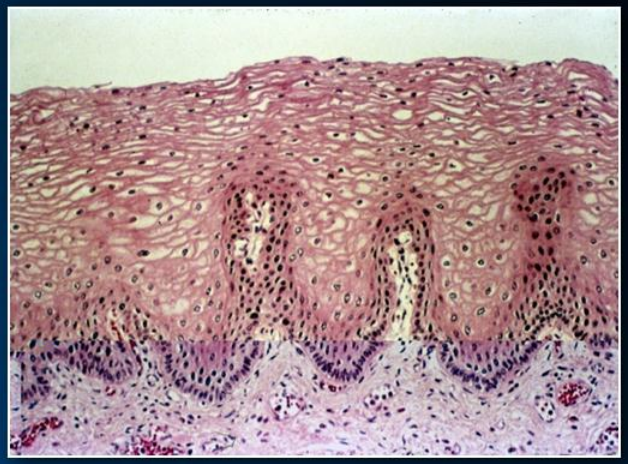
Insufficient Data Exist For Recommending Histology As A Tool To Diagnose Or To Exclude GERD In Children

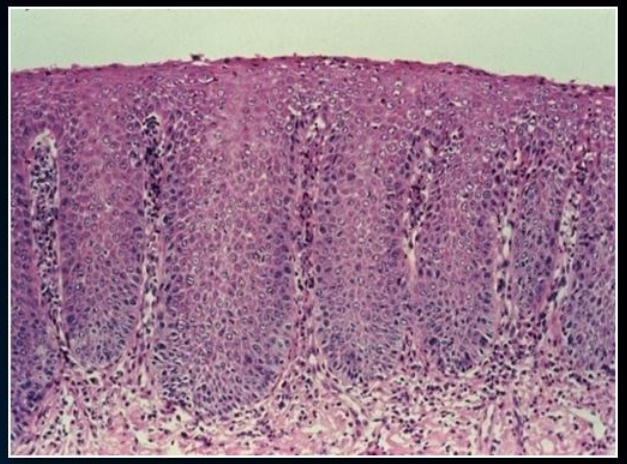
Advantages	Disadvantages
Enables evaluation of microscopic anatomy	Sampling error because of the patchy distribution of inflammatory changes
To rule out other conditions in the differential diagnosis (eosinophilic esophagitis, Crohn's Disease, Barrett's esophagus, infection)	Lack of standardization of 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

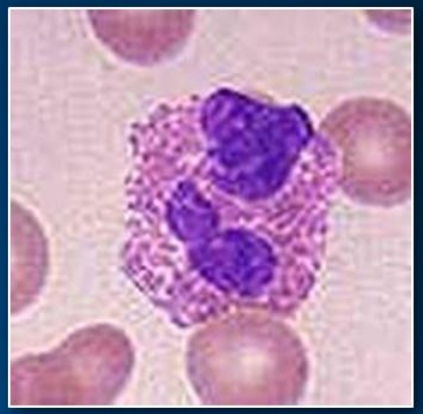


Vandenplas et al. *J Pediatr Gastroenterol Nutr.* 2009;49:498-547.
Sherman et al. *Am J Gastroenterol.* 2009;104:1278-95.

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

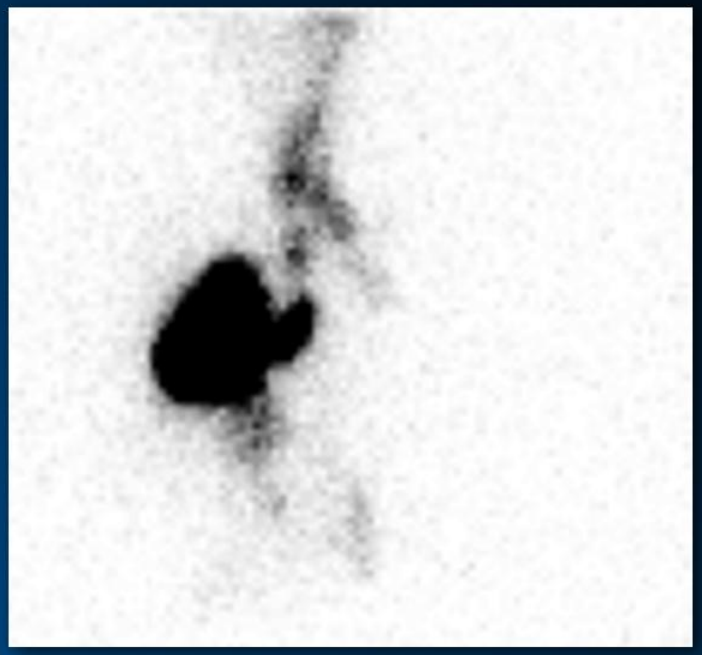
Advantages

- 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

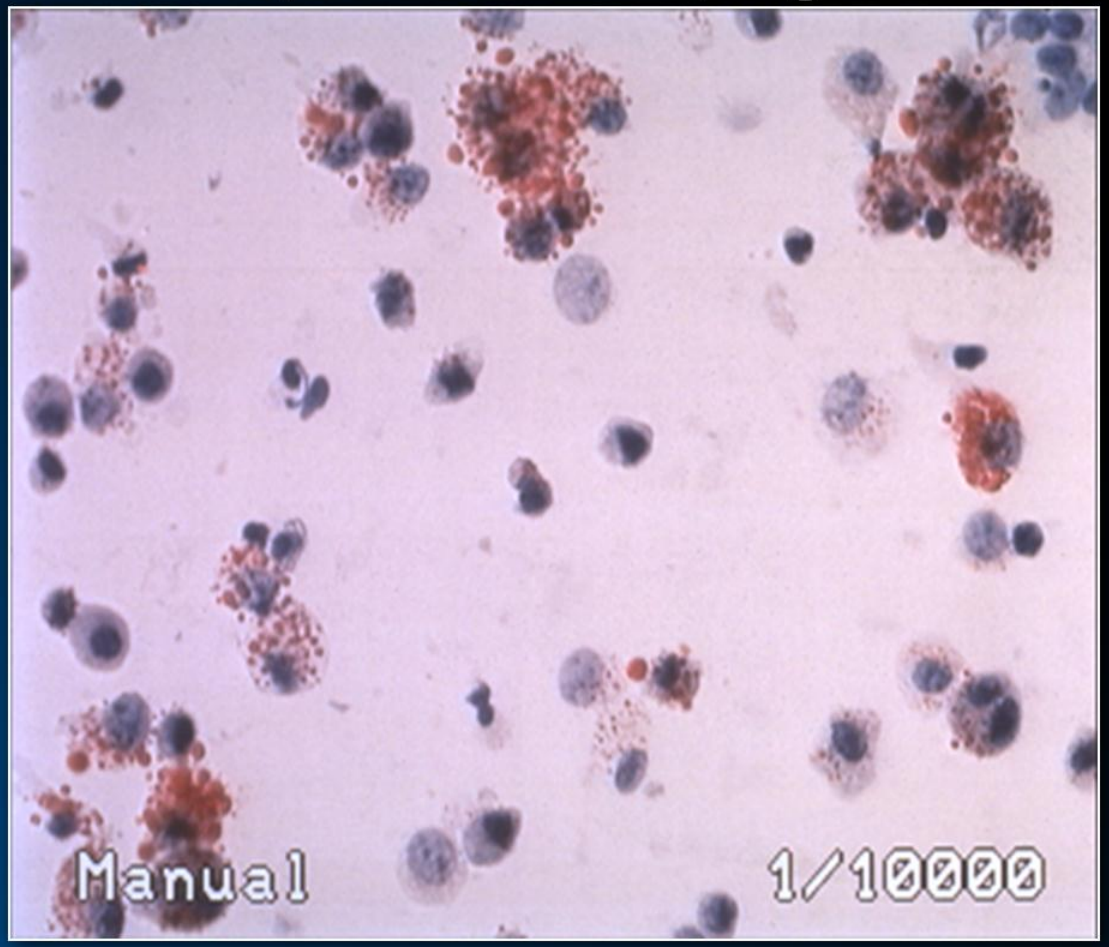
Bile

- 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

Blondeau et al. *J Pediatr Gastroenterol Nutr.* 2010;50(2):161-6.
Blondeau et al. *J Heart Lung Transplant.* 2009;28(2):141-8.
Rosen. *Pediatrics* 2008;121(4):e879-84.
Potluri et al. *Dig Dis Sci.* 2003;48:1813-17.

Aspiration From Swallowing or GER?

Lipid-Laden Macrophages



Rosen. *Pediatrics*. 2008;121(4):e879-84..
Vandenplas et al. *J Pediatr Gastroenter Nutr.* 2009;49:498-547.

New Technologies

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

Jadcherla et al. *Semin Respir Crit Care Med* 2010;31(5):554-560.
Othman . *Nucl Med Commun*. 2011;32(10):967-971.
Hammer . *Dig Dis*. 2009;27(1):14-17.

MANAGEMENT

- *Positioning and Feeding*
- *Pharmacologic Therapy*
- *Testing*

NASPGHAN FOUNDATION
For Children's Digestive Health & Nutrition

NASPGHAN
NORTH AMERICAN SOCIETY FOR PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

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

Vandenplas et al. *J Pediatr Gastroenterol Nutr.* 2009;49:498-547.
Kaltenbach et al. *Arch Intern Med.* 2006;166:965-71.
Tipnis , et al. *Curr Treat Options Gastroenterol.* 2007;10:391–400.

Positioning Therapy for Infants

Sitting

Supine

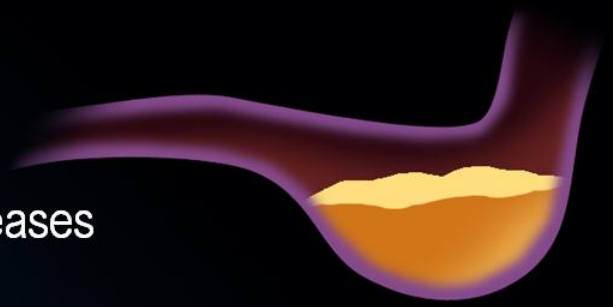
Prone

- 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.

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

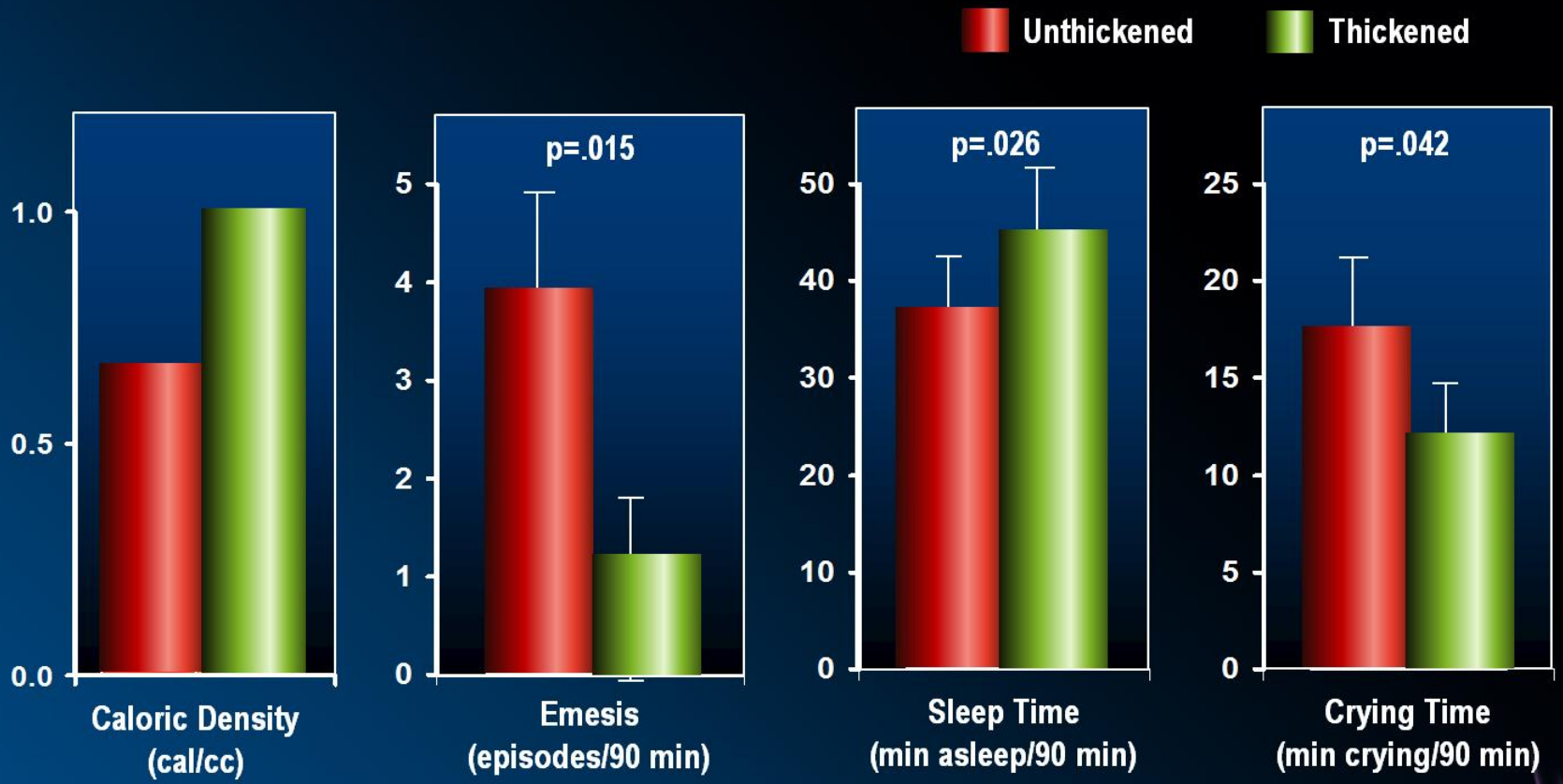


Left Side Down:
Pooling in the Fundus

Right Side Down:
Faster emptying but direct esophageal access

Omari et al. *J Pediatr*. 2004;145(2):194-200.

Effect of Thickening Milk Formula Feedings with Rice Cereal



Vandenplas. *Pediatrics*. 2009;123(3):e549-50.
Chao. *Dis Esophagus*. 2007;20(2):155-60.
Chao. *Nutrition*. 2007;23(1):23-28.

Management

Pharmacological Therapies

NASPGHAN FOUNDATION
For Children's Digestive Health & Nutrition

NASPGHAN
NORTH AMERICAN SOCIETY FOR PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

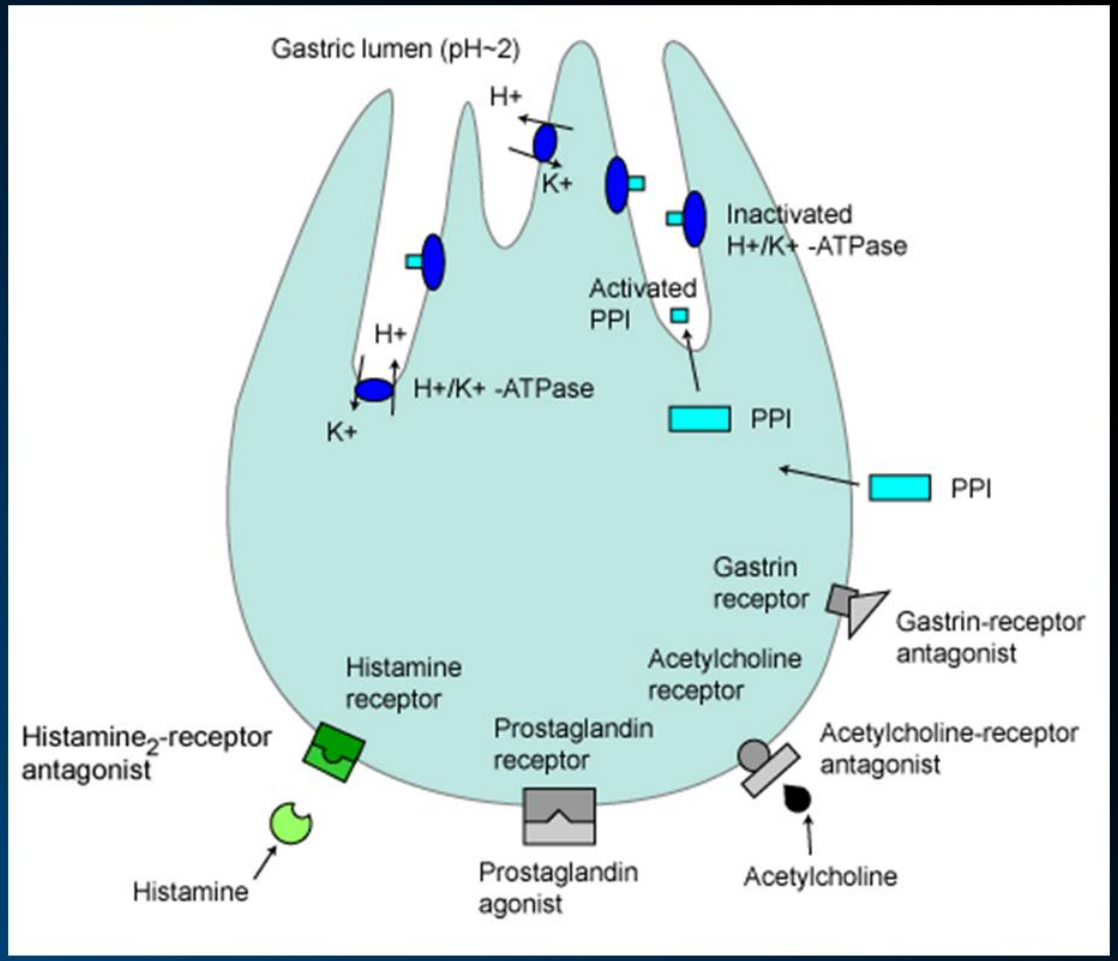
Goals of Pharmacotherapy

- 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 H_2RAs on Healing of Esophagitis

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

Significant symptom improvement with cimetidine, not placebo

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

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

Simeone et al. *J Pediatr Gastroenterol Nutr.* 1997;25:51-5.
Cucchiara et al. *J Pediatr Gastroenterol Nutr.* 1989;8:150-6.

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

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 than10 % 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

Barron et al. *J Pediatr Gastroenterol Nutr.* 2007;45:421-427.

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

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

Testing practice	Responders (%)
Treat (PPI or H_2RA) before testing	82
Order diagnostic testing for GERD in routine practice	66
Start testing in:	
Neonates	*54*
Infants > 1 month of age	*38*
Common tests ordered:	
Barium esophagram	*45*
Esophageal pH monitoring	*37*

Diaz D et al. *J Pediatr Gastroenterol Nutr.* 2007;45:56-64.

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

Orenstein SR et al. *J Pediatr.* 2008;152(3):310-314.

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.

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**

Tolia et al. *Dig Dis Sci.* 2008 Feb;53(2):385-93.

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

Ngamruengphong et al. *Am J Gastroenterol.* 2011 Jul;106(7):1209-18.
Yu et al. *Am J Med.* 2011;124:519-26.
Targownik et al. *Gastroenterology.* 2010;138:896-904.
Teramura-Gronblad et al. *Scand J Prim Health Care.* 2010;28(3): 154-159.

Proton Pump Inhibitor Use and Infections

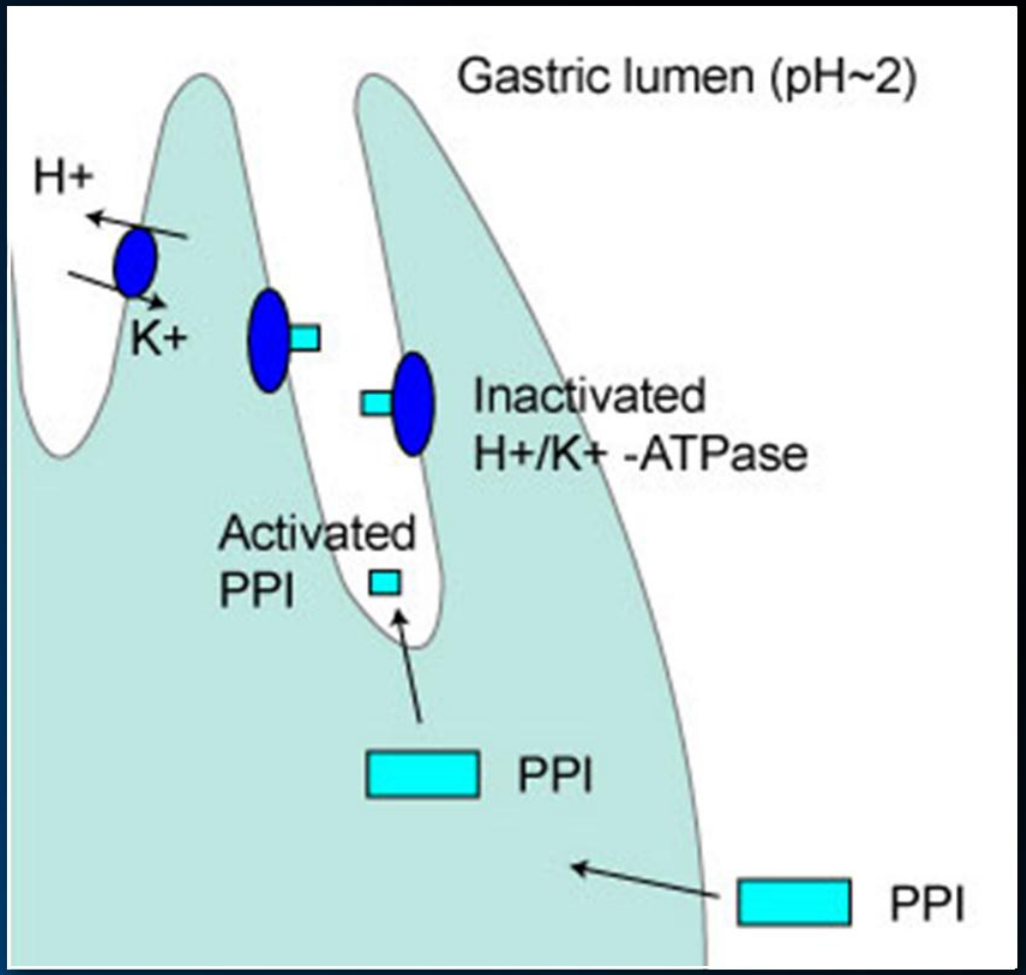
- There are limited pediatric data, particularly population-based;
  - Most conclusions regarding PPI risk in children arise from retrospective adult studies
- Children exposed to PPIs therapy seem to be at higher risk for the development of *Clostridium difficile*-associated disease
- Use of a proton 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

Turco et al. *Aliment Pharmacol Ther.* 2010 Apr;31(7):754-9.
Eom et al. *CMAJ.* 2011 Feb 22;183(3):310-9.
Lombardo et al. *Clin Gastroenterol Hepatol.* 2010 Jun;8(6):504-8.

Proton Pump Inhibitor Use: Other Considerations

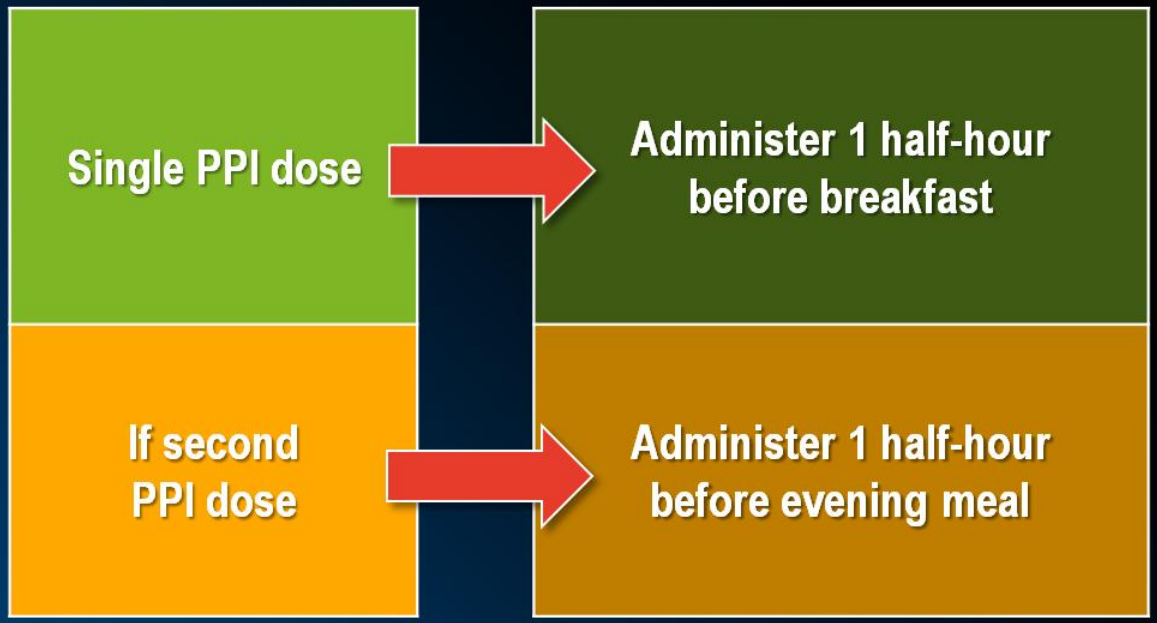
- There are case reports of low magnesium in patients taking PPI therapy
- Healthcare professionals should consider obtaining serum magnesium levels prior to initiation of prescription PPI treatment in patients expected to:
  - be on these drugs for long periods of time
  - patients who take PPIs with 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



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

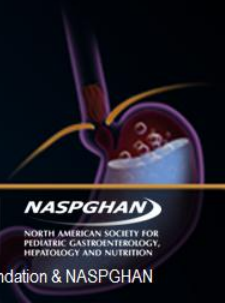
- A PPI for 3 months is recommended as initial therapy
- Increase the PPI dose at 4 weeks if symptom control is not adequate
- In most cases efficacy can be monitored by extent of symptom relief without routine endoscopic follow-up

- 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

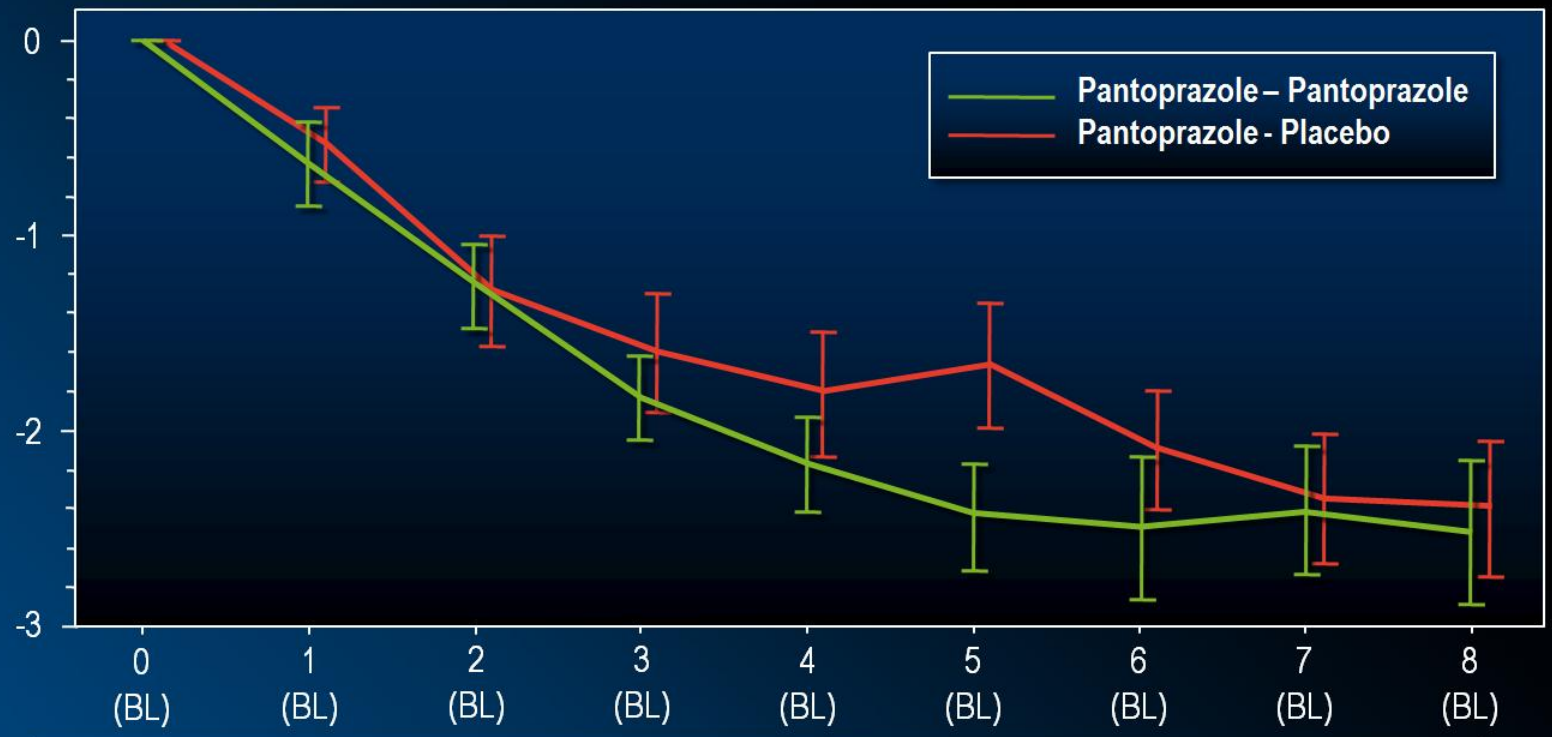


Vandenplas et al. *J Pediatr Gastroenterol Nutr.* 2009;49:498-547.

NASPGHAN FOUNDATION For Children's Digestive Health & Nutrition

NASPGHAN North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

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

Winter et al. *J Pediatr Gastroenterol Nutr.* 2010;50(6):609-18.

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

	Placebo	Omeprazole
Gastric pH: % time pH <4 (±SEM)	53.8 (6.8)	13.9 (5.1)***
Esophageal pH: % time pH <4 (±SEM)	19 (4.5)	4.9 (3.4)**
Number of Acid Reflux Episodes: Total number Number > 5 minutes	 119.4 (20.9) 8.0 (2.1)	 59.6 (26.7)* 3.0 (2.0)**
Duration of Acid Reflux Episodes: Longest (min)	48.6 (10.1)	16.3 (8.0)**

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

Omari et al. *J Pediatr Gastroenterol Nutr.* 2007;44(1):41-4.

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.

Orenstein et al. *J Pediatr.* 2009;154(4):514-20.
Omari et al. *J Pediatr.* 2009;155:222-8.
Moore et al. *J Pediatr.* 2003;143(2):219-23.

Randomized, Controlled Trial of Omeprazole and Placebo for Crying

	Cry fuss time in min/24 hour (mean ± SD)			
	Baseline	Period 1	Period 2	Combined*
Omeprazole (n=15)	246 ± 105	203 ± 113	179 ± 129	191 ± 120
Placebo (n=15)	287 ± 132	204 ± 87	198 ± 115	201 ± 100
Total (n=30)	267 ± 119†‡	203 ± 99†	188 ± 121‡	

* Mean of the combined data from Periods 1 and 2
† Baseline vs. Period1, *P=.040*
‡ Baseline vs. Period 2, *P=.008*

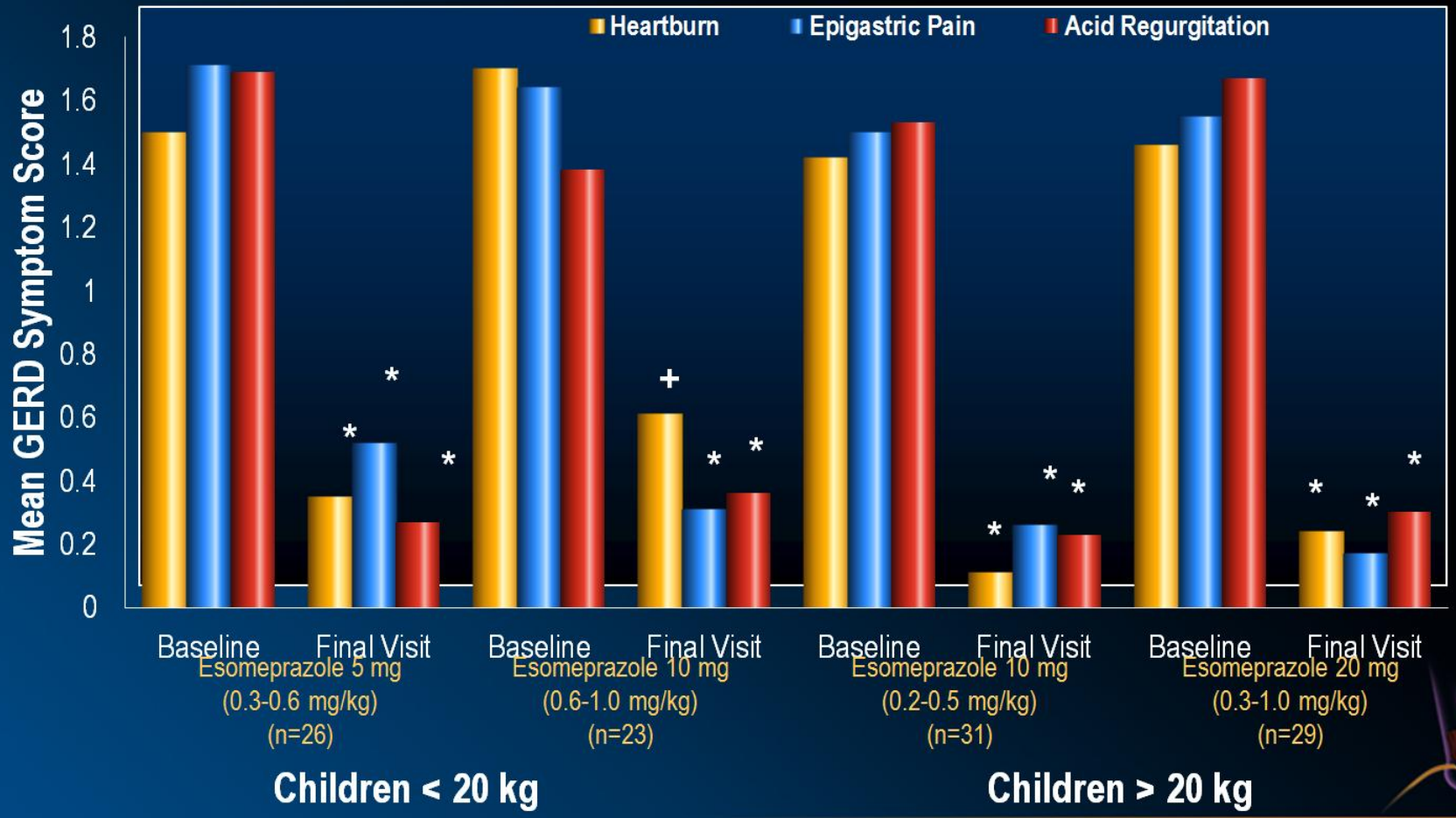
Moore et al. *J Pediatr.* 2003;143(2):219-23.

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

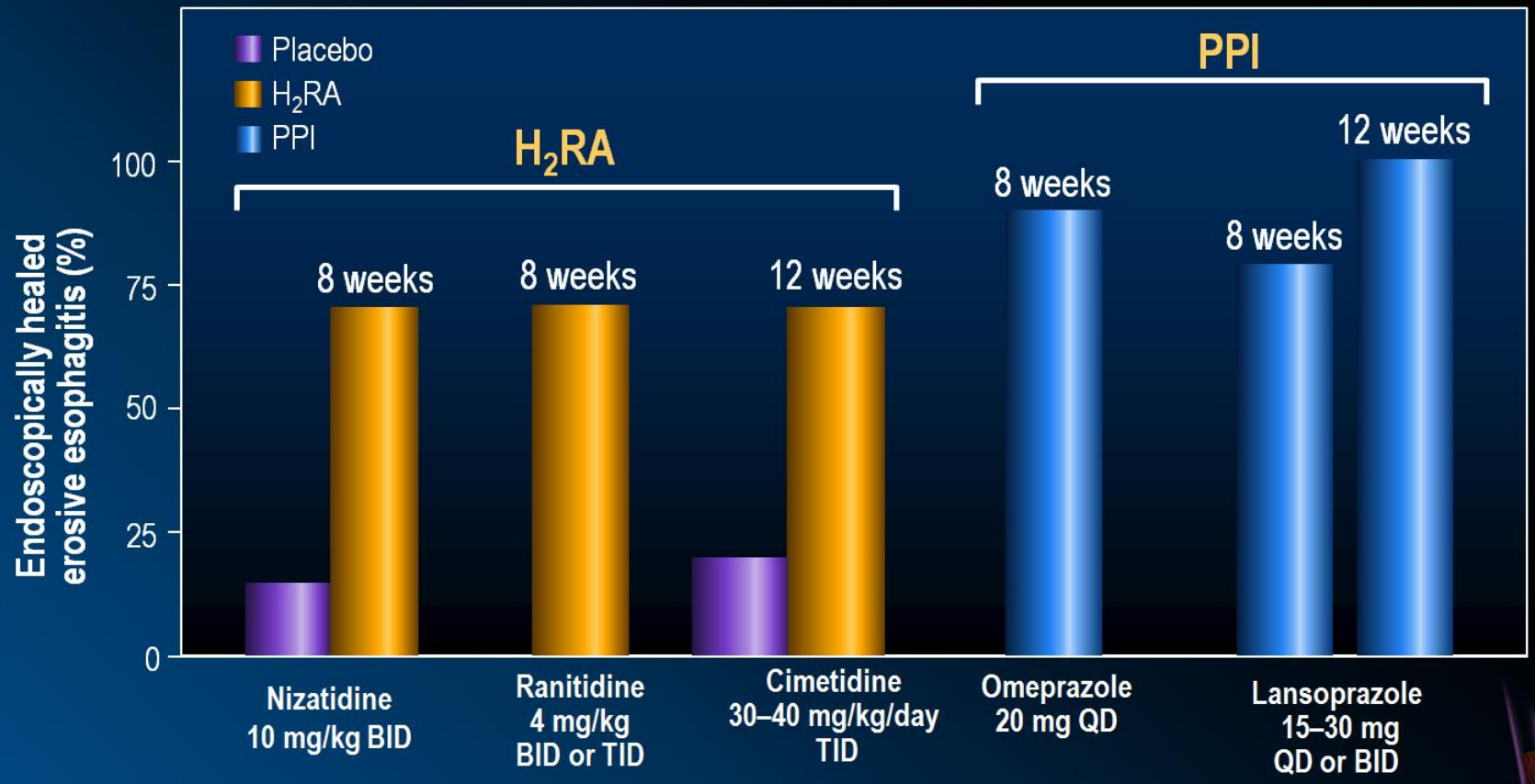
Omari et al. *J Pediatr Gastroenterol Nutr.* 2007; 45(5):530–537.
Winter et al. *J Pediatr Gastroenterol Nutr.* 2012; 55(1):14-20.
NEXIUM U.S.P.I. – FDA Prescribing information.

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



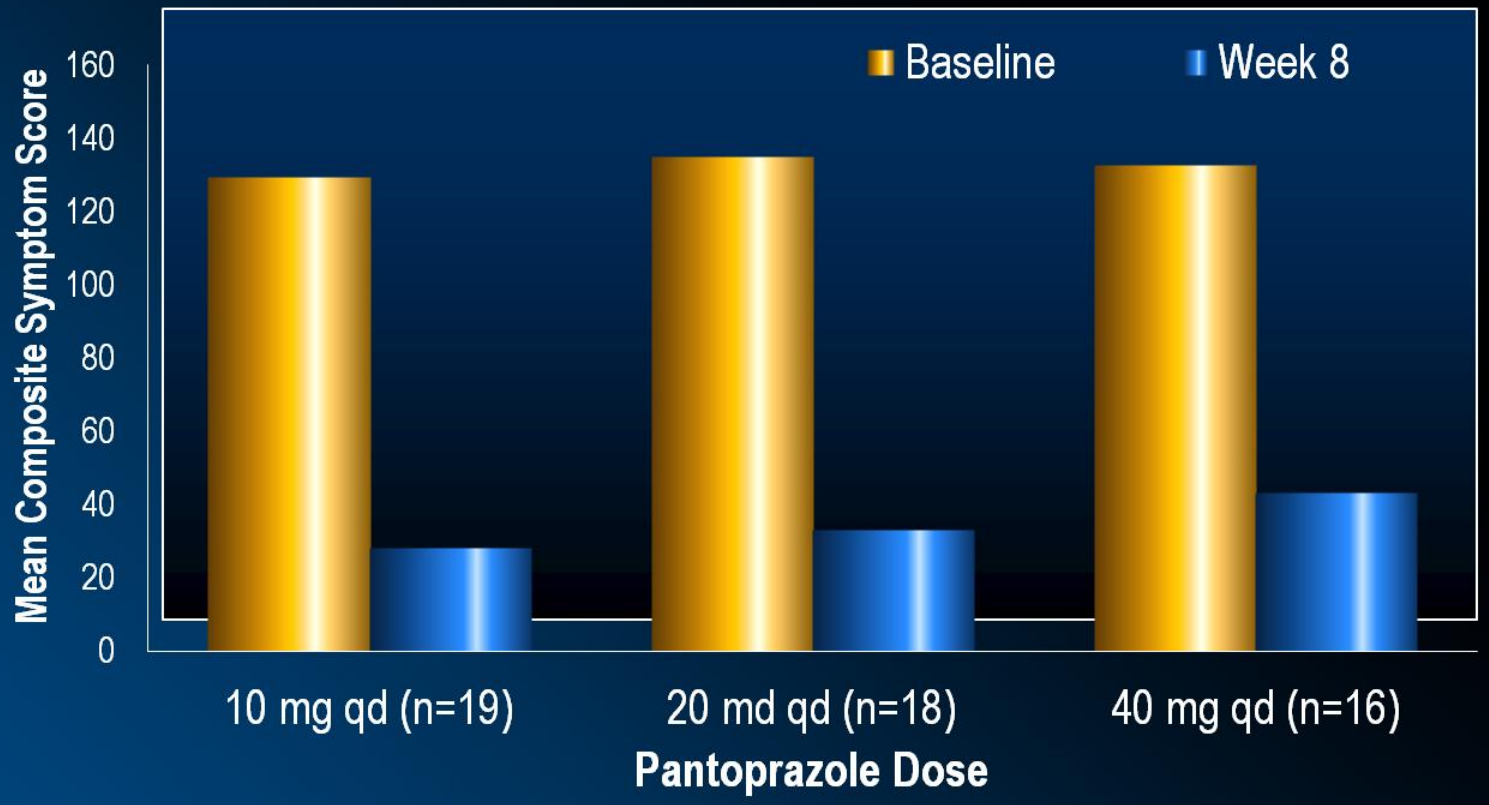
Gilger et al. J Pediatr Gastroenterol Nutr .2008;46:524-33.

Erosive Esophagitis Healing Rates of H2RAs and PPIs in Children



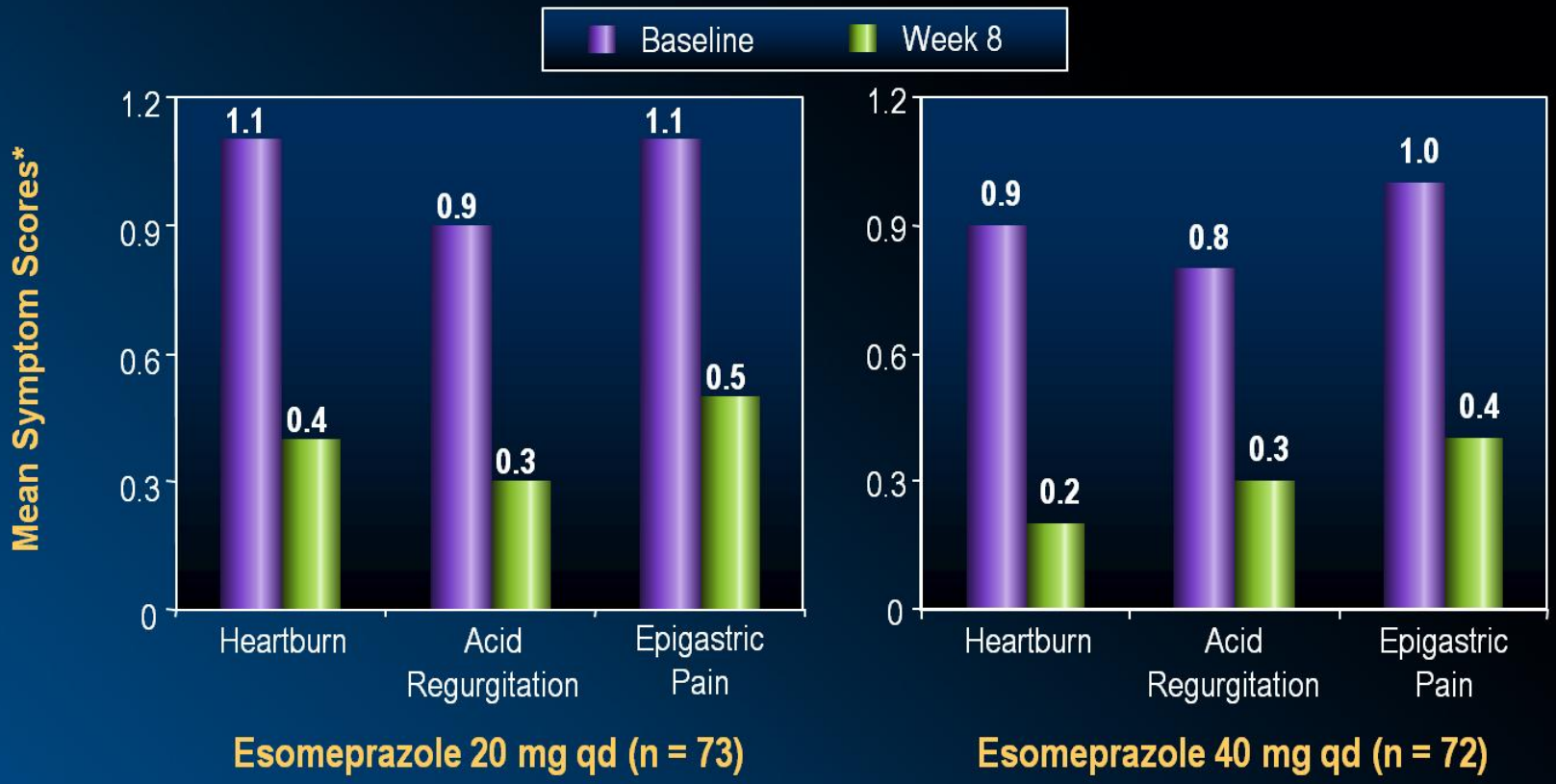
Vandenplas et al. *J Pediatr Gastroenterol Nutr.* 2009;49:498-547.

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



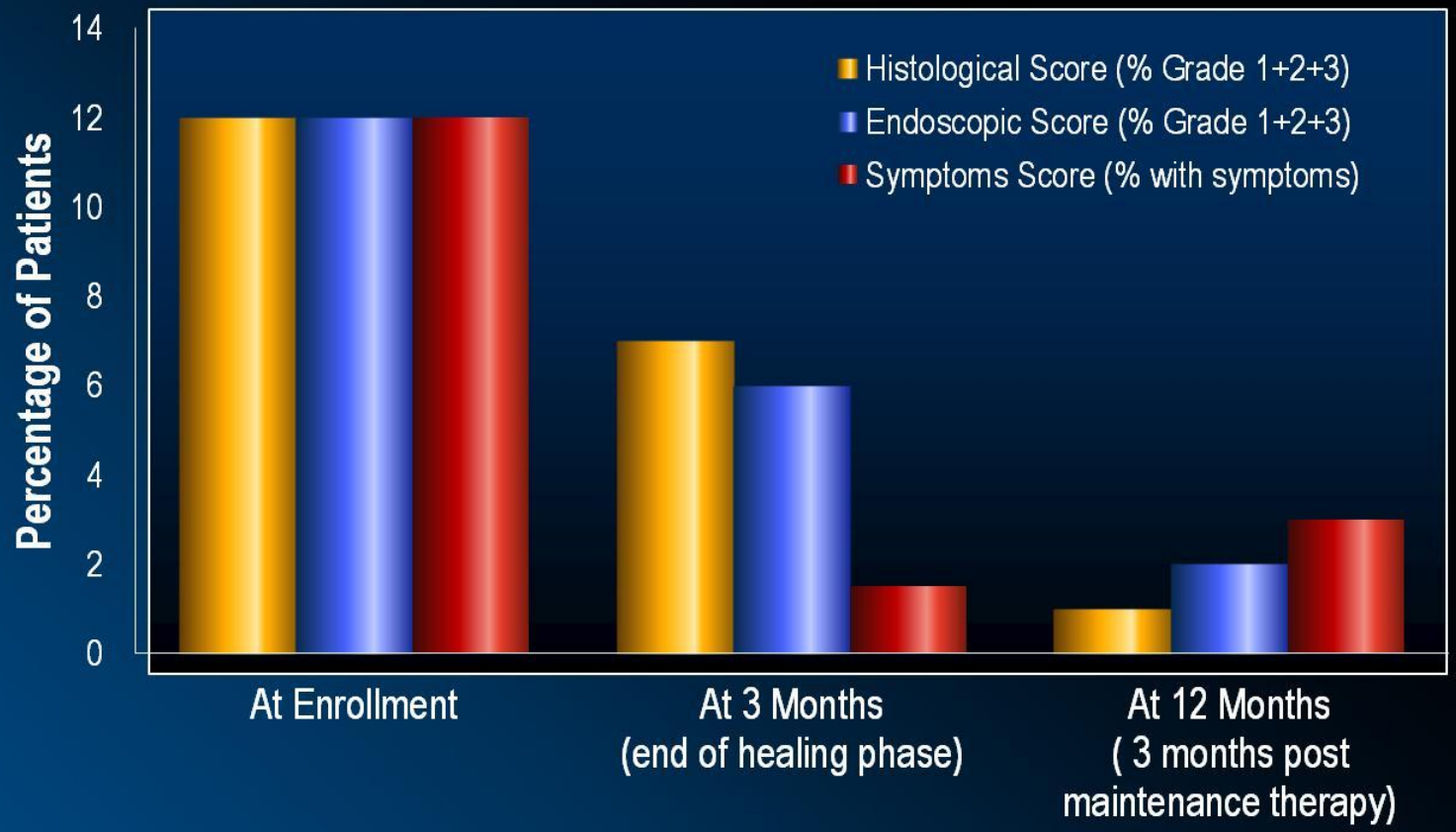
Tolia et al. *J Pediatr Gastroenterol Nutr.* 2006;42:384–391.

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



Gold. J Pediatr Gastroenterol Nutr. 2007;45:520-9.

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



Boccia et al. *Am J Gastroenterol*. 2007;102(6):1291-7.

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

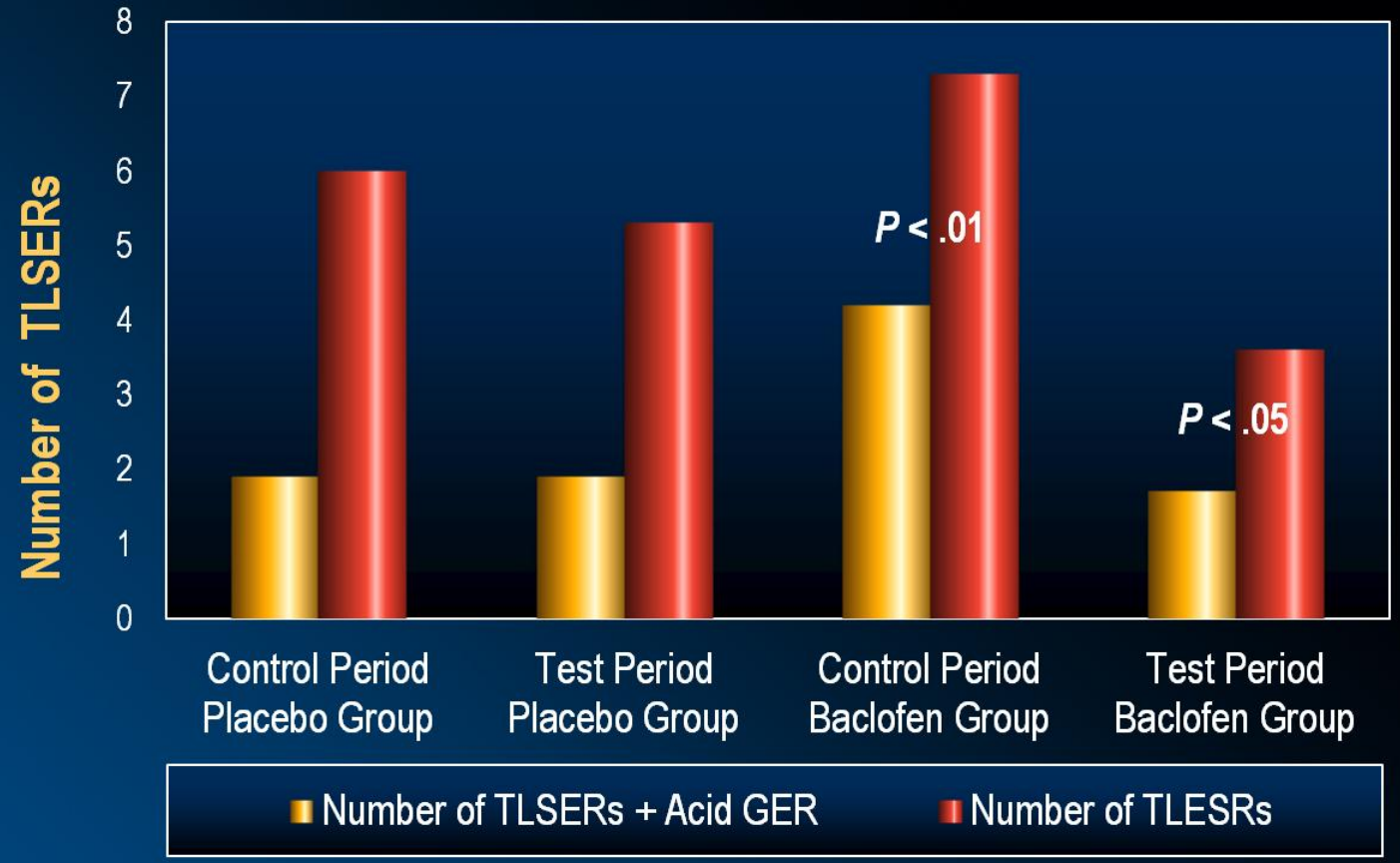
Ng et al. *J Pediatr Gastroenterol Nutr.* 2003;37(5):554-8.
Ng et al. *Gastroenterology.* 2007;132(5):1726-39.

Treatment with Metoclopramide

- Metoclopramide is a 5Ht4 agonist and dopamine antagonist
- It increases esophageal, fundic, and antral contrations
- 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.

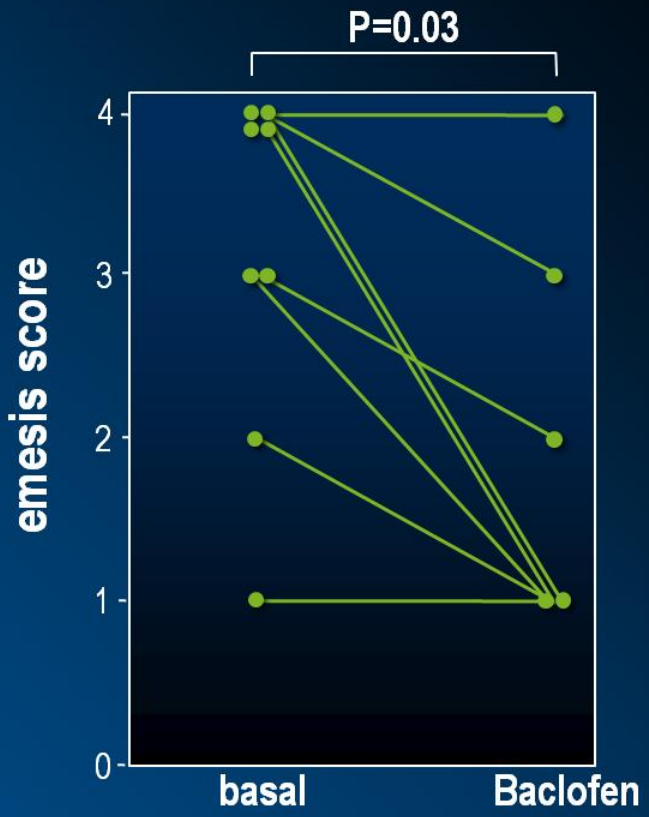
Kahrilas et al. *Gastroenterology.* 2008;135(4):1392-1413.
Tolia et al. *J Pediatr.* 1989;115(1):141-5.
Hyams et al. *J Pediatr Gastroenterol Nutr.* 1986;5(5):716-20.

Baclofen Reduces Transient Lower Esophageal Sphincter Relaxations and Acid Reflux



Omari et al. *J Pediatr.* 2006;149:468–74.

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

Kawai et al. *JPGN*. 2004. 38:3137-23.

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

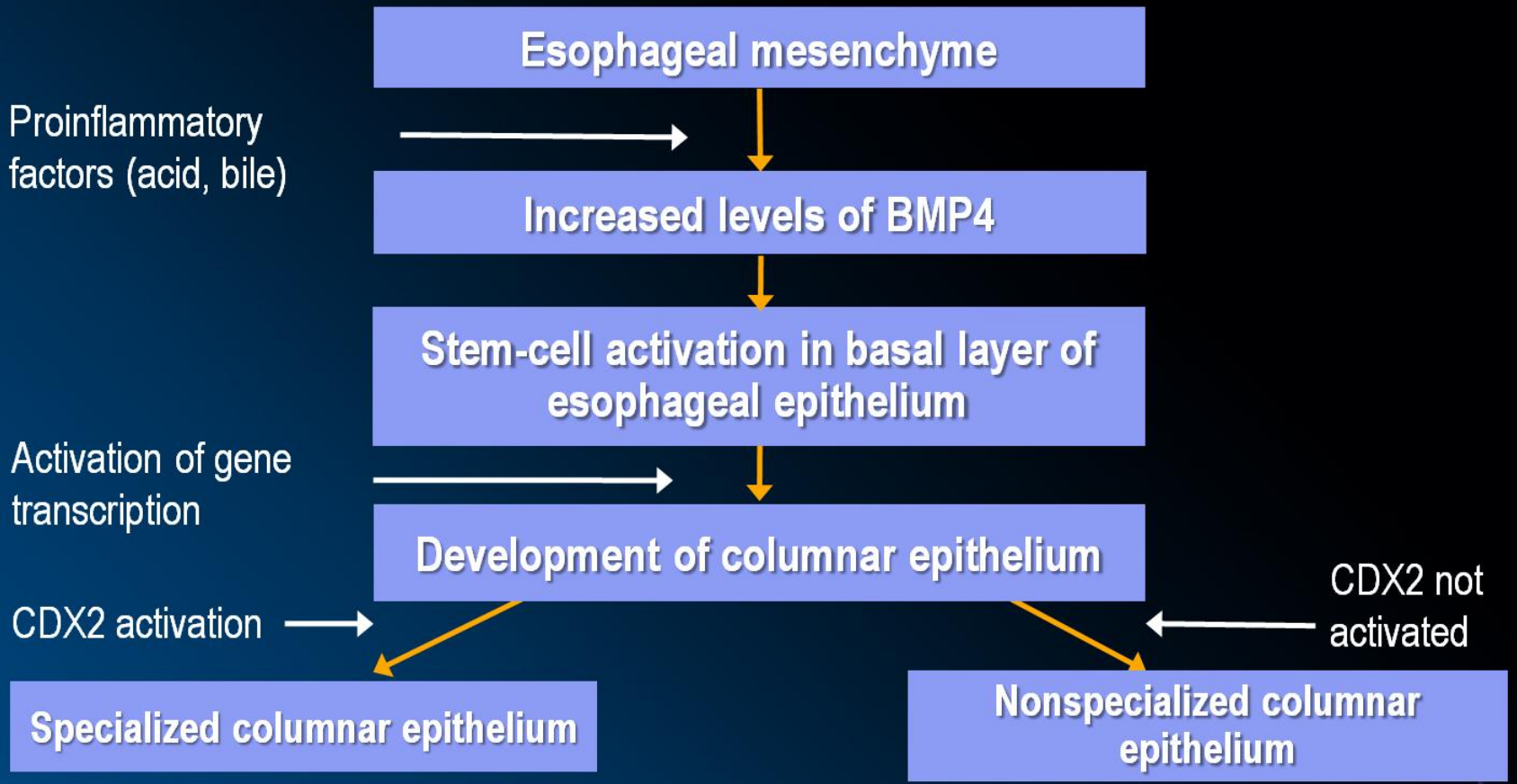
Rosen et al. *J Pediatr Gastroenterol Nutr.* 2011;52(5):532-5.
Mousa et al. *J Pediatr Gastroenterol Nutr.* 2011;52(2):129-139.
Malcolm. *J Perinatol.* 2009;29(5):372-5.
Srivastava. *Pediatrics.* 2009;123(1):338-45.

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; lengthy of the circumferential segment
  - Prague M – maximal extent; maximal length including tongues

Badreddine. *Nat Rev Gastroenterol Hepat*ol 2010;7:369-78.
Wang et al. *Am J Gastroenterol.* 2008;103:788-97.
Playford . *Gut* 2006;55:442.
Sharma et al. *Gastroenterology.* 2006;131:1392-99.

Barrett's Esophagus: Pathogenesis



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

Badreddine . *Nat Rev Gastroenterol Hepatol* 2010;7:369-78.

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

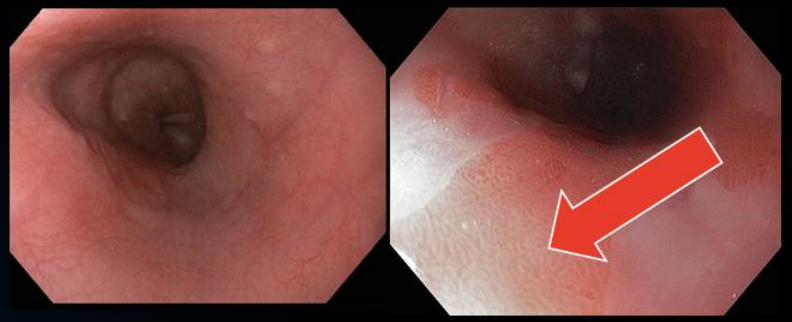
- Endoscopically suspected BE is rare (<0.25%) in children and adolescents
- Older age and the presence of hiatus hernia are possible risk factors for BE in this group
- Limitations: Lack of standardization for identifying and recording endoscopic landmarks

El-Serag et al. *Gastrointest Endosc.* *2006*;64(5):671-75.

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

High definition white light

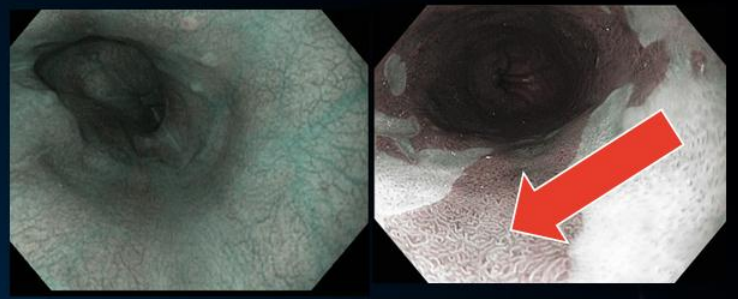


Normal

Barrett's esophagus*

*Courtesy of Olympus Corp

High definition narrow band imaging



Normal

Barrett's esophagus*

*Courtesy of Olympus Corp

Badreddine et al. *Nat Rev Gastroenterol Hepatol.* 2010;7:369–78.
Vandenplas et al. *J Pediatr Gastroenter Nutr .* 2009;49:498-547.
Sherman et al. *Am J Gastroenterol .* 2009;104:1278-95.
Hassall et al. *J Pediatr .*2007;150(3):262-7.

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

Badreddine et al. *Nat Rev Gastroenterol Hepatol.* 2010;7:369–78
Vandenplas et al. *J Pediatr Gastroenter Nutr.* 2009;49:498-547.
Sherman et al. *Am J Gastroenterol.* 2009;104:1278-95.

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

Fortunato et al. *Curr Gastroenterol Rep.* 2011; Mar 17 [Epub ahead of print].
Srivastava et al. *Pediatr Ann.* 2010;39(4): 225-31.

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

Vandenplas et al. *J Pediatr Gastroenterol Nutr.* 2009;49:498-547.
Fortunato et al. *Curr Gastroenterol Rep.* (2011).
Srivastava et al. *Pediatr Ann.* 2010; *39(4):* 225-231.
Ruigomez et al. *Scand J Gastroenterol. 2010;*45(2): 139-146.

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

	Baseline*	Proton Pump Inhibitors*	P value
Duration (days)	62 (28-356)	81 (42-157)	Not significant
Vomiting index†	0.4 (0.26-0.63)	0.2 (0.06-0.26)	<0.05
Gastrointestinal bleeding index†	0.014 (0-0.026)	0 (0-0.05)	Not significant
Pneumonia index†	0 (0-0.04)	0 (0-0.04)	Not significant

* The range is expressed in brackets

† Episode of event per day

Chong. *Curr Opin Pediatr*. 2001;13:441-446.
Cheung et al. *Hong Kong Med J*. 2001;7(4): 356-359.
Okada et al. Eur J Pediat Surg 2005;15(2):77-81.

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 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.

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

Management

Surgical Therapy

NASPGHAN FOUNDATION
For Children's Digestive Health & Nutrition

NASPGHAN
NORTH AMERICAN SOCIETY FOR PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

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.

Principles of Antireflux Surgery

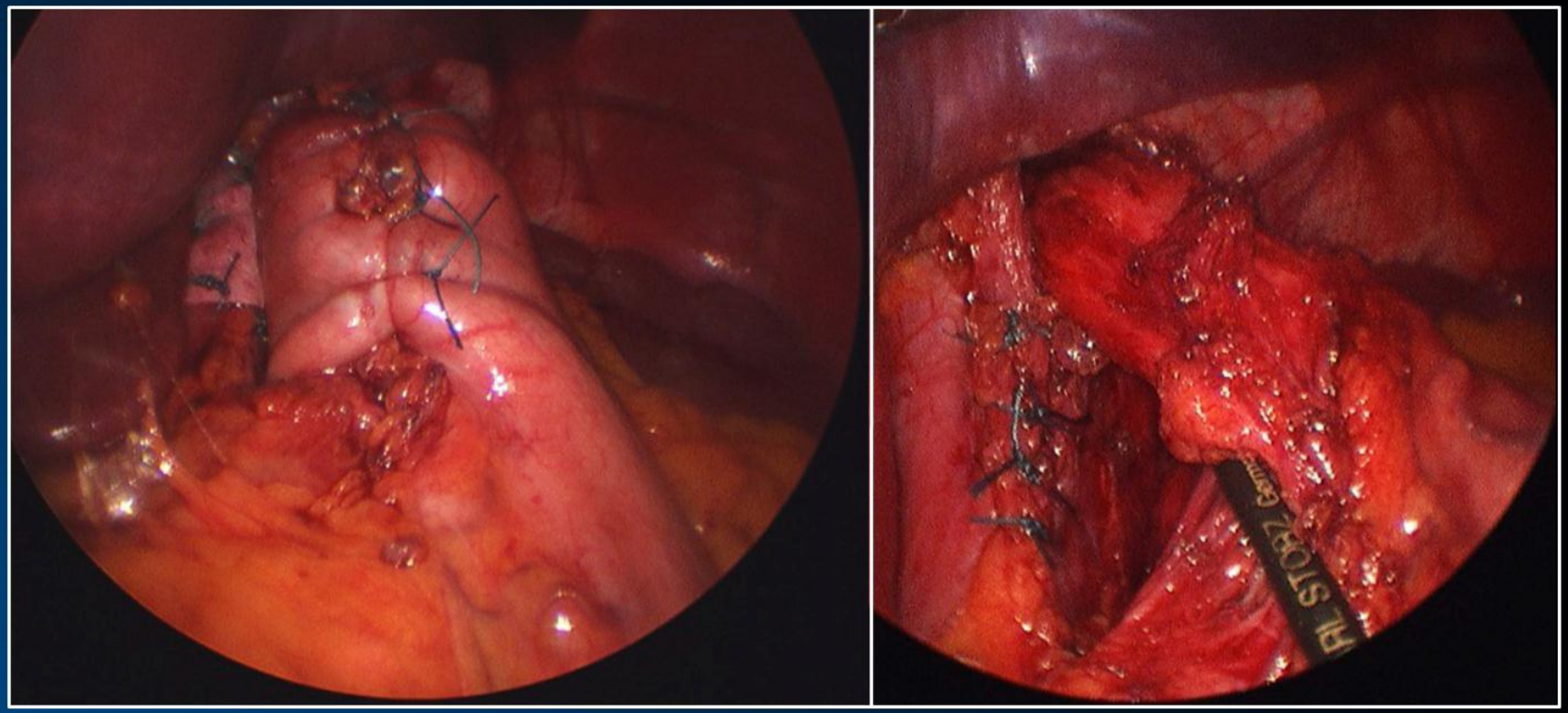
Restore intra-abdominal segment of esophagus

Approximate diaphagmatic Crurae

Reduce hiatal hernia when present

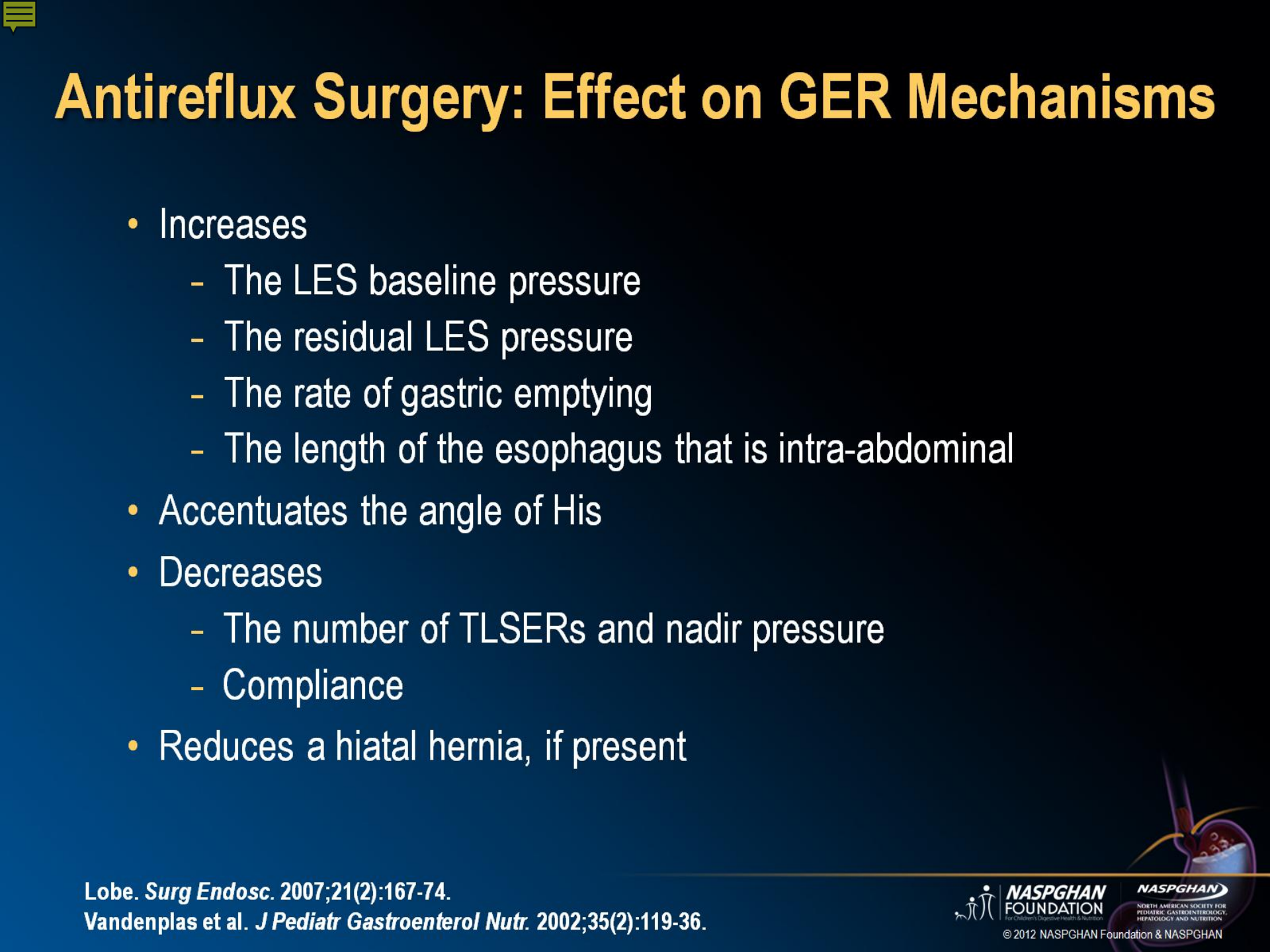
Wrap fundus around LES to reinforce antireflux barrier

Antireflux Surgery



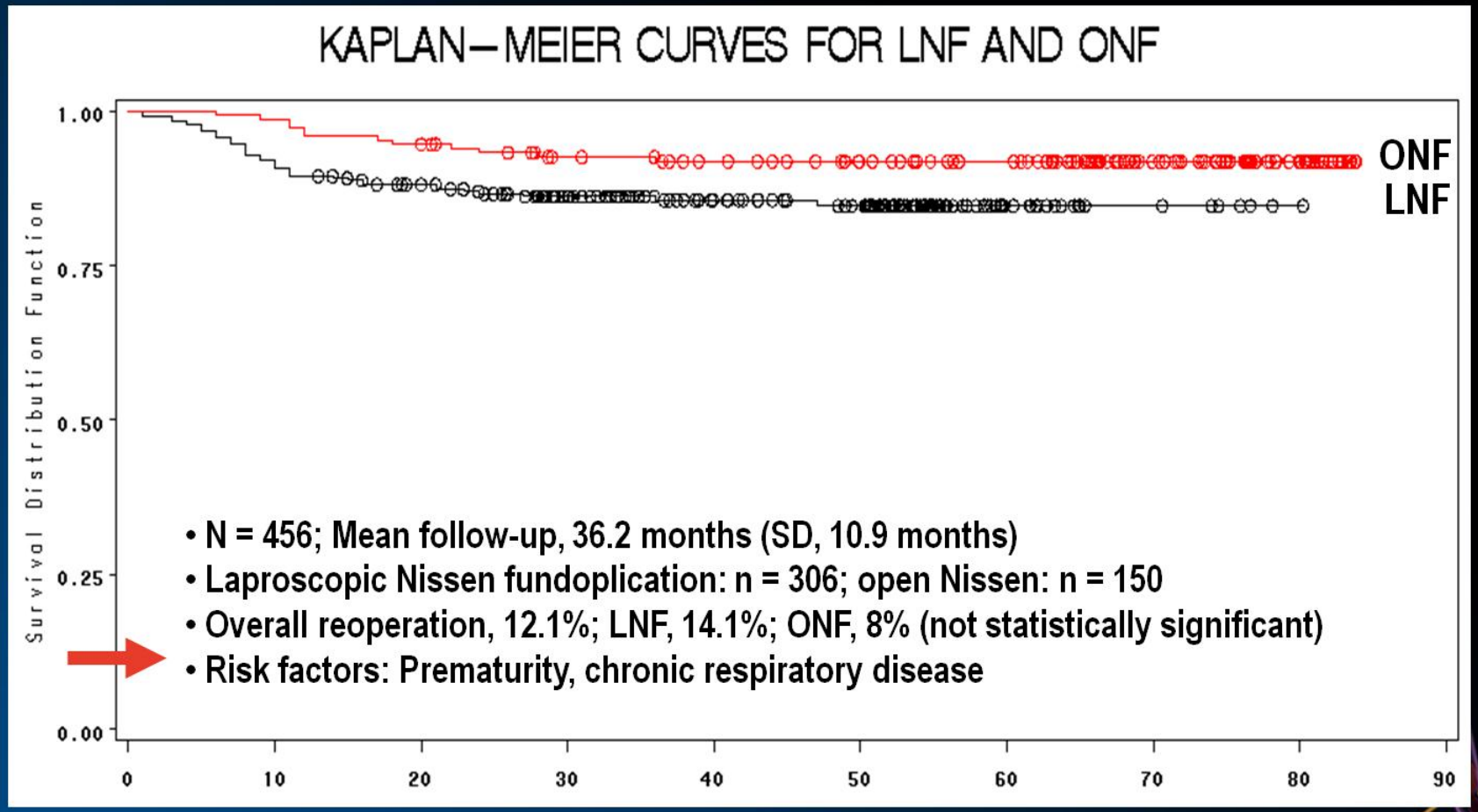
Antireflux Surgery: Effect on GER Mechanisms

- 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



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

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



Diaz et al. *Am J Gastroenterol.* 2005;100:1844–1852.

Antireflux Surgery: Outcomes in Children

• Success rate (complete relief of symptoms)	57 – 92%
• Mortality related to operation	0 – 5 %
• Overall complication rate	2 – 45%
• Dumping syndrome	NA
• Gas bloat syndrome	2 – 8 %
• Small-bowel obstruction	1 – 11 %
• Wrap failure	1 – 13%
• Continued medication	85%
• Reoperation rate	3 – 19%

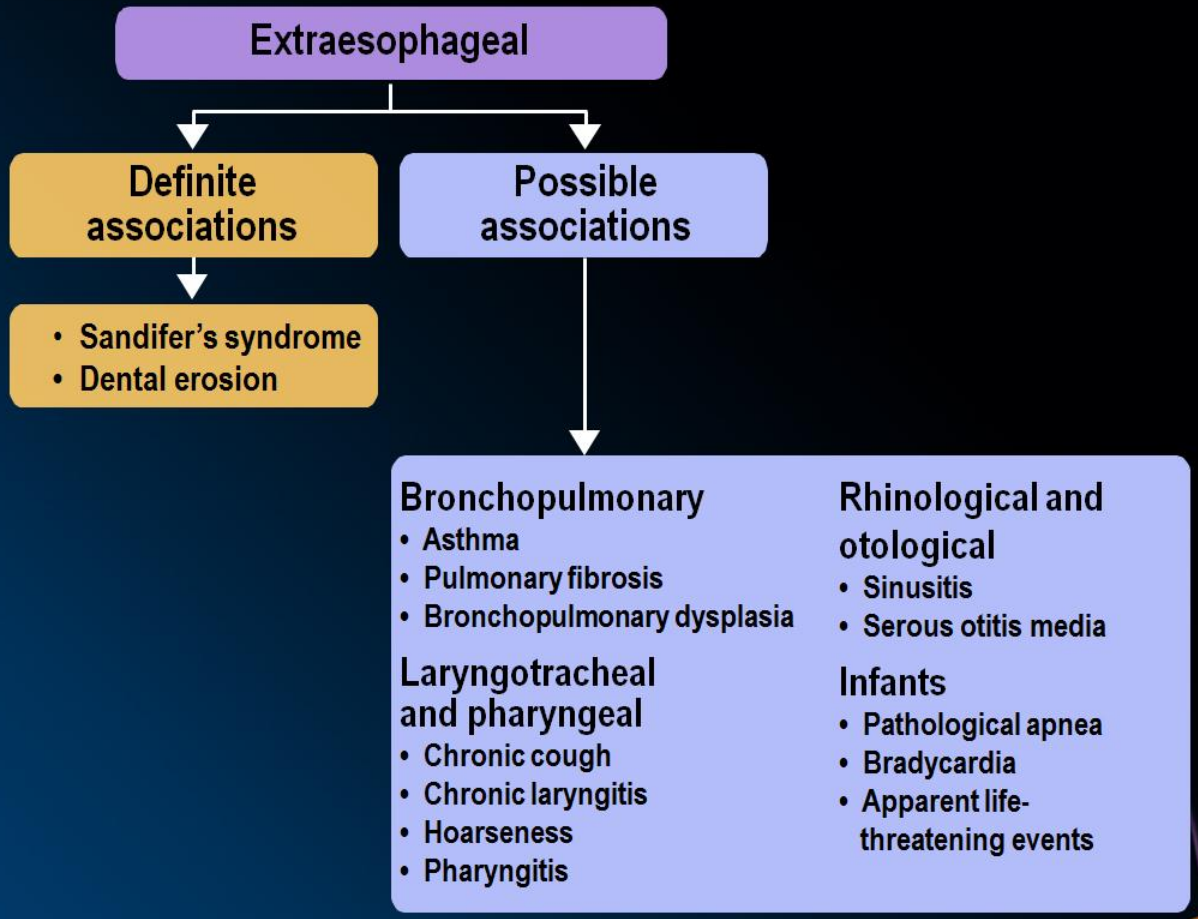
Vandenplas et al. *J Pediatr Gastroenterol Nutr.* 2009;49:498-547.
Lee et al. *Arch Surg.* 2008;143(9):873-6.

EXTRAESOPHAGEAL

NASPGHAN FOUNDATION
For Children's Digestive Health & Nutrition

NASPGHAN
NORTH AMERICAN SOCIETY FOR PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

Extraesophageal Associations of GERD: Global Consensus Definitions



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

Permission granted, V. Tolia.

Pace et al. *Aliment Pharmacol Ther*. 2008;27(12):1179-86.
Sherman et al. *Am J Gastroenterol*. 2009;104:1278-95.
Vandenplas et al. *J Pediatr Gastroenter Nutr*. 2009;49:498-547.

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

Sherman et al. *Am J Gastroenterol*. 2009;104:1278-95.
Vandenplas et al. *J Pediatr Gastroenter Nutr*. 2009;49:498-547.
Cerimagic et al. *Med Hypotheses*. 2008;70(5):957-61.

Extraesophageal Manifestations of GERD are Possible

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

- Sinusitis
- Pulmonary firbrosis
- 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

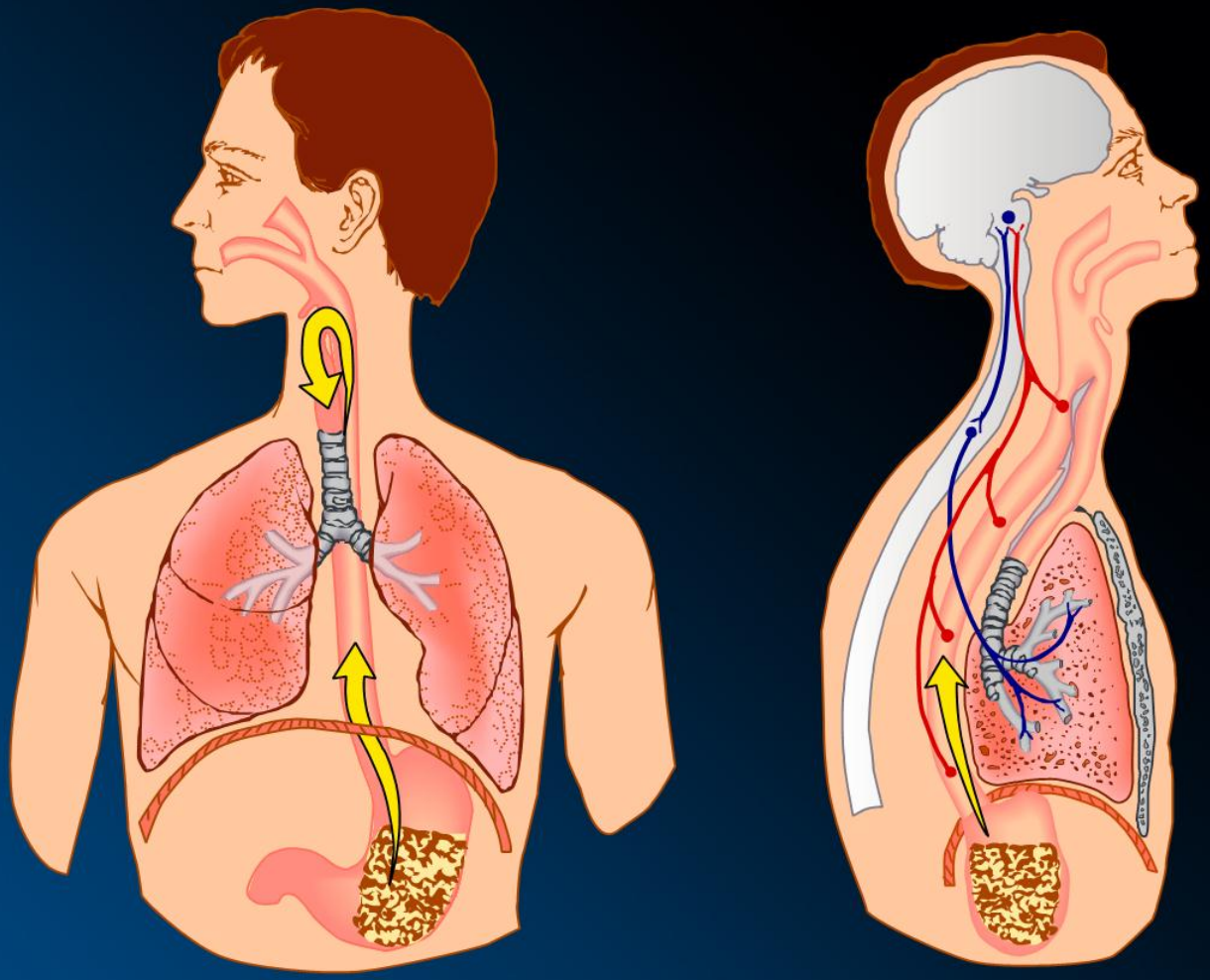
Sherman et al. *Am J Gastroenterol*. 2009;104:1278-95.
Vandenplas et al. *J Pediatr Gastroenter Nutr*. 2009;49:498-547.

Respiratory

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

Pearson JP S et al. *Aliment Pharmacol Ther.* 2011;33 Suppl 1:1-71.
May JG et al. *Ann Otol Rhinol Laryngol.* 2011;120(2):116-122.
Ghezzi M et al. *Respir Med*. 2011;105(7):972-978.

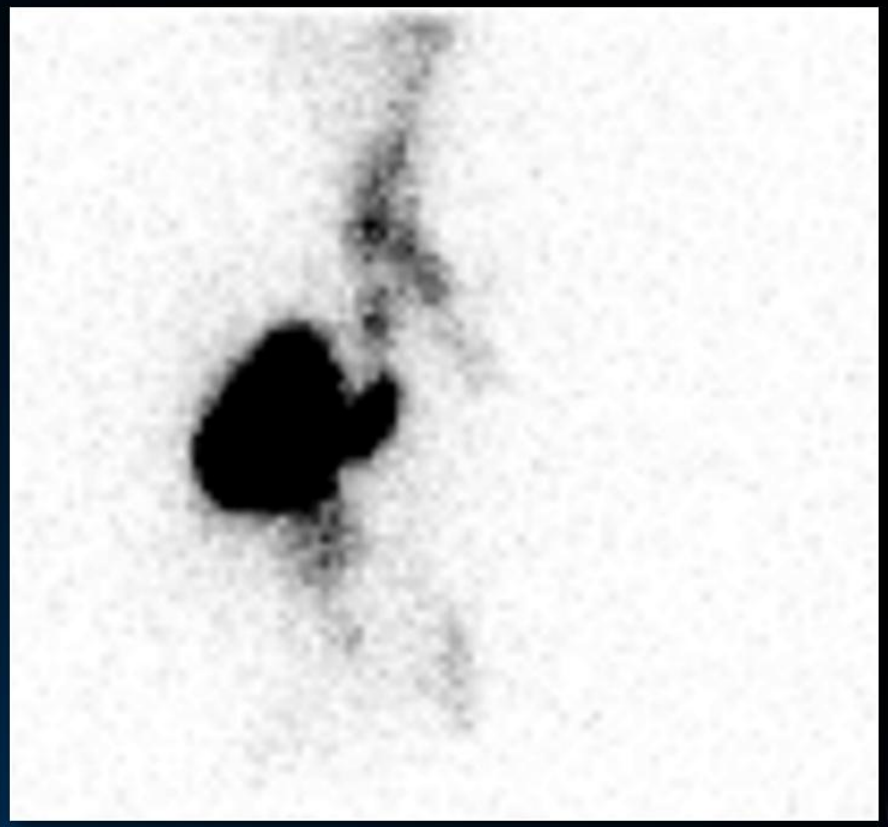
Respiratory: Mechanism of Responses to GER



Lodi et al. *Chest*. 1997;111:65-70.
Schan et al. *Chest*. 1994;106:731-7.

Aspiration From Swallowing or GER?

Barium Swallow



Technetium-99m Salivagram

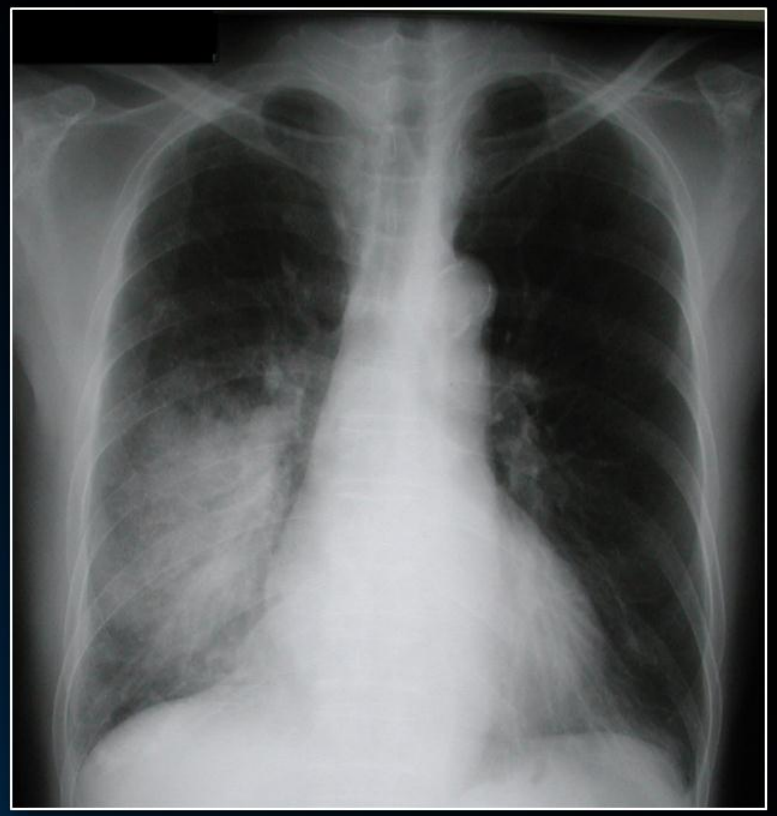
RECURRENT PNEUMONIA

NASPGHAN FOUNDATION
For Children's Digestive Health & Nutrition

NASPGHAN
NORTH AMERICAN SOCIETY FOR PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

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



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

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
  - Cystic fibrosis
  - Bronchiectasis
  - Ciliary diskinesia
  - Achalasia for other cause of recurrent pneumonia

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

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

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

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

Srivastava. *Pediatrics*. 2009;123(1):338-45.
Srivastava. *BMJ*. 2010;340(7737):85.

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

Srivastava . *BMJ.* 2010;340(7737):85.
Srivastava et al. *BMJ.* 2009;18;339:b4411.
Srivastava . *Pediatrics.* 2009;123(1):338-45.
Lee et al. *J Pediatr Surg.* 2008;43(1):59-63.

Apnea/ALTE

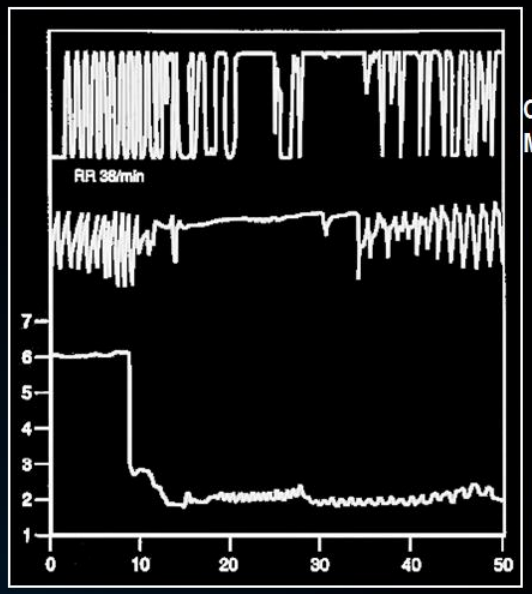
NASPGHAN FOUNDATION
For Children's Digestive Health & Nutrition

NASPGHAN
NORTH AMERICAN SOCIETY FOR PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

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



Vandenplas et al. *J Pediatr Gastroenter Nutr.* 2009;49:498-547.
Sherman et al. *Am J Gastroenterol.* 2009;104:1278-95.
DiMario. *Pediatrics* 2008;22:190-1.
Mousa et al. *J Pediatr Gastroenterol Nutr.* 2005;41:169-77.

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

Vandenplas et al. *J Pediatr Gastroenter Nutr.* 2009;49:498-547.
Malcolm et al. *J Perinatol.* 2009;29:372-375.
DiMario. *Pediatrics.* 2008;22:190-1.
Mirsa et al. *Acta Paediatr.* 2007;96:1426-1429.

ASTHMA

NASPGHAN FOUNDATION
For Children's Digestive Health & Nutrition

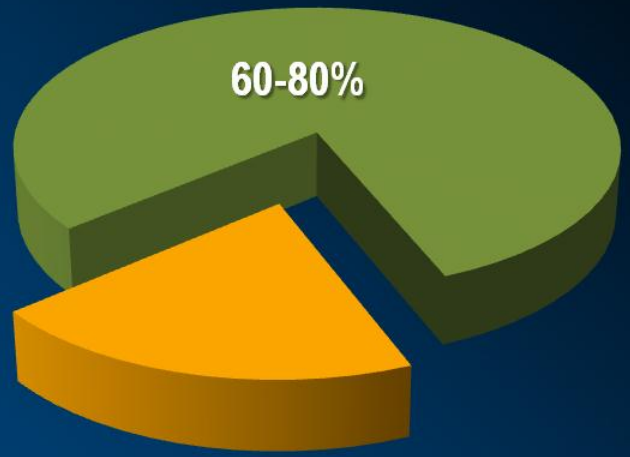
NASPGHAN
NORTH AMERICAN SOCIETY FOR PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

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

Sherman et al. *Am J Gastroenterol.* 2009;104:1278-95.
Vandenplas et al. *J Pediatr Gastroenter Nutr.* 2009;49:498-547.
Field . *Chest.* 1999;115:848-56.

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

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

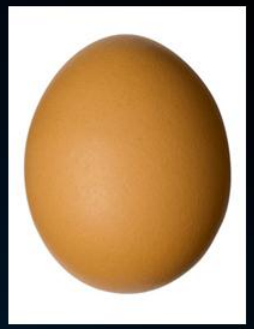
Asthma: Does GER Cause It?

GER → Asthma

GER ← Asthma

GER ⇄ Asthma

GER ⇏ Asthma

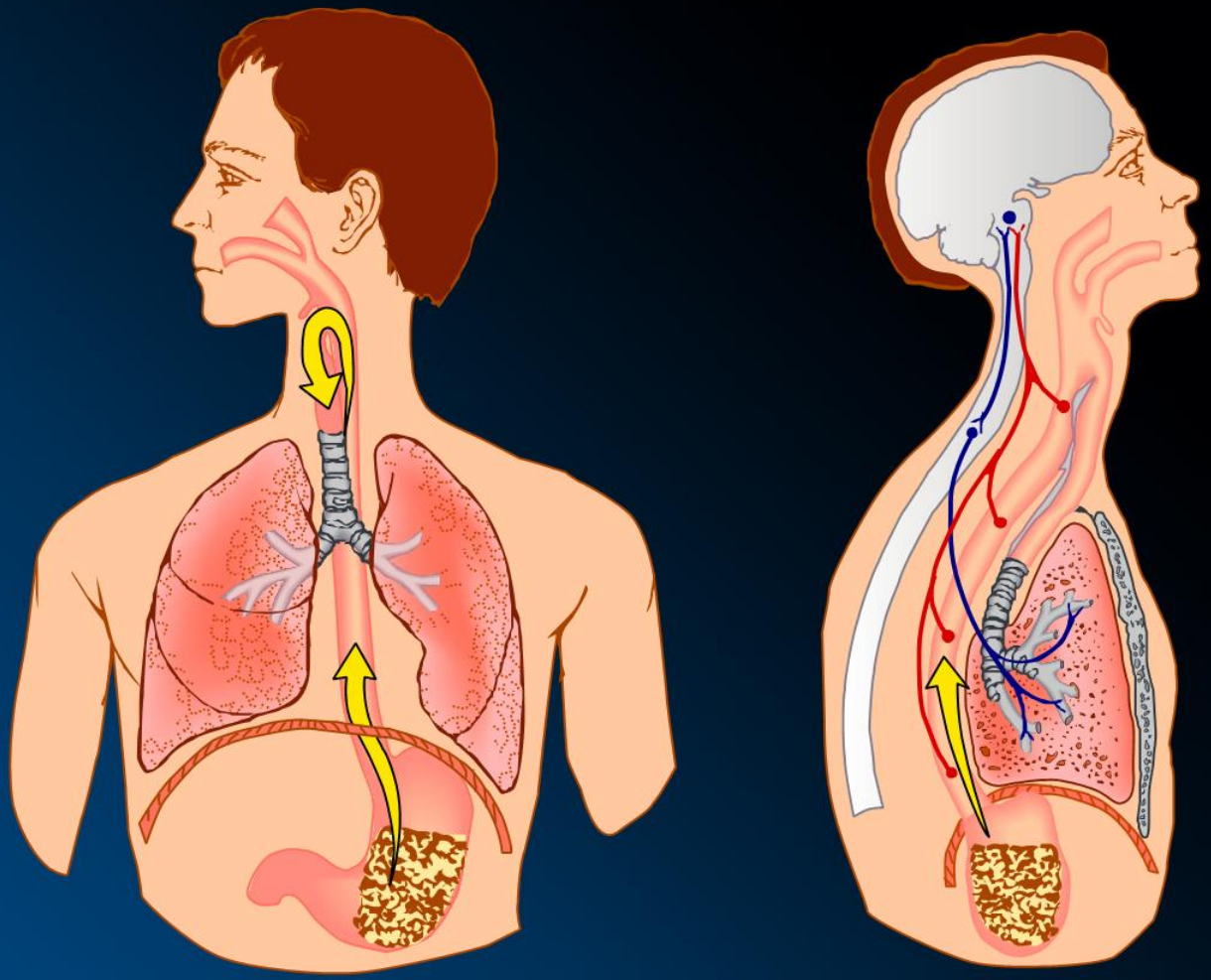


Baer et al. *J Pediatr Gastroenterol Nutr.* 1986;5:187-90.
Shapiro et al. *Pediatrics.* 1979;63:207-12.

NASPGHAN FOUNDATION For Children's Digestive Health & Nutrition

NASPGHAN North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

Respiratory: Mechanism of Responses to GER

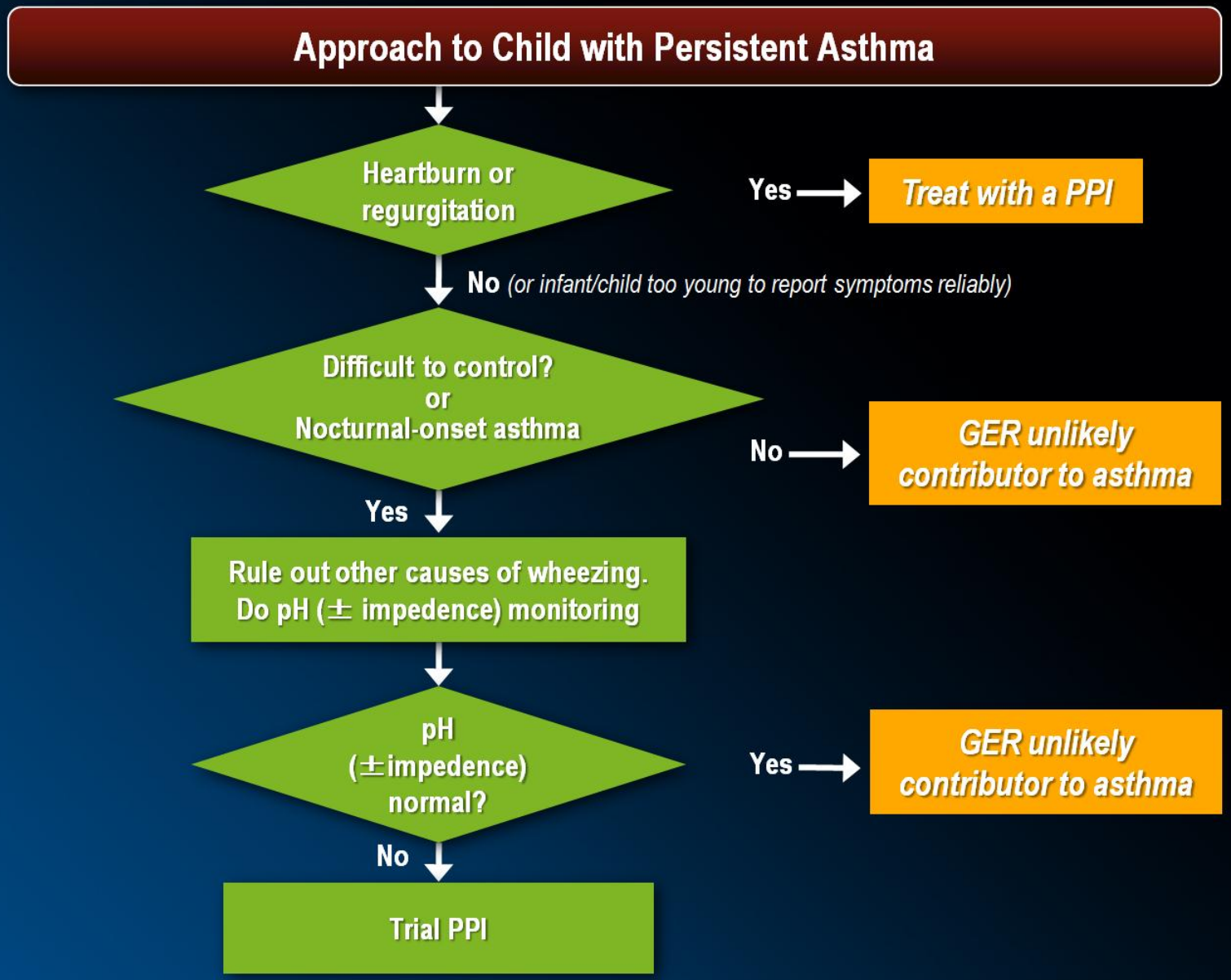


Lodi et al. *Chest* 1997;111:65-70.
Schan et al. *Chest* 1994;106:731-7.

Asthma: When to Treat for GERD

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

Mastronarde et al. *N Engl J Med*. 2009;360:1487-99.
Vandenplas et al. *J Pediatr Gastroenter Nutr.* 2009;49:498-547.
Sherman et al. *Am J Gastroenterol.* 2009;104:1278-95.



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

Varying Results of Using Acid Suppression in Children with Asthma

Randomized, controlled trial	Open label study
36 children with asthma and GERD	44 children with asthma and GERD
Omeprazole vs. placebo	Esomeprazole/metoclopramide vs. ranitidine
No difference in any of the study parameters	Ranitidine patients had significantly more exacerbations

Khoshoo et al. *J Pediatr Gastroenterol Nutr.* 2007;44(3):331-5.
Størdal et al. *Arch Dis Child.* 2005 Sep;90(9):956-60.

No Effect of Omeprazole and Placebo for Asthmatic Children with GER

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

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 H_2RA (i.e. ranitidine)
  - Asthma symptom scores improved
  - Pulmonary function, asthma medication use similar improvements for both medication and surgery

Orenstein et al. *J Pediatr.* 2009;154(4):514-520.
Khoshoo et al. *J Pediatr Gastroenterol Nutr.* 2007;44(3):331-5.
Størdal et al. *Arch Dis Child.* 2005;90(9):956-60.
Khoshoo et al. *Chest.* 2003;123(4):1008-13..

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

Orenstein et al. *J Pediatr.* 2009;154(4):514-520.
Khoshoo et al. *J Pediatr Gastroenterol Nutr.* 2007;44(3):331-5.
Størdal et al. *Arch Dis Child.* 2005;90(9):956-60.
Khoshoo et al. *Chest.* 2003;123(4):1008-13.

LARYNGEAL

NASPGHAN FOUNDATION
For Children's Digestive Health & Nutrition

NASPGHAN
NORTH AMERICAN SOCIETY FOR PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

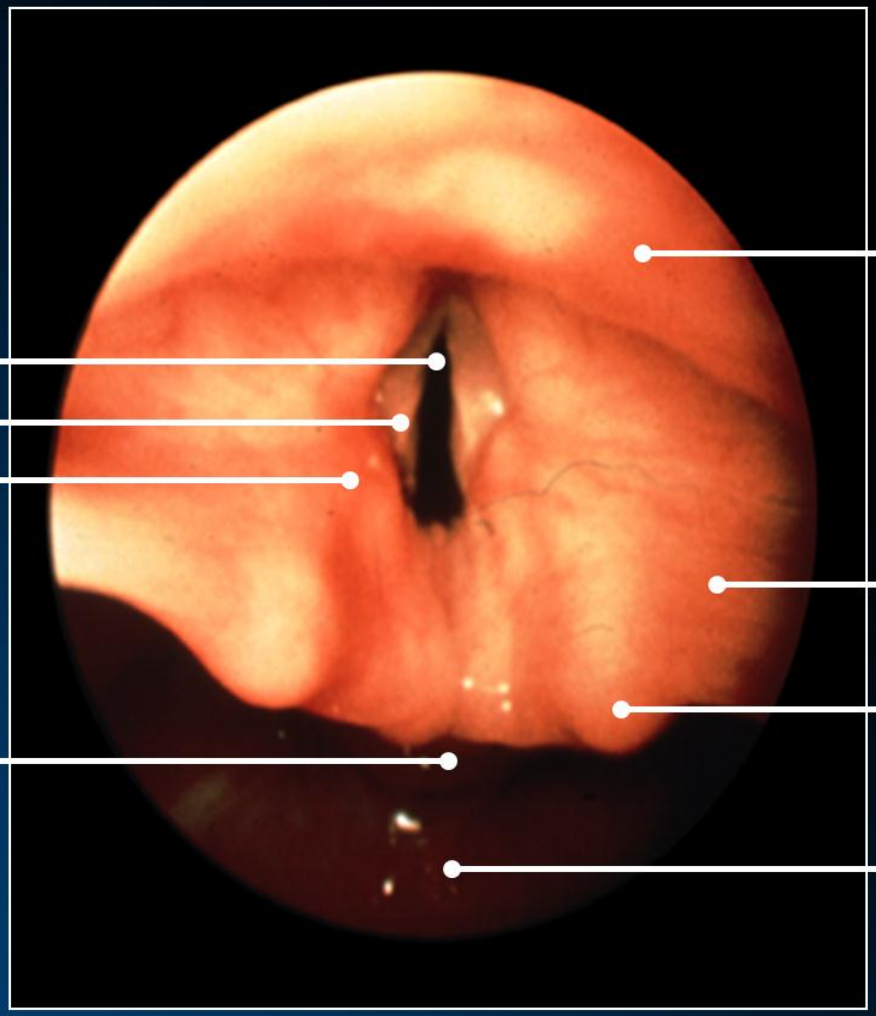
The Relationship Between Laryngeal Symptoms/Findings and GER

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

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

Laryngeal: Anterior

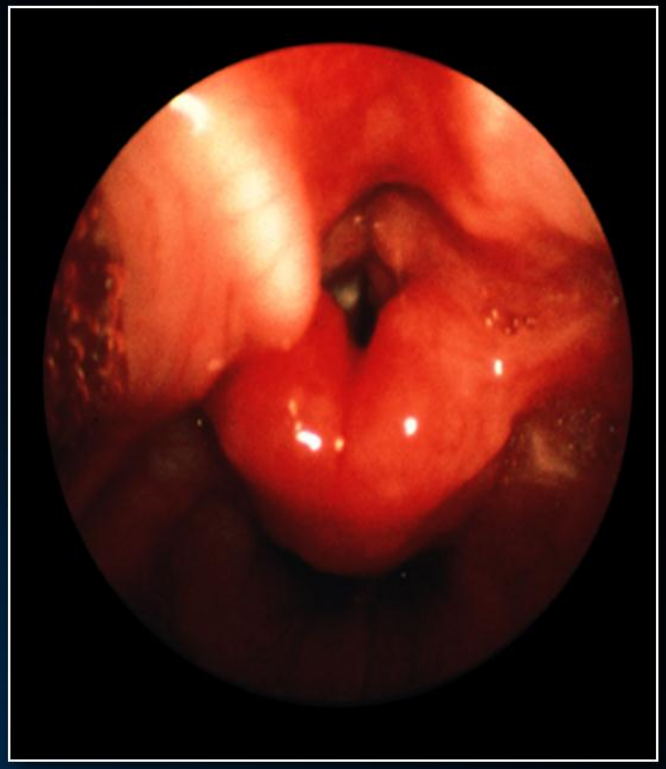


Posterior

Laryngeal: Normal vs. Erythema

Not all *red* in the airways = reflux!

Normal



Laryngeal Pharyngeal Reflux

Gumpert et al. *J Laryngol Otol.* 1998;112:49-54.

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

Chang. *Otolaryngol Clin North Am.* 2010;43(1):181-98.
Vandenplas et al. *J Pediatr Gastroenter Nutr.* 2009;49:498-547.
Sherman et al. *Am J Gastroenterol.* 2009;104:1278-95.
Kahrilis et al. *Gastroenterology.* 2008;135(4):1392-1413.

Nocturnal Acid Breakthrough: Presentation

Patients with Nocturnal Acid Breakthrough (NAB) may have:

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

Rudolph et al, *J Pediatr Gastroenterol Nutr* 2001;32:S1.
Katz. *Aliment Pharmacol Ther.* 2005;22 Suppl 3:31-8.

Nocturnal Acid Breakthrough: Management

- The pharmcodynamics of PPIs limit their control of night time acidity
- Night time acidity may be improved by:
  - Attention to PPI dosing schedule
  - Using higher doses of PPIs
  - Adding an H_2-RA at bedtime to an QD or BID PPI

Rudolph et al, *J Pediatr Gastroenterol Nutr* 2001;32:S1.
Katz. *Aliment Pharmacol Ther.* 2005;22 Suppl 3:31-8.

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 + H_2RA

	%age with NAB	%age time intragastric pH <4		
		Upright	Recumbent	Entire Period
PPI bid	64	29 +/-3	33.5 +/-3.4	31.5 +/-2.8
PPI bid + H2RA qhs	17	18 +/-2.9	12.5 +/-3.1	18 +/-3

- H_2RAs may be considered as adjunct therapy when suppression of night time gastric acid is required

Rudolph et al, *J Pediatr Gastroenterol Nutr* 2001;32:S1.
Mainie et al *J Clin Gastroenterol*. 2008;42(6):676-9.

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)

Jansson et al. Clin Gastroenterol Hepatol. 2009 Sep;7(9):960-5.
Gunasekaran et al. *BMC Gastroenterol.* 2009 Nov 18;9:84.

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.

Pfefferkorn et al. *J Pediatr Gastroenterol Nutr.* 2006;42(2):160-5.

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

Gunasekaran et al. *BMC Gastroenterol.* 2009 Nov 18;9:84.

Nocturnal Acid Breakthrough: Children vs. Adults

	Adult (Farup et al)	Children (Molle et al)
Prevalence of nocturnal GER	10% in a random phone survey of the population	8.7% in children with asthma
Mechanism	Impaired esophageal clearance due to reduced swallows and saliva volume	Not studied
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

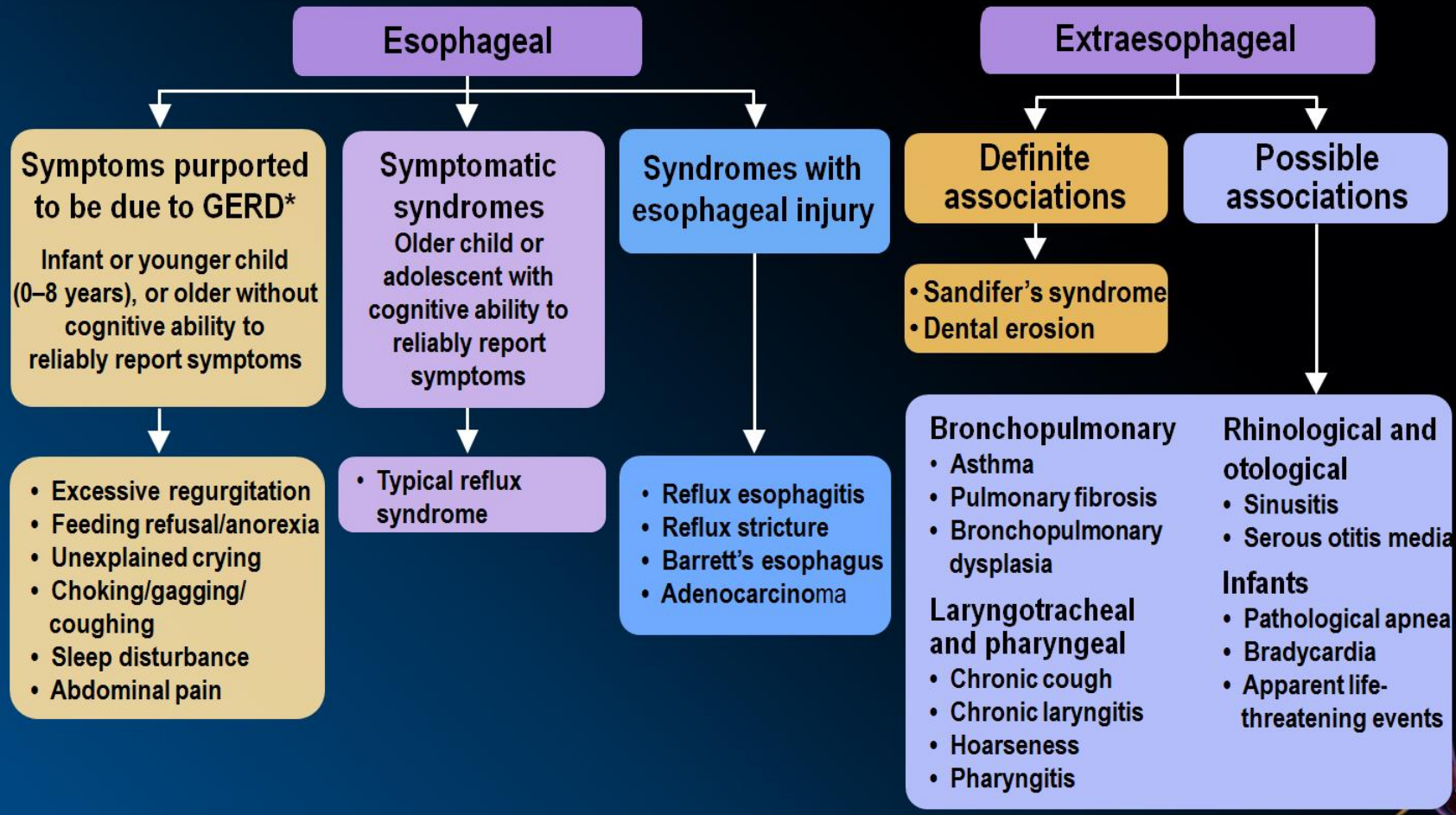
Molle et al, *Journal of Asthma*. 2009 46(4):347-350.
Farup et al, *Arch Intern Med*. 2001. Jan 8;161(1):45-52.

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



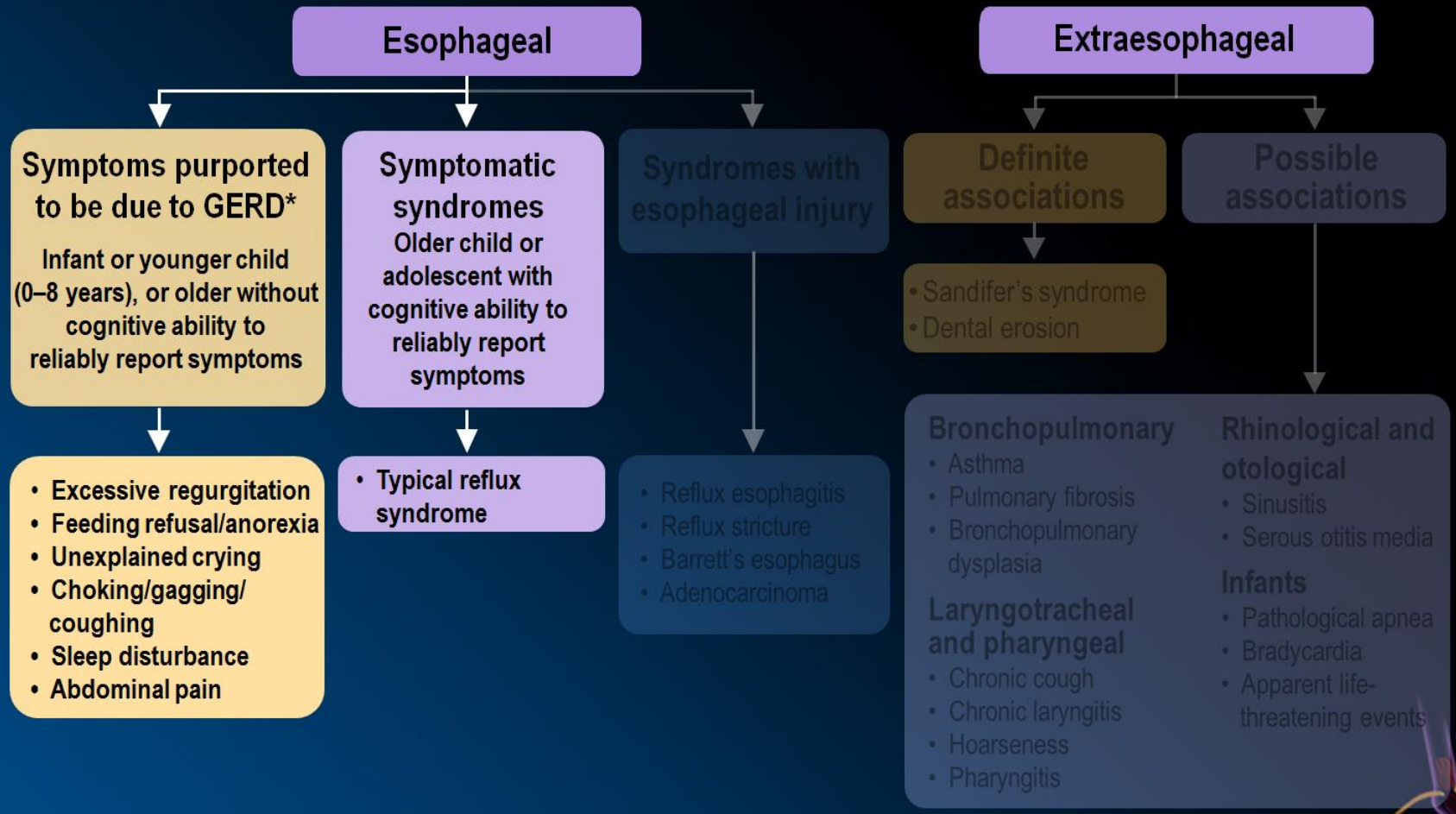
* Where other causes have been ruled out (e.g. food allergy, especially in infants)

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

NASPGHAN FOUNDATION For Children's Digestive Health & Nutrition

NASPGHAN North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

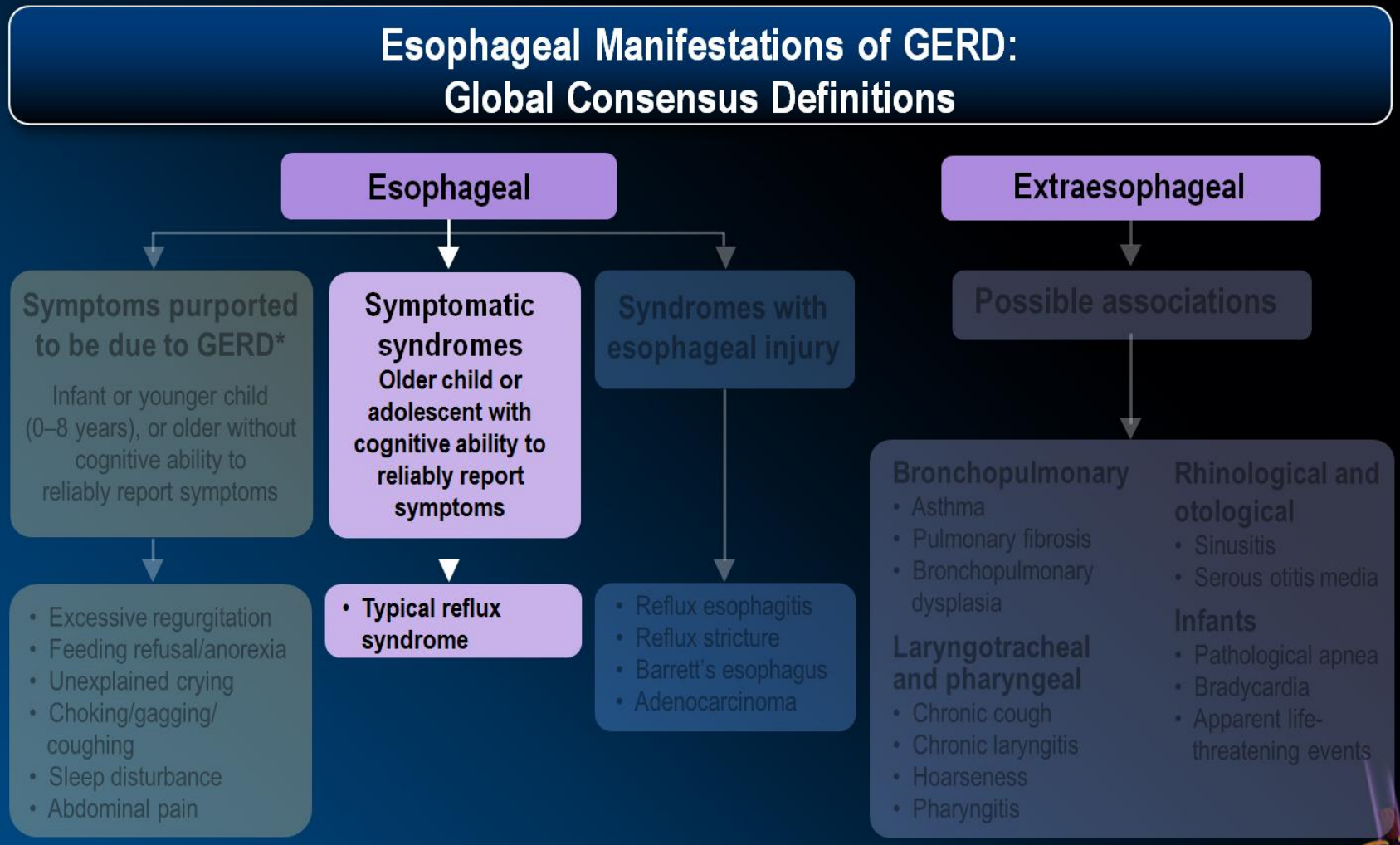
Esophageal Manifestations of GERD: Global Consensus Definitions



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

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

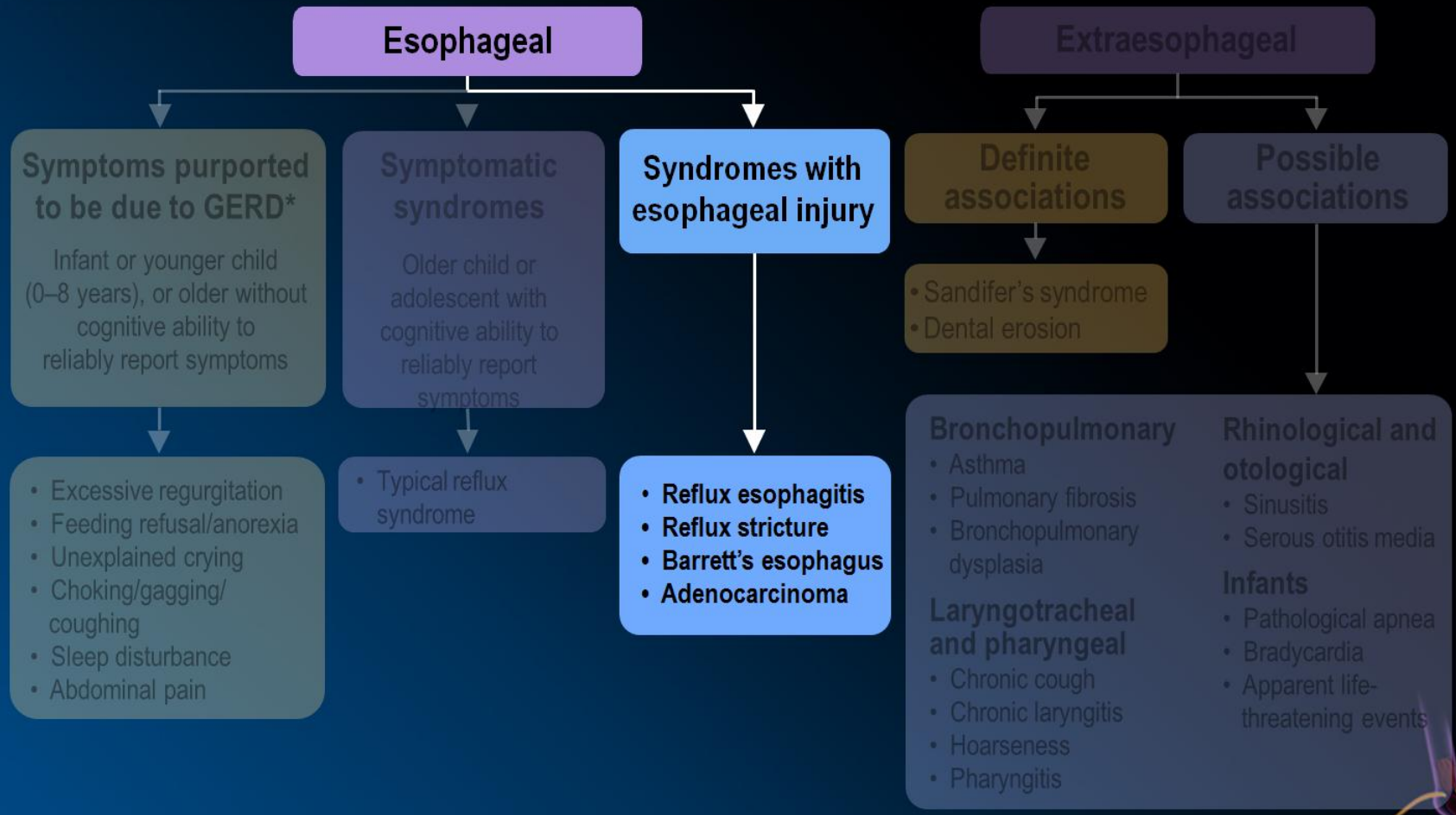
Definition of GERD in Pediatric Patients



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

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

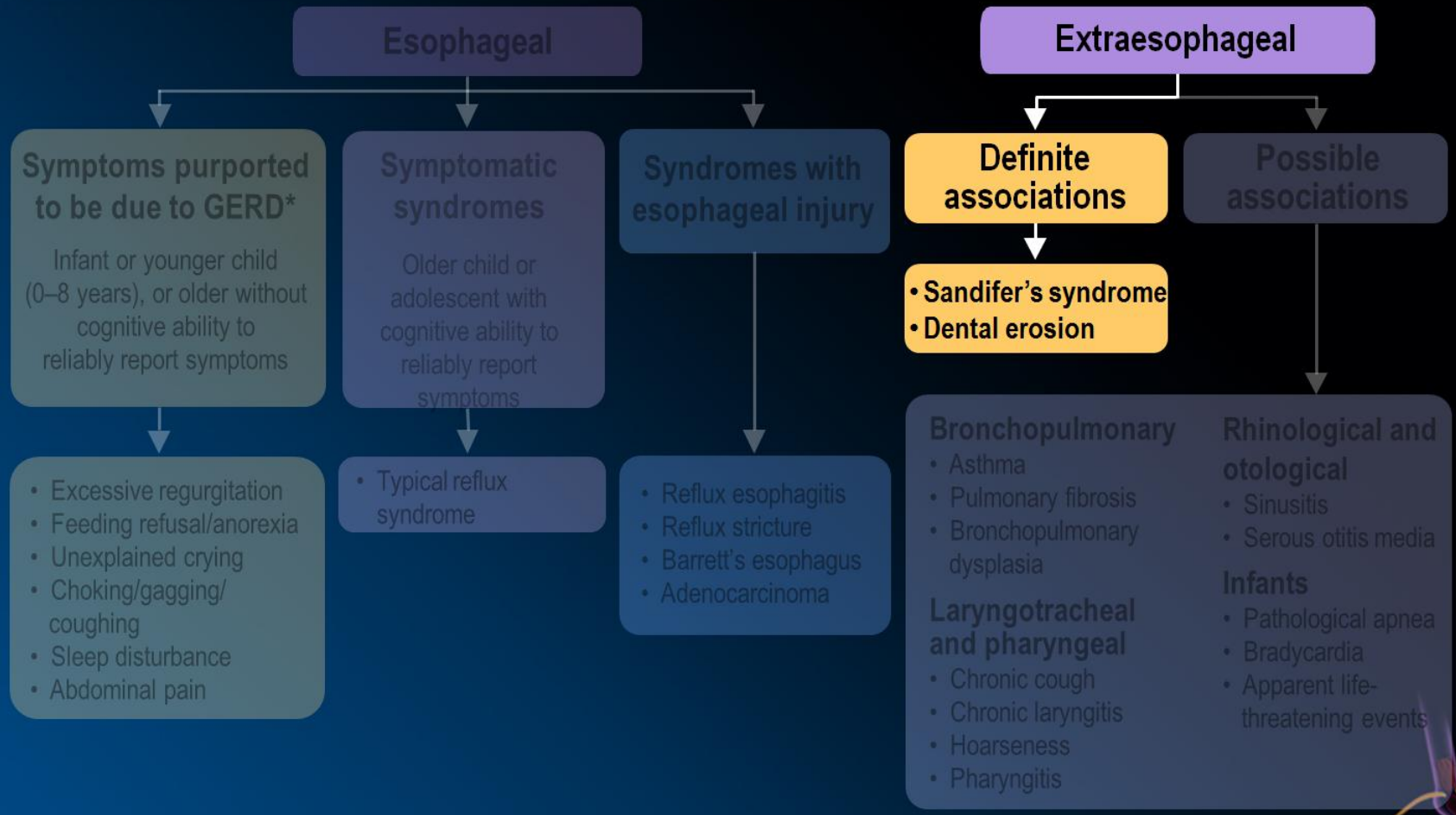
Esophageal Manifestations of GERD: Global Consensus Definitions



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

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

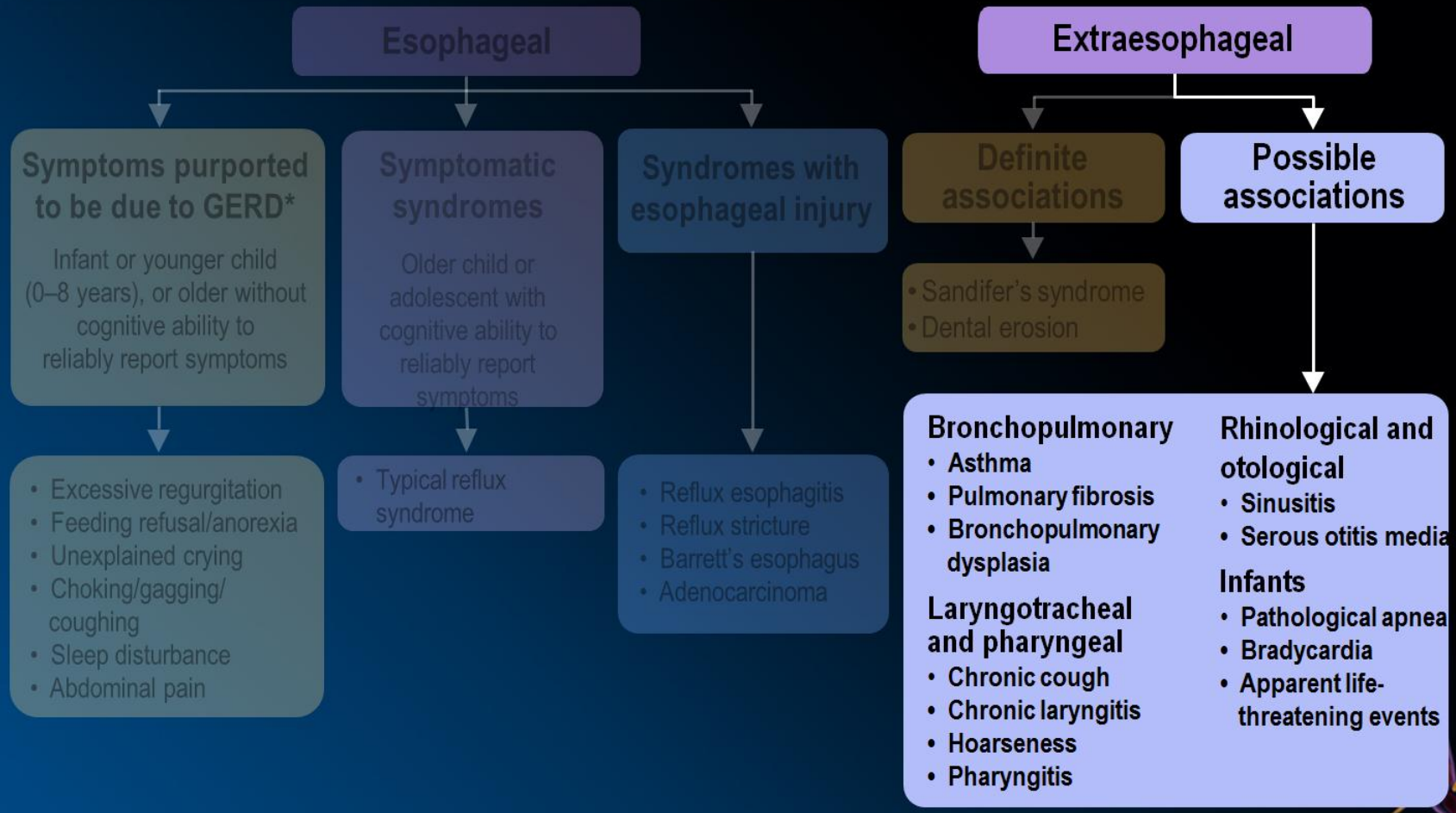
Extraesophageal Associations of GERD: Global Consensus Definitions



*** 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



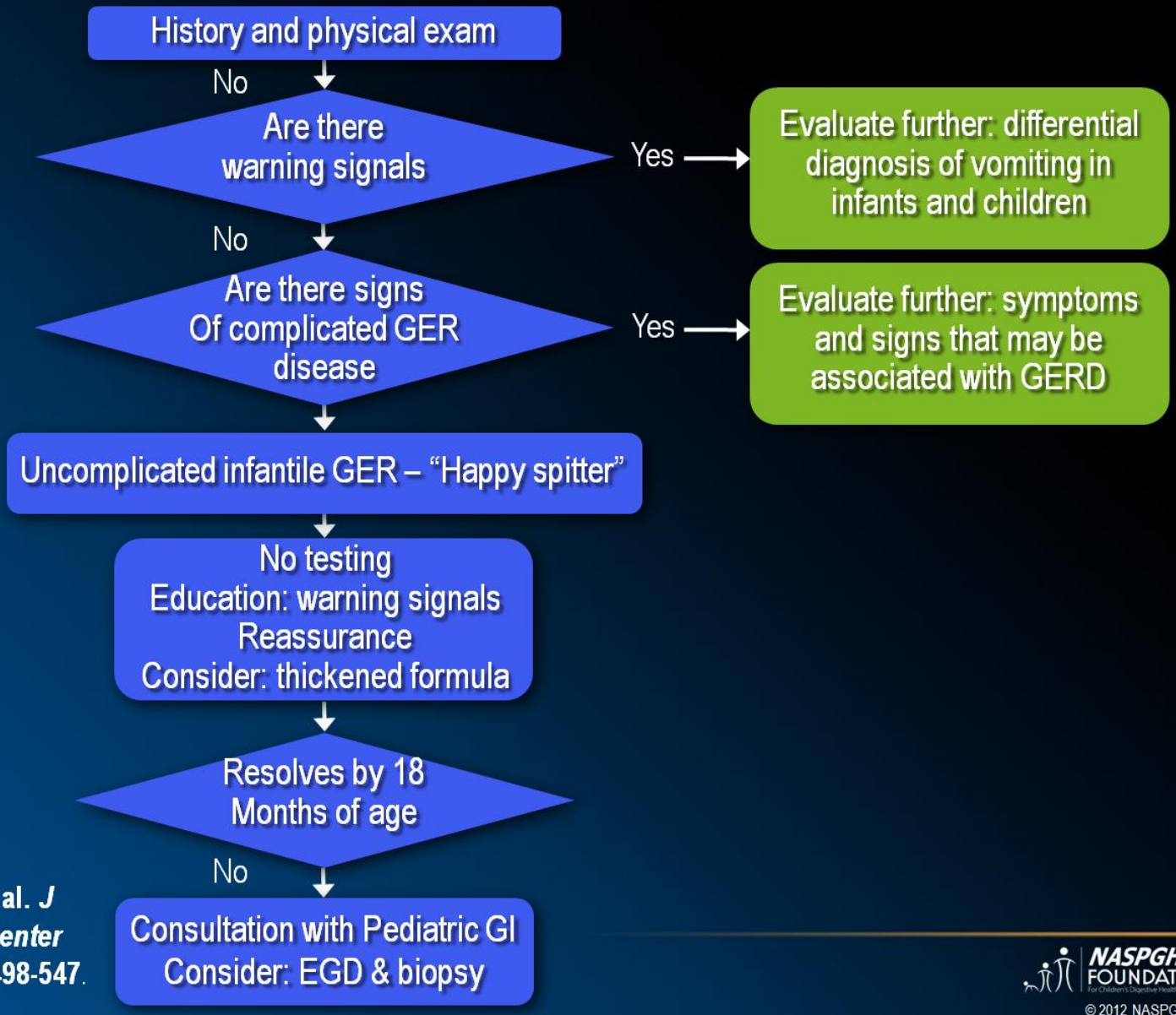
* Where other causes have been ruled out (e.g. food allergy, especially in infants)

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

NASPGHAN FOUNDATION For Children's Digestive Health & Nutrition

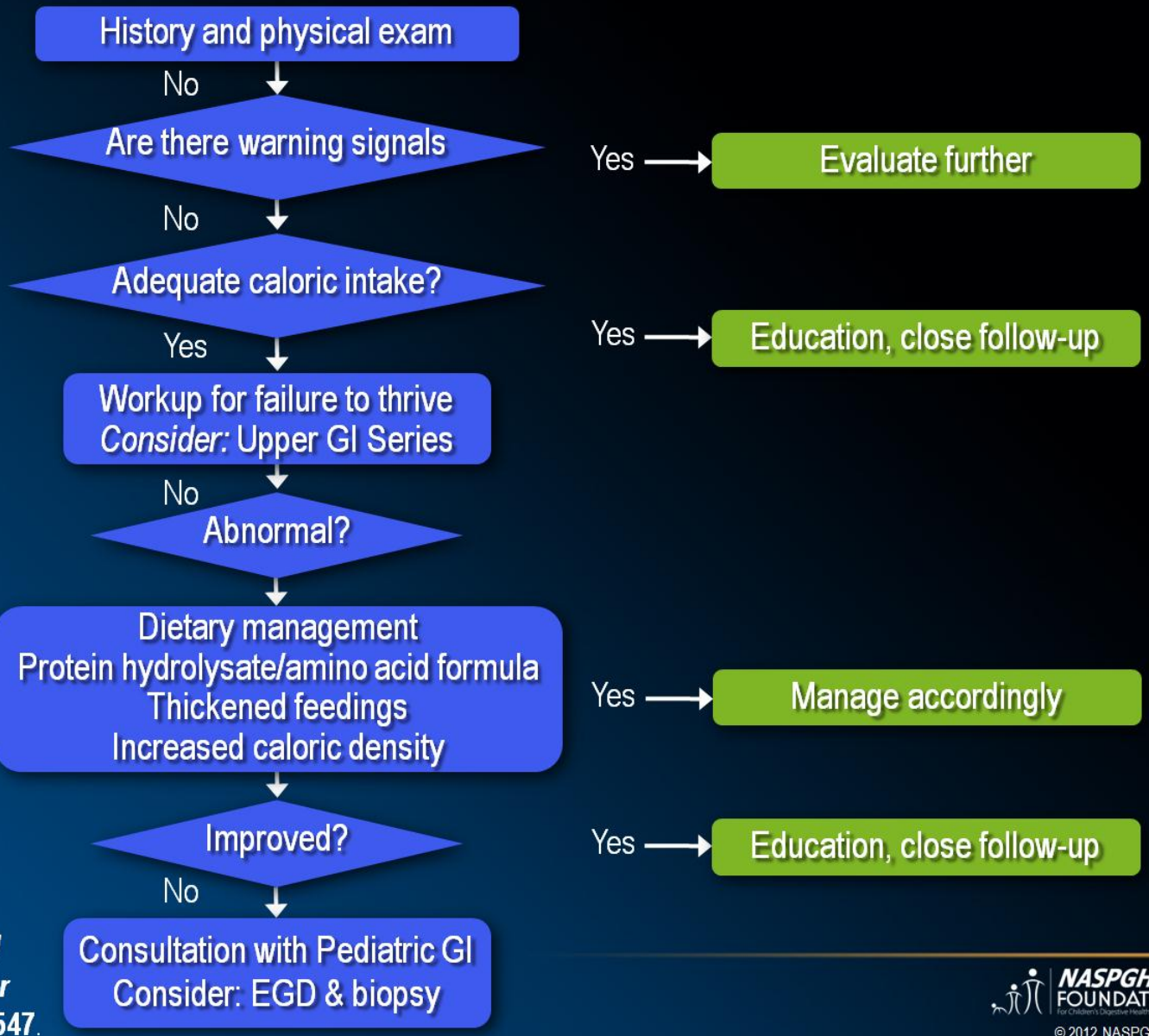
NASPGHAN NORTH AMERICAN SOCIETY FOR PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

Approach to the Infant with Recurrent Regurgitation and Vomiting



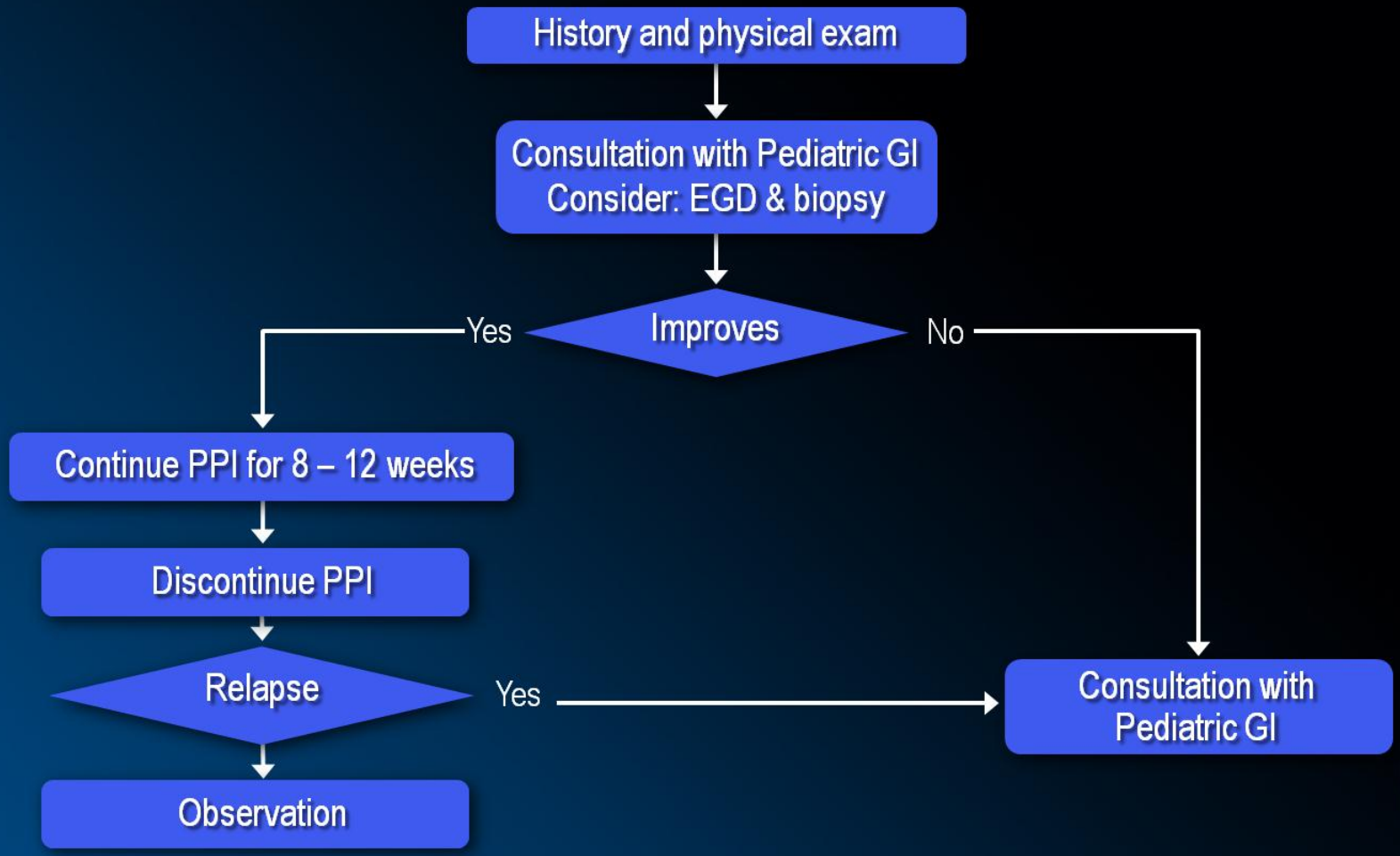
Vandenplas et al. *J Pediatr Gastroenter Nutr.* 2009;49:498-547.

Approach to the Infant with Recurrent Regurgitation and Weight Loss



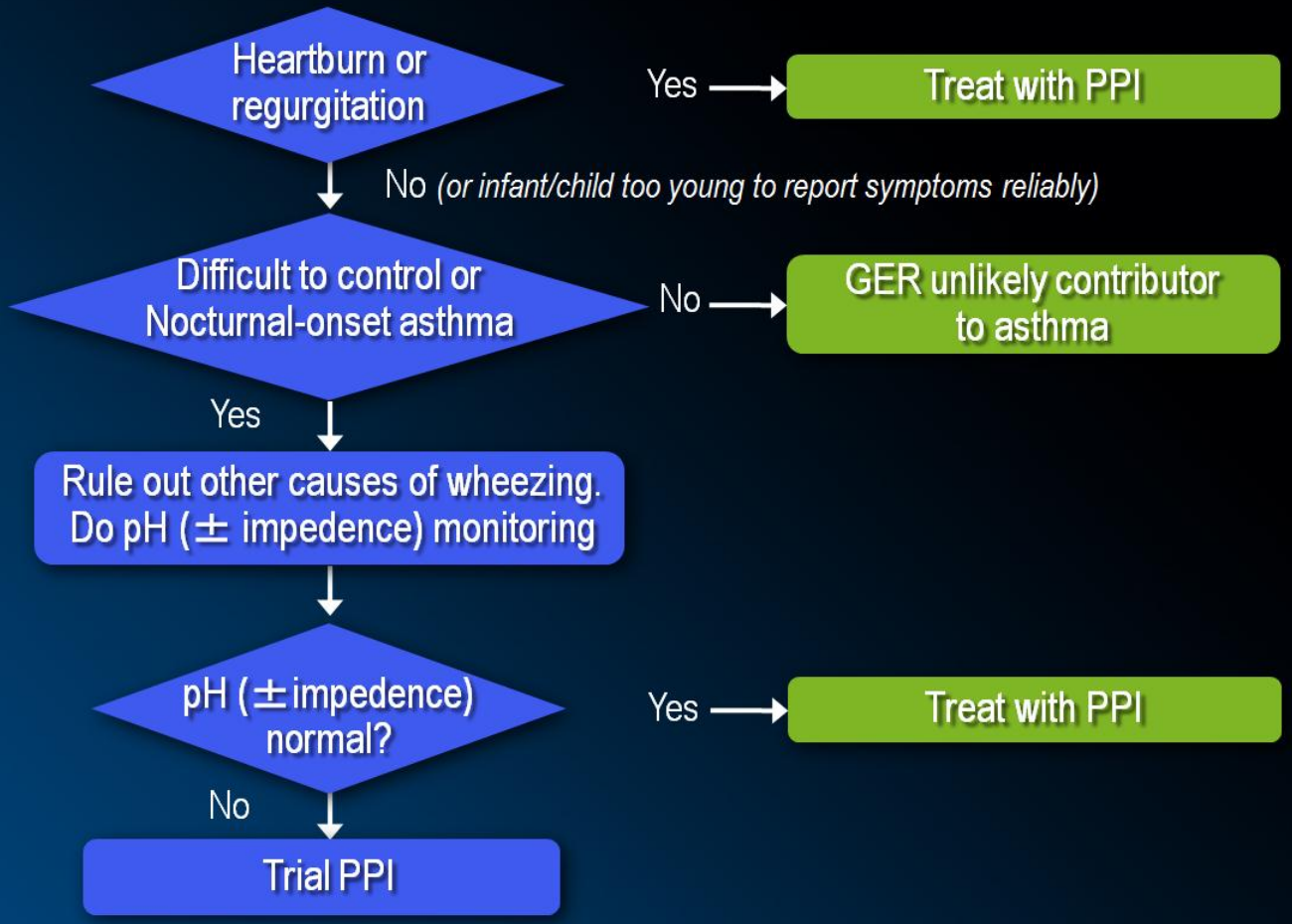
Vandenplas et al. *J Pediatr Gastroenter Nutr.* 2009;49:498-547.

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.

SUMMARY

NASPGHAN FOUNDATION
For Children's Digestive Health & Nutrition

NASPGHAN
NORTH AMERICAN SOCIETY FOR PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

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