Extra-Esophageal Gastroesophageal Reflux (GERD)

Real or Fake news?

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GICAN FOR K

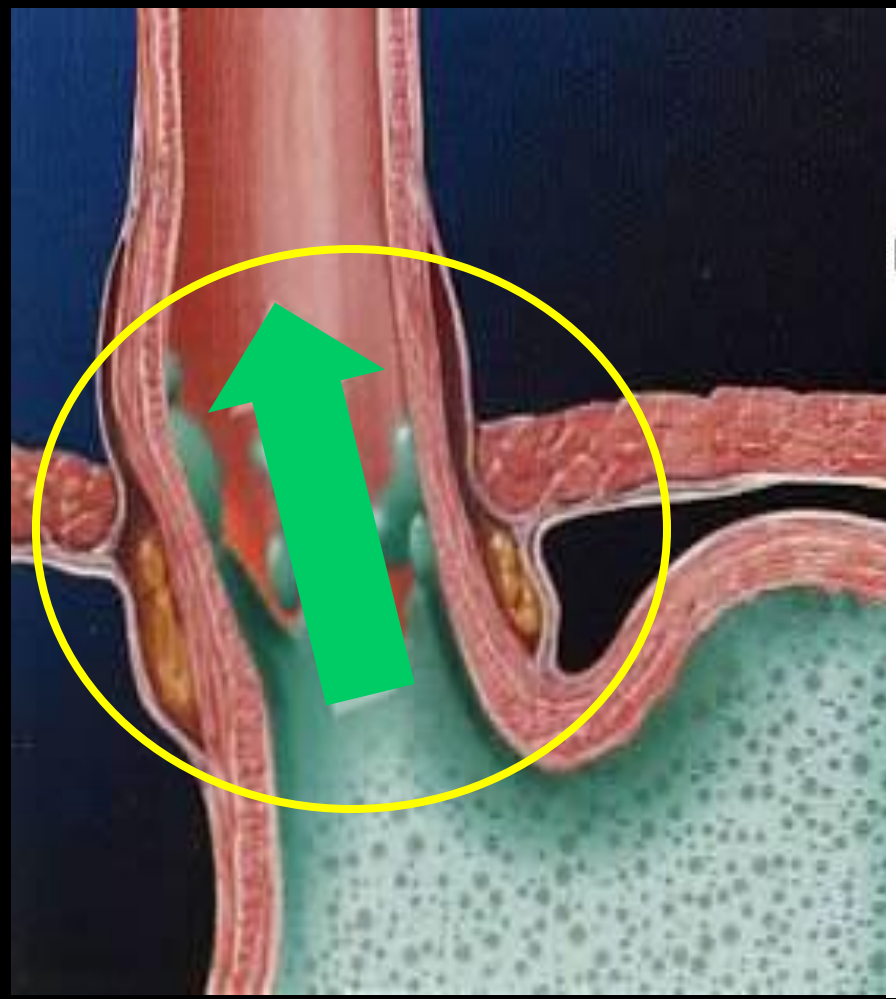
Faculty Disclosure

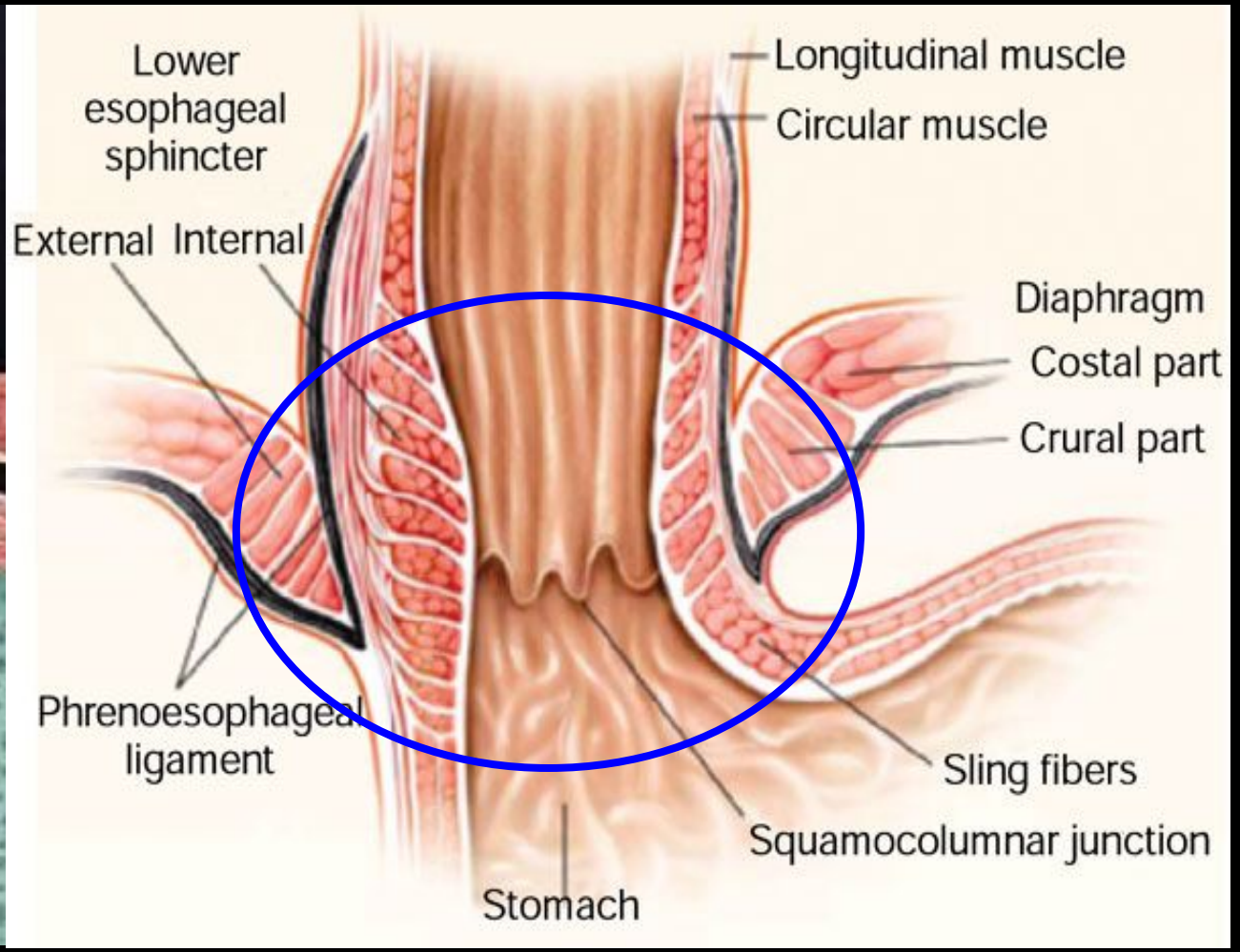
- **Do intend to discuss use of a commercial product/service – *Pharmacological agents for treatment of esophageal diseases***
- **Do intend to discuss FDA and non-FDA approved, off-label uses of products/providers of service**
- **Do have significant financial relationships:**
  - **Grants/Research Support: *None***
  - **Speakers Bureau/Honoraria: *Mead Johnson Nutrition/Reckitt***
  - **Consulting Fees: *Janssen/Johnson & Johnson; Takeda Global Research and Development; Evolve BioSystems, Inc.; Mead Johnson Nutrition; Nutricia North America; Ironwood Pharmaceuticals; Regeneron/Sanofi Pharmaceuticals***
  - **Other: *None***
- ***None of these relationships had anything to do with the content or preparation of this presentation***

Learning Objectives

- Define gastroesophageal reflux (GER) in comparison to gastroesophageal reflux disease (GERD) in pediatrics
- Discuss the phenotypes of GERD, and that all reflux doesn't respond to acid suppression i.e. wait before you prescribe the PPI
- Review the extra-esophageal manifestations of reflux and
- Provide an overview of what conditions are biologically plausible, an association and what extra-esophageal disorders are actually are caused by reflux

Gastroesophageal Reflux (GER)





Vandenplas Y, Rudolph C , Hassall E et al. J Pediatric Gastroenterol Nutr 2009; R Rosen et al J Pediatr Gastroenterol Nutr. 2018 March ; 66(3): 516–554.

Springer Link

Reviews | Published: 19 April 2022

The Pathway from Anatomy and Physiology to Diagn and D

C. J. Mayer

Dysphagia

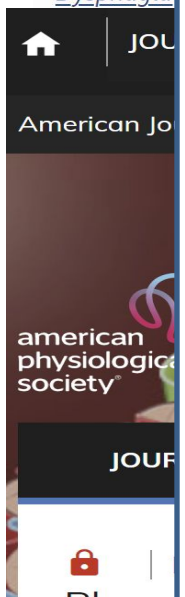
Springer Link

Original Article | Published: 12 February 2021

Characterization of Esophageal and Sphincter Reflexes

Aerodigestive reflexes are intact by 38 weeks gestation…

thus, it isn't an "immature" LES that leads to GERD



Phary impor

Zakia Sultana, Kathryn A. Hasenstab, and Sudarshan R. Jadcherla

23 JUL 2021 // https://doi.org/10.1152/ajpgi.00480.2020

TOOLS

GERD in pediatric patients is present when reflux of gastric contents is the cause of troublesome symptoms and/or complications

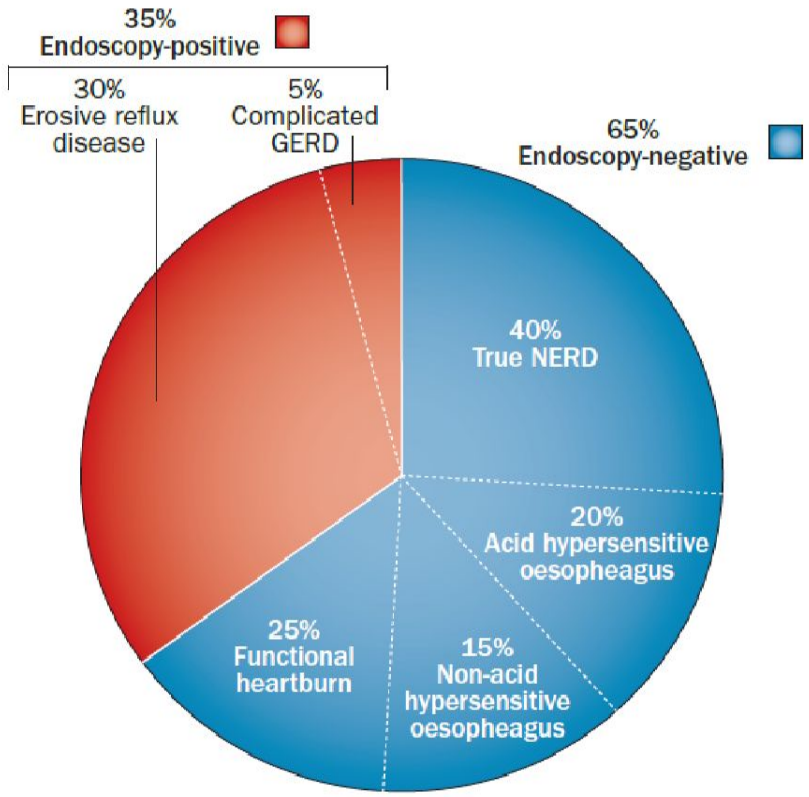
Sherman PM, Hassall E, Fagundes-Neto U, Gold BD, Kato S, Koletzko S, Orenstein SR, Rudolph D, Vakil N, Vandenplas Y. Am J Gastroenterol, April 2009

Do we need a PCDAI or PUCAI or an I-SEE for GERD to better phenotype disease?

Collaborative, interdisciplinary research in children with GERD to better phenotype disease, assuring optimal treatment - critically needed!!!

Rosen R et al J Pediatr Gastroenterol Nutr 2018

Incidence of Reflux Disease Subtypes in Adults



Reprinted by permission from Macmillan Publishers Ltd. [1]

- In 221 adult patients, 54% did not have a diagnosis that would respond to PPI therapy [2]
- There are no pediatric studies that systematically address this clinical challenge

1. Savarino E et al. *Nat Rev Gastroenterol* 2013;10:371-80.
2. Cheng FK et al. *Clinical Gastroenterol Hepatol* 2015;13:867-73.

Can GERD be Phenotyped?

Persistent Reflux and + SAP	Physiologic Reflux and + SAP	Persistent Reflux and - SAP	Physiologic Reflux and - SAP	Pathological and +/- SAP
GERD	NERD Hypersensitive Esophagus	GERD or Hypersensitive esophagus ?	Functional Heartburn	Rumination Supra-gastric Belching "No Burp Syndrome (RPCD)"
PPI Anti-reflux Therapy	PPI + Modulators of Perception	Symptoms not directly related to acid exposure	Alternative therapies	

SAP: symptom association probable

GERD: gastroesophageal reflux disease

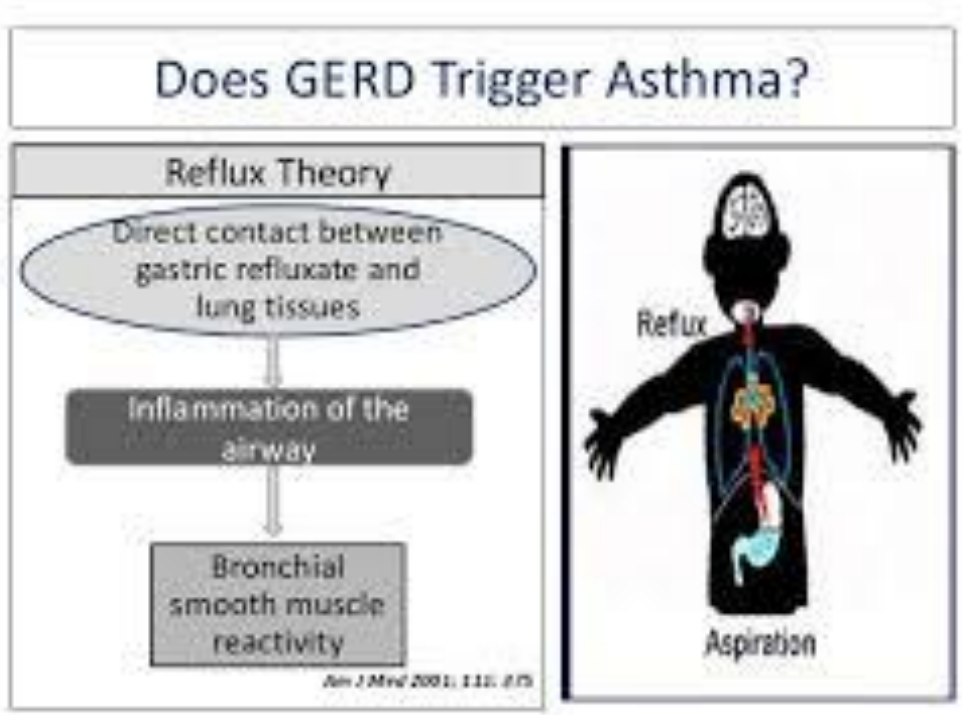
NERD: non erosive reflux disease

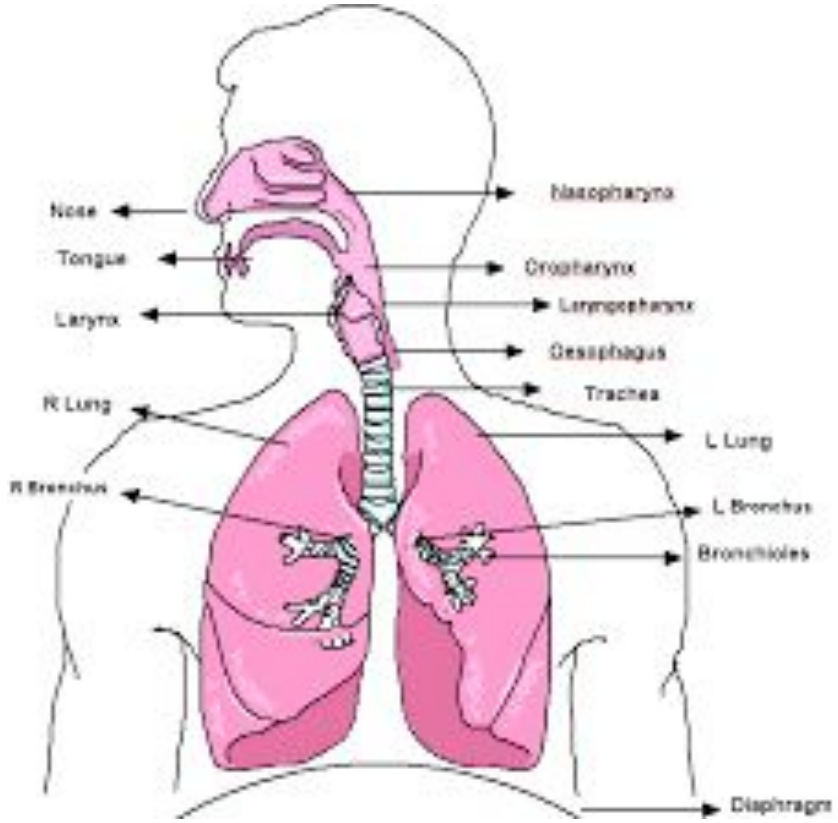
Modulators of perception:
- Elavil; anti-anxiety; Periactin

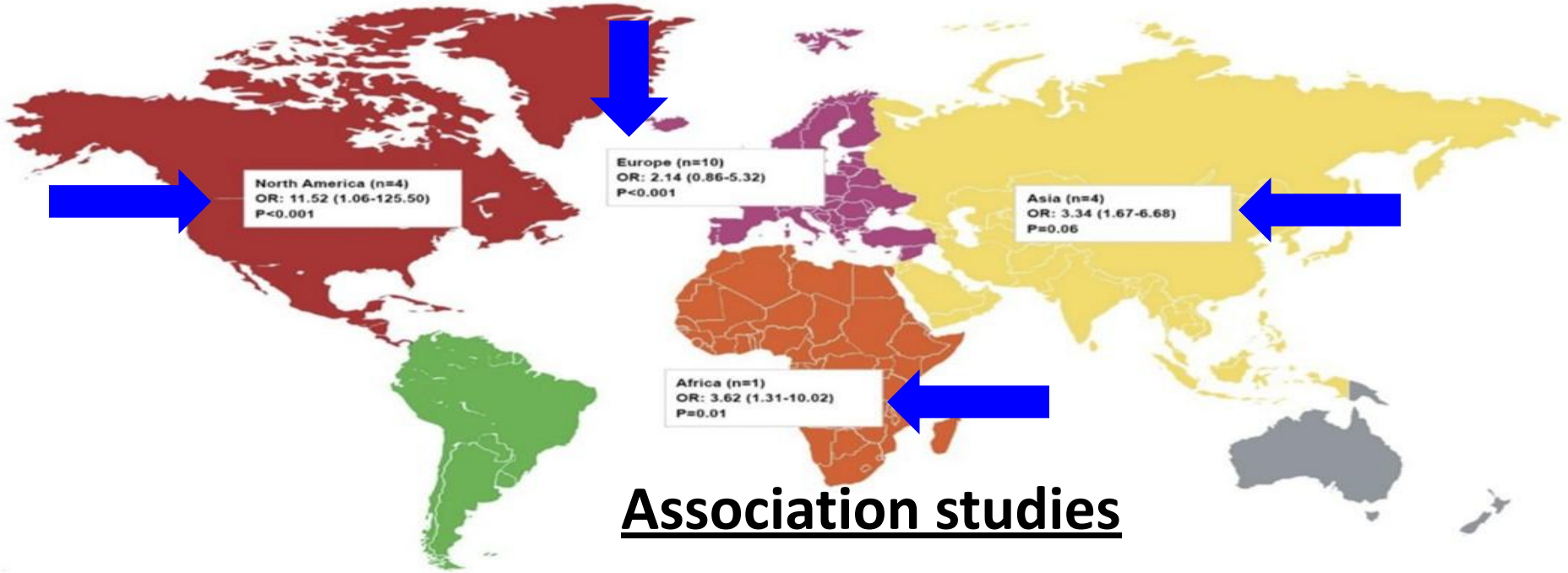
Alternative therapies:
- Cognitive behavioral therapy; hypnotherapy

Boeckxstaens G, Postgrad Med J 2015

What about extra-esophageal GERD… Association or Causation?







Association studies

FIGURE 1: Pooled frequency of ETW in patients with GERD in different regions of the world

Adapted and recreated from reference [15]

ETW: Erosive tooth wear; GERD: Gastroesophageal reflux disease; OR: Odds ratio; n: number of studies.

Patients with GERD have a 2-4-fold increased odds ratio of presenting with ETW compared with patients without GERD [15]. A systematic review reported that the mean prevalence of dental erosion in children with GERD was higher than in healthy children (57.2%; SD:34.5 vs. 12.5%; SD:9.3) [16]. The studies included were heterogeneous in diagnostic methodology but they suggested the probable involvement of gastric acid reflux in ETW development. In adult patients with GERD, the prevalence of ETW ranged between 14.4% and 98.1%, with a mean prevalence of 83%, reflecting a strong association between both conditions in adults [17,18]. Furthermore, a high association between GERD and ETW was also found in special populations like the neurodivergent community, 46% had ETW, of which 65% had GERD [11,19]. Likewise, the adult psychiatric inpatients showed a strong association between ETW and gastric reflux (adjusted OR=2.1;

GERD and Dental Disease

- **Biologically plausible**
  - ✔ Yes
- **Association via Epidemiology**
  - ✔ Yes
- **Causality**
  - ✔ Yes in animal models
  - ✔ More research needed; i.e. clinical trials with validated outcomes

Apparent Life Threatening Episodes (ALTE) and Apnea cont'd

ORIGINAL ARTICLES

www.jpeds.com • The Journal of Pediatrics

Respiratory Events in Infants Presenting with Apparent Life Threatening Events: Is There an Explanation from Esophageal Motility?

Kathryn A. Hasenstab, BS, BME[1], and Sudarshan R. Jadcherla, MD, FRCPI, DCH, AGAF[1,2]

- In infants with ALTE, prolonged SREs are associated with ineffective esophageal dysmotility characterized by frequent primary peristalsis and significant propagation failure…
- Thus this suggests dysfunctional regulation of swallow-respiratory junction interactions
- Further, the authors recommend that treatment NOT target gastroesophageal reflux but proximal aerodigestive tract

Hasenstab KA and Jadcherla, SR. J Pediatr 2014;165:250-5

Am J Perinatol 2025; 42(04): 486-494
DOI: 10.1055/a-2405-1545

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Original Article

Evaluation of Gastroesophageal Reflux in Symptomatic Young Infants Using Multichannel Intraluminal pH-Impedance Testing: A large Cohort Study from a Single Center

Rochelle Sequeira Gomes , Michael Favara , Sheeja Abraham , Joan Di Palma [†] , Zubair H. Aghai

› Author Affiliations

Abstract

Objective This study aimed to assess the use of combined multichannel intraluminal impedance and pH studies (MII–pH) in a large group of symptomatic young infants, to characterize the occurrence of gastroesophageal reflux disease (GERD), and to establish temporal association of the reflux behaviors with gastroesophageal reflux using symptom indices.

Study Design This is a retrospective cohort study on 181 infants who underwent MII–pH studies for clinical behaviors that were suggestive of GERD. Symptom index (SI) and symptom association probability (SAP) were used to establish symptom association with reflux. More than 100 GER episodes in 24 hours or acid reflux index > 10% was considered pathological reflux.

Results A total of 181 infants (median age: 60 days, interquartile range [IQR]: 34–108) underwent MII–pH studies with median study duration of 22.41 hours (IQR: 21.5–23.32). A total of 4,070 hours of data were analyzed, with 8,480 reflux events (2,996 [35%] acidic, 5,484 [65%] nonacidic). A total of 2,541 symptoms were noted, 894 (35%) were temporally related to reflux events. A total of 113 infants (62.4%) had positive symptom association with SI > 50% and/or SAP > 95% for at least one symptom. There was modest symptom association for choking and gagging, but apnea, bradycardia, and desaturations had poor symptom association. Only 29 infants (16%) had pathological reflux, and only 18 infants (10%) had both pathological reflux and positive symptom association.

Conclusion MII–pH can be used to characterize GERD in young infants, along with establishing temporal association with symptoms. Pathological reflux in symptomatic young infants is not common, but symptom association may occur without frequent or acidic reflux.

Keywords

- GERD
- MII–pH
- symptom association
- neonates

Outcomes for infants with BRUE diagnosed with oropharyngeal dysphagia or gastroesophageal reflux disease: a multicenter study from the Pediatric Health Information System Database

European Journal of Pediatrics

Aims and scope →

Submit manuscript →

RESEARCH | Published: 14 January 2025

Volume 184, article number 134, (2025) Cite this article

Daniel R. Duncan ✉, Enju Liu, Clare Golden, Amanda S. Growdon, Dionne A. Graham, Christopher P. Landrigan & Rachel L. Rosen

Abstract

abstract

We aimed to determine the prevalence of gastroesophageal reflux disease (GERD) and oropharyngeal dysphagia as explanatory diagnoses, risk factors for acid suppression treatment, and risk factors for repeat hospital visit in infants hospitalized after brief resolved unexplained event (BRUE) using a multicenter pediatric database. We performed a multicenter retrospective database study of infants admitted with BRUE in the Pediatric Health Information System between 2016 and 2021. Data included diagnostic testing, explanatory diagnoses, treatment with acid suppression, and related repeat hospital visits within 6 months. Multivariable logistic regression models were used to determine risk factors for treatment with acid suppression and repeat hospital visit. Of 17,558 subjects admitted to 47 hospitals, 34% were given an explanatory diagnosis of GERD and 1.4% oropharyngeal dysphagia. Twelve percent were treated with acid suppression, with some centers having rates as high as 26%. Multiple factors, including most notably the GERD diagnosis, were associated with increased prescribing risk. Ten percent of subjects had repeat hospital visits. Subjects given an explanatory diagnosis of GERD (OR 1.66, 95% CI 1.48–1.86, $p < 0.001$) or oropharyngeal dysphagia (OR 2.13, 95% CI 1.55–2.91, $p < 0.001$) had increased risk for repeat hospital visit as did those treated with acid suppression.

Conclusion

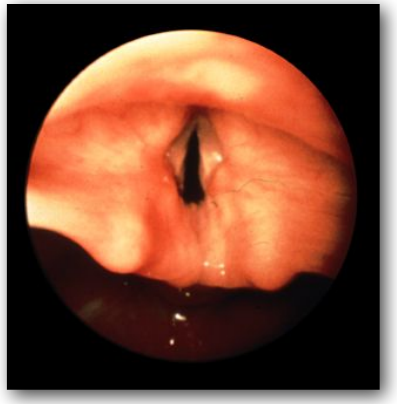
GERD as an explanatory diagnosis was associated with increased risk of repeat hospital visit, despite its conception as a benign, treatable condition. Treatment with acid suppression was common but did not prevent repeat hospitalization. Oropharyngeal dysphagia as an explanatory diagnosis was also associated with increased risk of repeat hospital visit.

GERD and ALTE and/or BRUE

- **Biologically plausible**
  - ✔ **Yes**
- **Association via Epidemiology**
  - ✔ **Yes**
- **Causality**
  - ✔ **Not well-established; many apneas occur independently of GERD episodes, and apnea events often precede GERD in cases where they coexist**
  - ✔ **More research is needed**

ENT Manifestations of GERD

Have they met the burden of proof for causality?



Laryngeal: Normal vs. Erythema Or is All that is 'red' reflux?

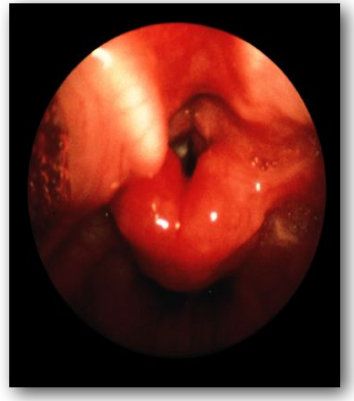


Table 1. Differences Between GERD and LPR	
GERD	**LPR**
Accompanied by esophagitis and/ or heartburn	Esophagitis or heartburn is rarely present
Reflux is nocturnal or in supine position	Reflux during daytime or in upright position
Abnormal esophageal motility and prolonged esophageal acid exposure	Intermittent episodes of reflux
Dysfunction of the lower esophageal sphincter	Dysfunction of the upper esophageal sphincter
Throat related symptoms are sometimes present	Leads to throat related symptoms and damage to the laryngopharyngeal epithelium

GERD, gastroesophageal reflux disease; LPR, laryngopharyngeal reflux.

CL Kuo Archives of Otorhinolaryngology-Head & Neck Surgery. 2019;3(1)
Keesecker, S. E., et al. Laryngoscope 2015; 125(3): 667-673

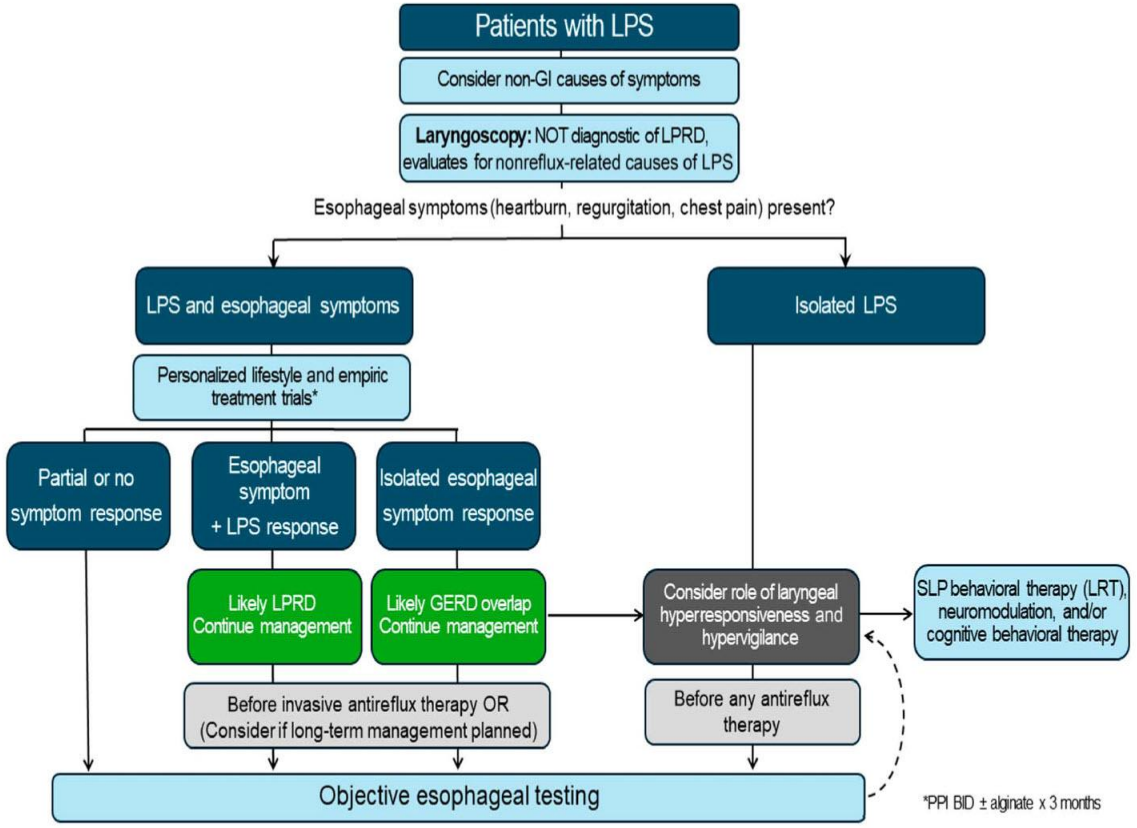


Figure 1. San Diego Consensus for laryngopharyngeal symptoms and laryngopharyngeal reflux disease. The initial evaluation for patients meeting definition for LPS include considering non-GI causes of symptoms, laryngoscopy to evaluate for nonreflux-related causes of LPS, and discerning presence of concomitant esophageal reflux symptoms (heartburn, regurgitation). For LPS with concomitant esophageal reflux symptoms (left side of diagram), personalized lifestyle and empiric trials of acid suppression are appropriate, followed by symptom assessment in 3 months. Those with esophageal symptom and LPS response likely have LPRD and can continue management. Those with isolated esophageal symptom response may have ongoing LPS with GERD overlap; while they can continue management, it is also important to consider a disordered laryngeal behavioral response. For patients with partial or no response of esophageal symptoms or LPS, the next step is objective esophageal testing and consideration of a disordered laryngeal behavioral response. For any patient with LPS and concomitant esophageal reflux symptoms, objective esophageal testing to assess for GERD/LPRD is indicated before invasive antireflux therapy such as endoscopic or surgical intervention and should also be considered if long-term antireflux management is planned. On the other hand, for patients with isolated LPS (right side of diagram), it is critical to consider a disordered laryngeal behavioral response at the outset, and it is suggested to proceed with objective esophageal testing before any antireflux management to personalize management. The dashed curved arrow highlights that disordered laryngeal behaviors can coexist/overlap in the setting of objective GERD/LPRD and be a driver of symptoms. If disordered laryngeal behaviors are suspected, speech-language pathology-guided behavioral therapy (e.g., laryngeal recalibration therapy), neuromodulation, and/or cognitive behavioral therapy can be trialed. GERD, gastroesophageal reflux disease; GI, gastrointestinal; LPRD, laryngopharyngeal reflux disease; LPS, laryngopharyngeal symptom.

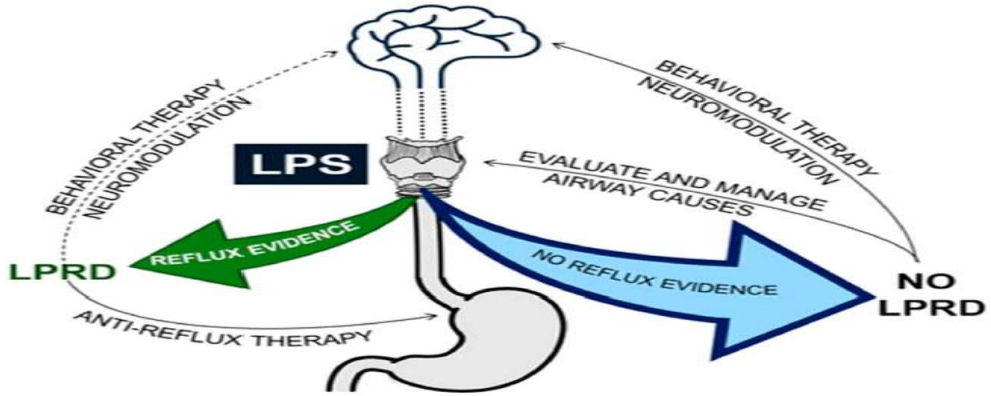


Figure 2. Paradigm of laryngopharyngeal symptoms and laryngopharyngeal reflux disease. The presence of LPS does not equate to LPRD. More commonly, patients with LPS have no objective evidence of reflux, in which case the evaluation should focus on nongastrointestinal causes of symptoms including the brain-larynx interaction. For patients with objective evidence of LPRD therapeutic constructs include anti-reflux management and therapy focused on laryngeal behavioral responses. LPRD, laryngopharyngeal reflux disease; LPS, laryngopharyngeal symptom.

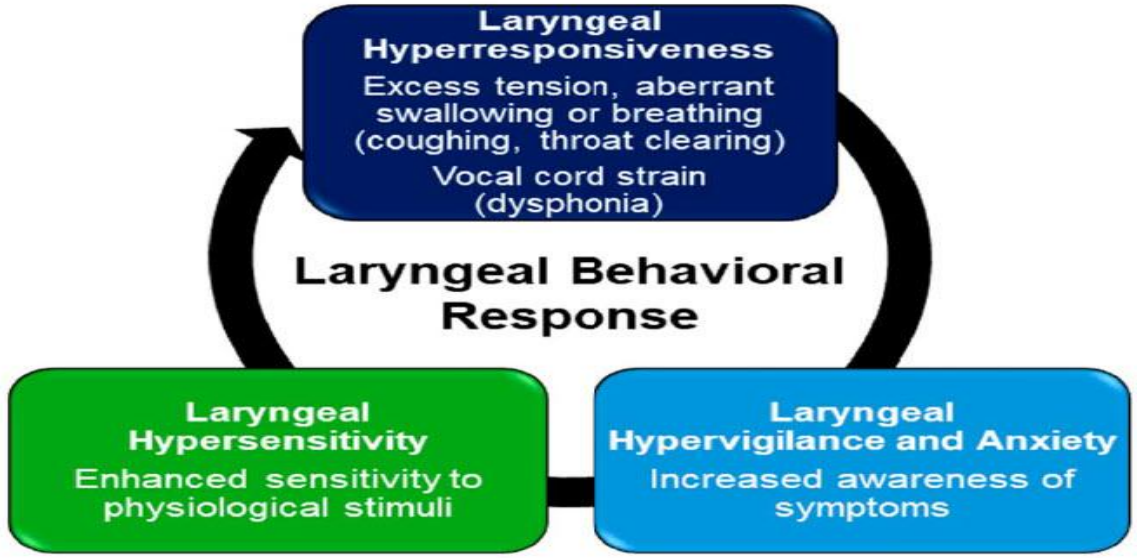
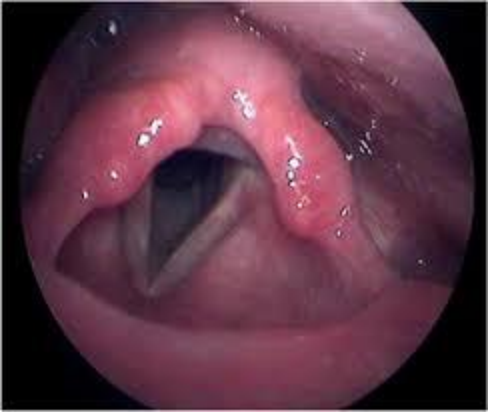
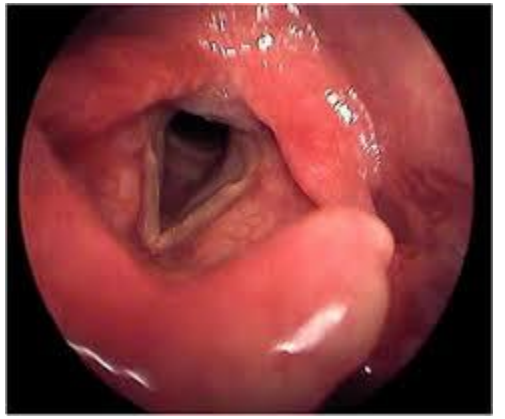


Figure 3. Laryngeal behavioral response. The model of laryngeal behavioral responses involves a cyclical relationship between laryngeal hypersensitivity, laryngeal hyperresponse, and laryngeal hypervigilance, which can contribute to or drive LPS burden. LPS, laryngopharyngeal symptom.



GERD and Laryngo-pharyngeal Disease



- **Biologically plausible**
  - ✔ Yes
- **Association via Epidemiology**
  - ✔ Yes
- **Causality**
  - ✔ Growing body of data in select populations
  - ✔ More research is needed

Clinical Gastroenterology and Hepatology 2023;21:1414–1421

CLINICAL PRACTICE UPDATE

AGA Clinical Practice Update on the Diagnosis and Management of Extraesophageal Gastroesophageal Reflux Disease: Expert Review

Joan W. Chen,[1] Marcelo F. Vela,[2] Kathryn A. Peterson,[3] and Dustin A. Carlson[4]

[1]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, Michigan; [2]Division of Gastroenterology and Hepatology, Mayo Clinic, Scottsdale, Arizona; [3]Division of Gastroenterology, University of Utah, Salt Lake City, Utah; and [4]Division of Gastroenterology and Hepatology, Northwestern University Feinberg School of Medicine, Chicago, Illinois

DESCRIPTION: The purpose of this American Gastroenterological Association (AGA) Institute Clinical Practice Update is to review the available evidence and expert advice regarding the clinical management of patients with suspected extraesophageal gastroesophageal reflux disease.

METHODS: This article provides practical advice based on the available published evidence including that identified from recently published reviews from leading investigators in the field, prospective and population studies, clinical trials, and recent clinical guidelines and technical reviews. This best practice document is not based on a formal systematic review. The best practice advice as presented in this document applies to patients with symptoms or conditions suspected to be related to extraesophageal reflux (EER). This expert review was commissioned and approved by the AGA Institute Clinical Practice Updates Committee (CPUC) and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership and underwent internal peer review by the CPUC and external peer review through standard procedures of *Clinical Gastroenterology and Hepatology*. These Best Practice Advice (BPA) statements were drawn from a review of the published literature and from expert opinion. Because systematic reviews were not performed, these BPA statements do not carry formal ratings of the quality of evidence or strength of the presented considerations.

BEST PRACTICE ADVICE 1: Gastroenterologists should be aware of potential extraesophageal manifestations of gastroesophageal reflux disease (GERD) and should inquire about such disorders including laryngitis, chronic cough, asthma, and dental erosions in GERD patients to determine whether GERD may be a contributing factor to these conditions.

BEST PRACTICE ADVICE 2: Development of a multidisciplinary approach to extraesophageal (EER) manifestations is an important consideration because the conditions are often multifactorial, requiring input from non-gastroenterology (GI) specialties. Results from diagnostic testing (ie, bronchoscopy, thoracic imaging, laryngoscopy, etc) from non-GI disciplines should be taken into consideration when gastroesophageal reflux (GER) is considered as a cause for extraesophageal symptoms.

BEST PRACTICE ADVICE 3: Currently, there is no single diagnostic tool that can conclusively identify GER as the cause of EER symptoms. Determination of the contribution of GER to EER symptoms should be based on the global clinical impression derived from patients' symptoms, response to GER therapy, and results of endoscopy and reflux testing.

BEST PRACTICE ADVICE 4: Consideration should be given toward diagnostic testing for reflux before initiation of proton pump inhibitor (PPI) therapy in patients with potential extraesophageal manifestations of GERD, but without typical GERD symptoms. Initial single-dose PPI trial, titrating up to twice daily in those with typical GERD symptoms, is reasonable.

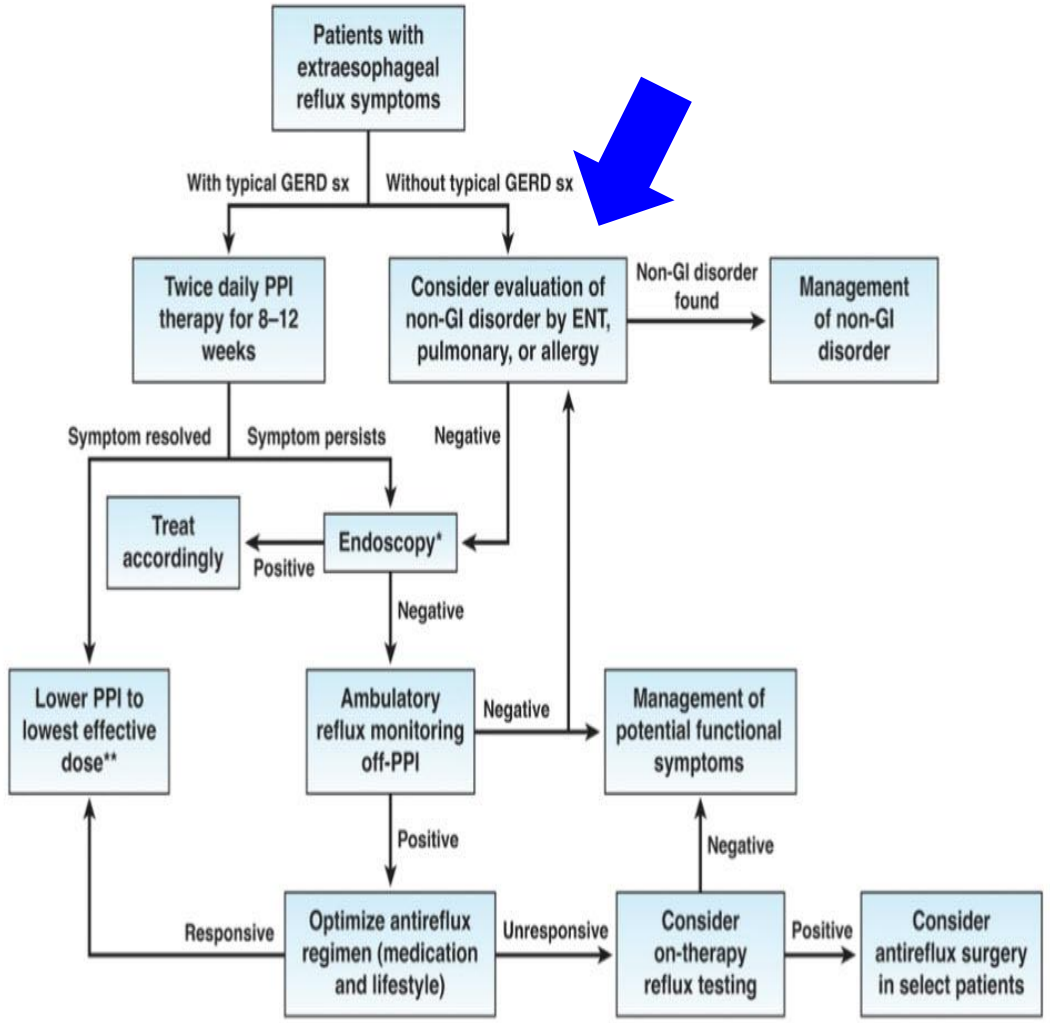


Figure 1. Algorithm for the evaluation of suspected EER. An empiric PPI trial can be considered in patients with extraesophageal and concurrent typical reflux symptoms, whereas early reflux testing should be considered in those with extraesophageal symptoms alone. To avoid long-term PPI use for a placebo effect, patients responsive to a trial of PPI should be titrated to the lowest effective dose and should be considered for off-therapy endoscopy or reflux testing. In patients without typical reflux symptoms or those with negative reflux workup, early involvement of multidisciplinary services should be considered. GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; Sx, symptoms.

Cough and Reflux…a Possibility

- Biological plausibility?

✔ Yes

- Association?

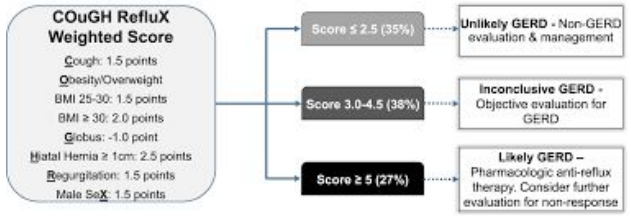
✔ Yes

- Causality?

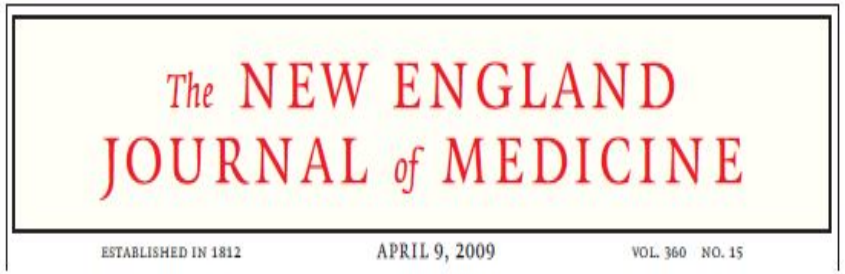
✔ Likely multi-factorial

- Is there a role for a PPI, acid suppression?

✔ In select individuals



Asthma and GER


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 9, 2009 VOL. 360 NO. 15

Efficacy of Esomeprazole for Treatment of Poorly Controlled Asthma

The American Lung Association Asthma Clinical Research Centers*

CONCLUSIONS

Despite a high prevalence of asymptomatic gastroesophageal reflux among patients with poorly controlled asthma, treatment with proton-pump inhibitors does not improve asthma control. Asymptomatic gastroesophageal reflux is not a likely cause of poorly controlled asthma. (ClinicalTrials.gov number, NCT00069823.)

Adult

Lansoprazole for Children With Poorly Controlled Asthma

A Randomized Controlled Trial

Results The mean age was 11 years (SD, 3 years). The mean difference in change (lansoprazole minus placebo) in the ACQ score was 0.2 units (95% CI, 0.0-0.3 units). There were no statistically significant differences in the mean difference in change for the secondary outcomes of forced expiratory volume in the first second (0.0 L; 95% CI, –0.1 to 0.1 L), asthma-related quality of life (–0.1; 95% CI, –0.3 to 0.1), or rate of episodes of poor asthma control (relative risk, 1.2; 95% CI, 0.9-1.5). Among the 115 children with esophageal pH studies, the prevalence of GER was 43%. In the sub-

Increased risk for pneumonia and respiratory infection in PPI-treated cohort

Pediatric

Asthma and Reflux

- Biological plausibility?
  - ✔ Yes
- Association?
  - ✔ Yes
- Causality?
  - ✔ Likely multi-factorial
- Is there a role for a PPI, acid suppression?
  - ✔ More studies are needed

Extra-Esophageal GERD Summary

- Provided an overview of the pathophysiology of GERD and the proposed extra-esophageal manifestations of reflux disease
- Briefly discussed the phenotypes of GERD and why this is important
- Reviewed the extra-esophageal manifestations of reflux
  - Dental disease, Apnea/ALTE/BRUE
  - Laryngeal manifestations, Cough and Asthma
- Provide an overview of what conditions are biologically plausible, what are simply association and what disorders have evidence to demonstrate causation by reflux

The littlest Gold – “OG” Oliver Gold

The Gold Family

Thank You!!


Questions