Proton Pump Inhibitors: To use or not to use… *That* is the question!

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Disclosures

Jenifer R Lightdale, MD is a consultant for Covidien, Perrigo and Mead Johnson.

Carlo Di Lorenzo, MD is a consultant for QOL, Inc. and Epstein Associates.

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Presenter and Disclosure Information

Put Information here.

Introduction

- There has been a tremendous rise in use of proton pump inhibitors (PPIs) in children over past 15 years[1]
  - Particularly an issue in infants <12 months of age [2]
- Preponderance of evidence that PPIs ***do not***
  - reduce GER symptoms in infants [3, 4] or
  - decrease infant crying and irritability [5]

1. Ruigomez A et al. *Eur J Gastroenterol Hepatol* 2011;23:232-7.
2. Orenstein SR. *Curr Gastroenterol Rep* 2013;15:353.
3. Davidson G et al. *J Pediatr* 2013;163;692-8.
4. Van der Pol RJ et al. *Pediatr* 2011;127:925–35.
5. Gieruzczak-Bialek D et al. *J Pediatr* 2015;166:767-70.

Introduction

- PPIs are extremely effective at acid suppression[1]
  - Preferred treatment for a number of acid related disorders [2]
  - Relatively safe medications [3]
- However, there are growing concerns over risks associated with PPI utilization
- Important to know pediatric indications
  - To use vs. when not to use PPIs
  - Recommended durations of use

1. Romano C et al. *Curr Clin Pharmacol* 2011;6:41-7.
2. Tighe M et al. *Cochrane Database Syst Rev* 2014;24:11:CD008550.
3. Czinn SJ, Blanchard S. *Paediatr Drugs* 2013;15:19-27.

Introduction

- Aim of this talk is to discuss evidence-basis for **using versus not using PPIs**
  - In infants
  - In older children and adults

Learning Objectives

- To review evidence-based indications for treating infants and older children with PPI
- To discuss the risks of treatment, as well as why, when, and how to stop treatment
- To review current evidence for extra-esophageal associations with reflux disease
- To review new understandings of reflux related disorders

Evidence-Based Indications for Treatment with PPIs

CASE

- 4-month old infant with frequent spit-ups
  - Effortless, not associated with crying
  - Occurs after every feed
  - Fusses between 7-8pm every night prior to sleep
  - Sleeps from 8pm to 2am
  - Weight and length are each at the 50th percentile

Section Objectives

To understand:

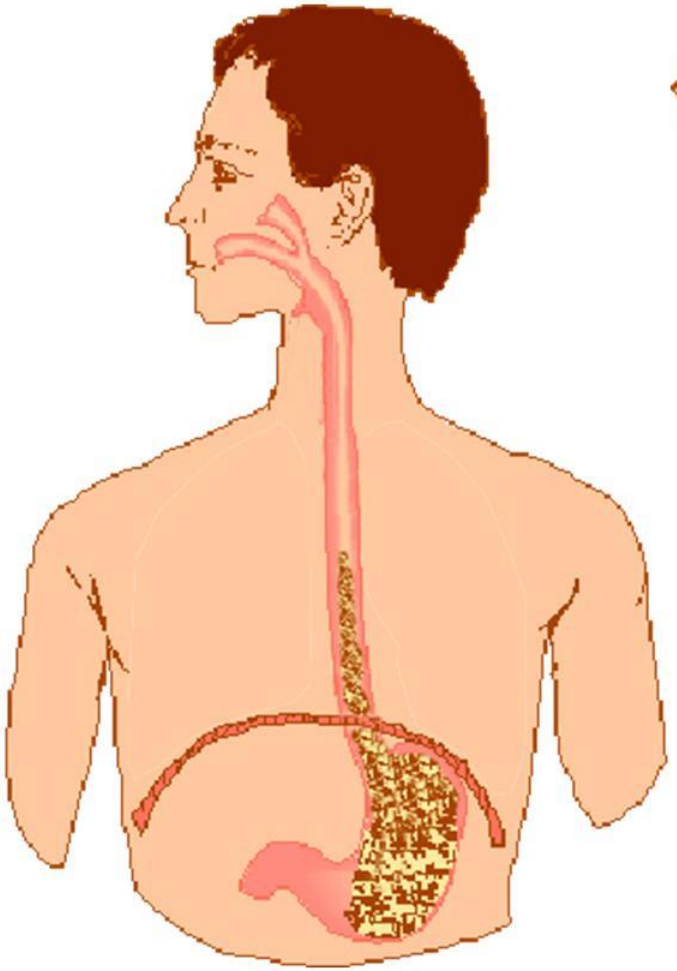
- Difference between GER and GERD
- Management of infants with regurgitation
- Erosive esophagitis as an indication for using PPI
- Other indications for using PPIs
  - PPI – REE
  - GI Bleeding
  - NSAID prophylaxis
  - H. pylori
- What to do when PPIs don't work

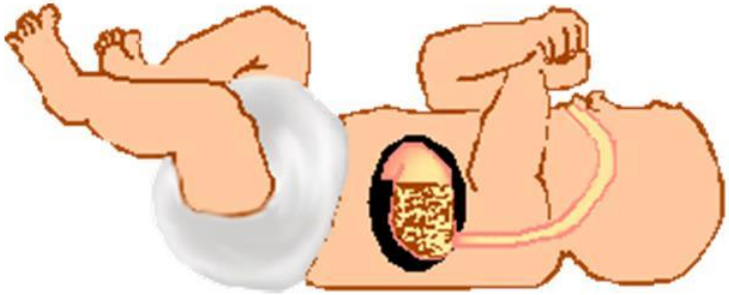
GER vs. GERD

- Gastroesophageal reflux (GER)
  - A physiologic phenomenon that occurs at all ages to allow depressurization of the stomach
- Gastroesophageal reflux disease (GERD) in pediatric patients
  - A pathological condition that is present when reflux of gastric contents causes ***troublesome symptoms and/or complications***

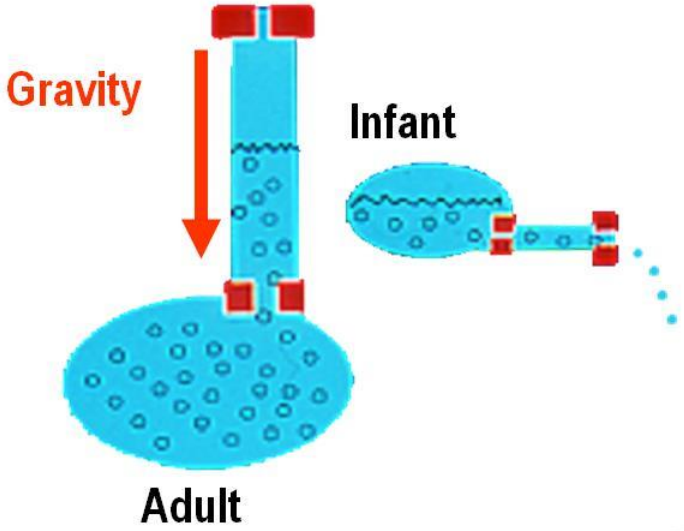
Sherman et al. *Am J Gastroenterol* 2009;104:1278-95.

Esophageal Capacitance



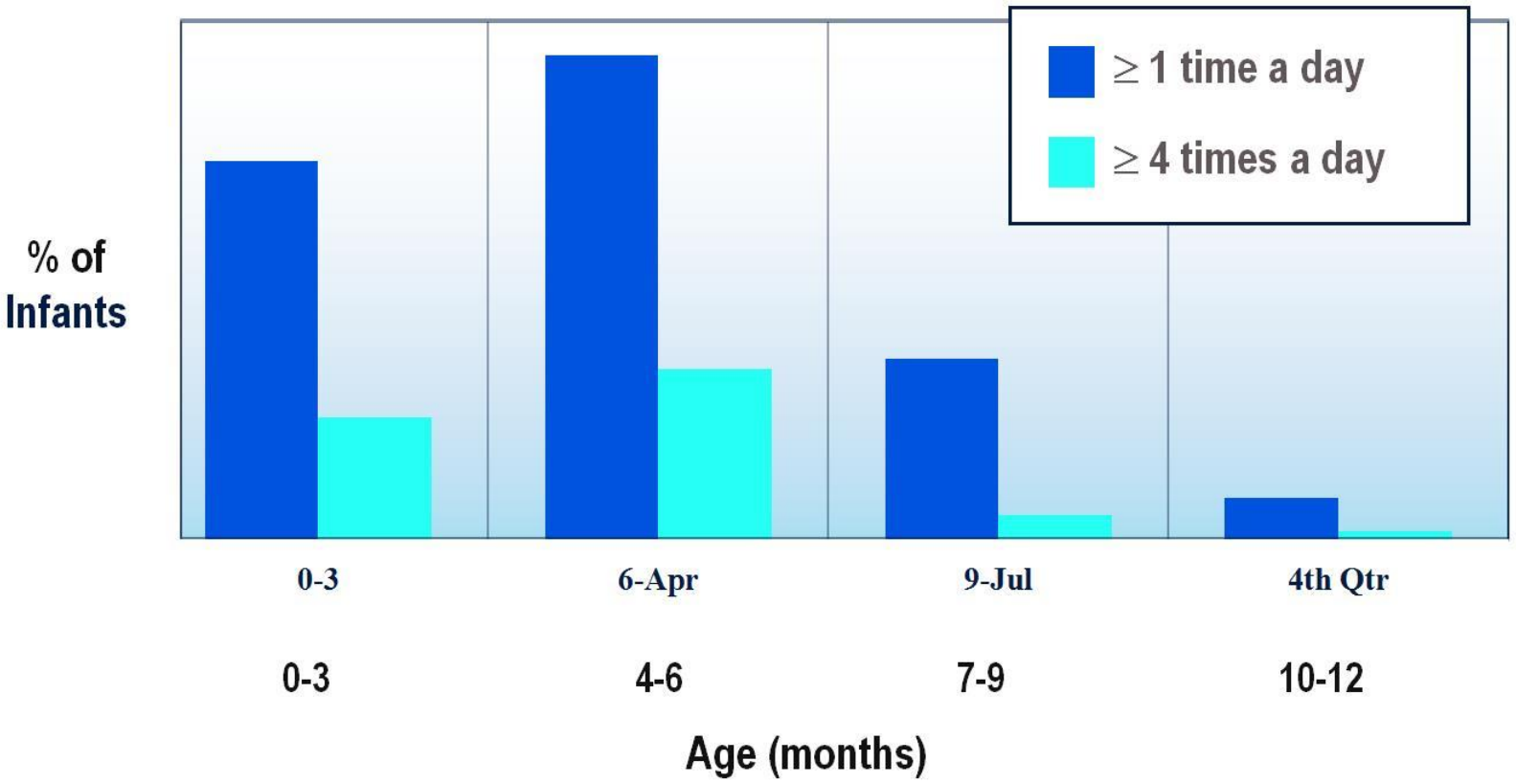


- Shorter esophagus
- Smaller capacity



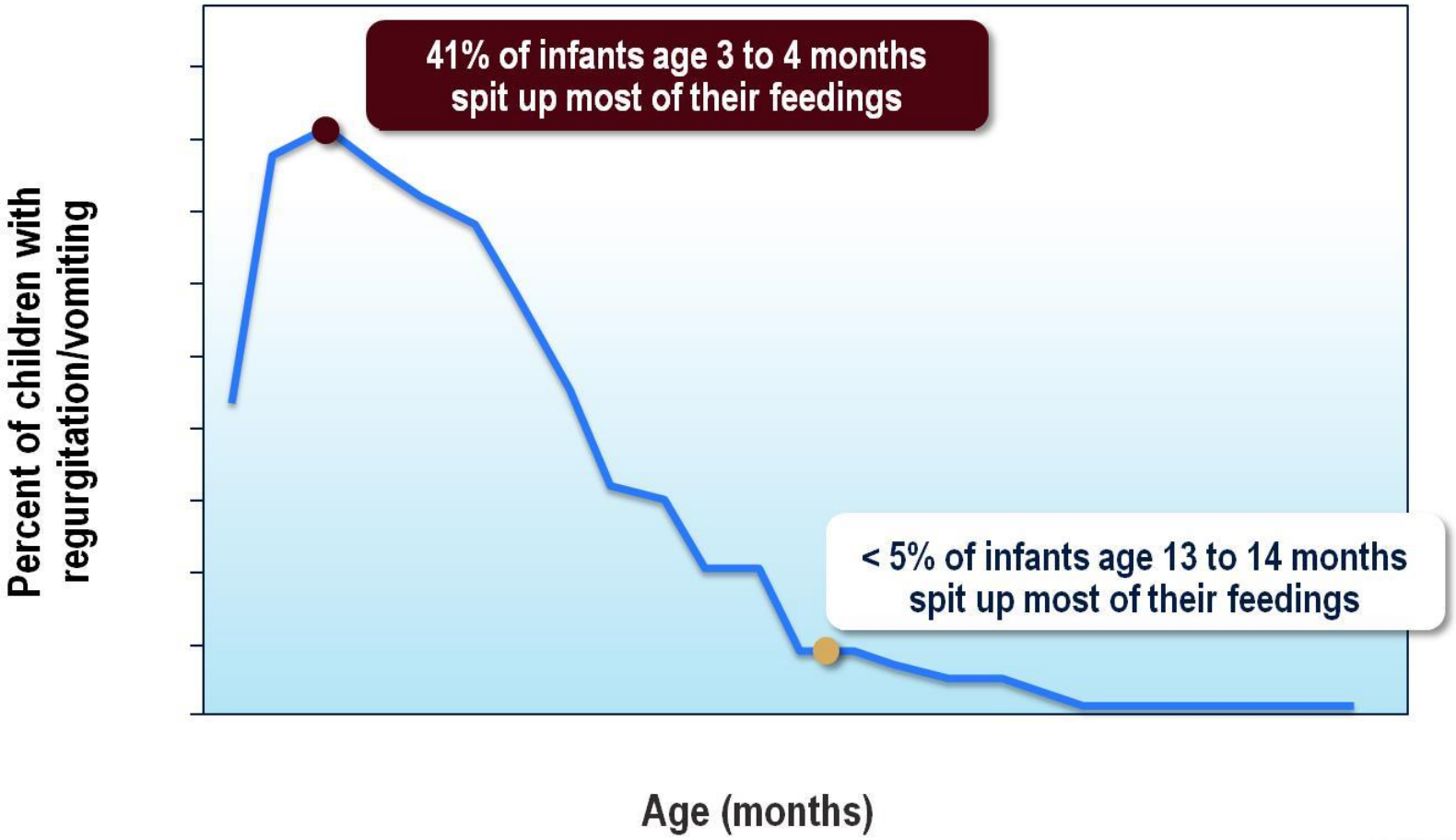
Weaver TL. Anatomy and embryology. In: Walker WA et al, eds. *Pediatric Gastrointestinal Disease*, 1st ed. 1991:195-216.

Prevalence of Regurgitation in Infancy



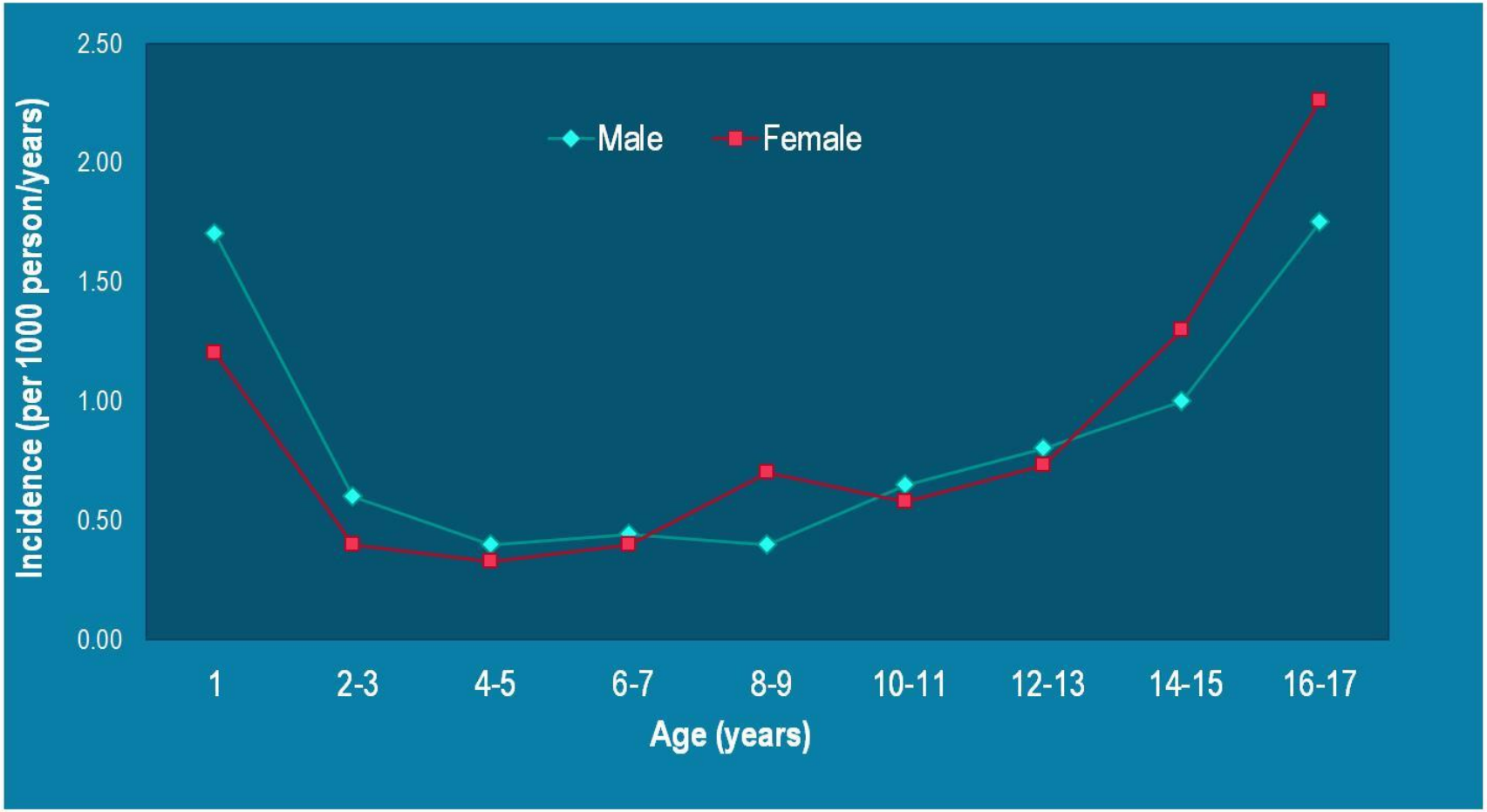
Adapted from Nelson et al. *Arch Pediatr Adolesc Med* 1997;151:569.

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



Martin AJ et al. *Pediatrics* 2002;109(6):1061-1067.

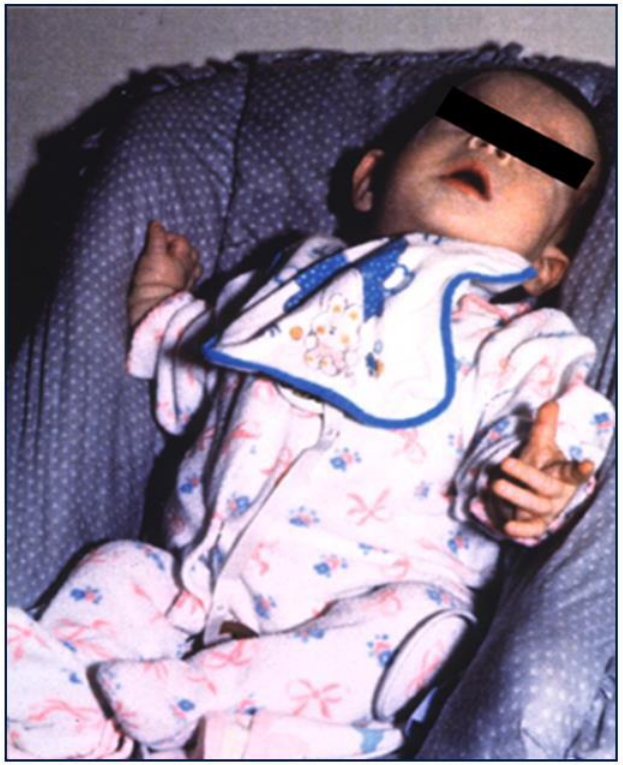
Estimated Incidence Rates of GERD in Children and Adolescents from 2000-2005



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

Preponderance of Evidence that Treating Infants for GERD with PPI Does Not Reduce Crying and Irritability

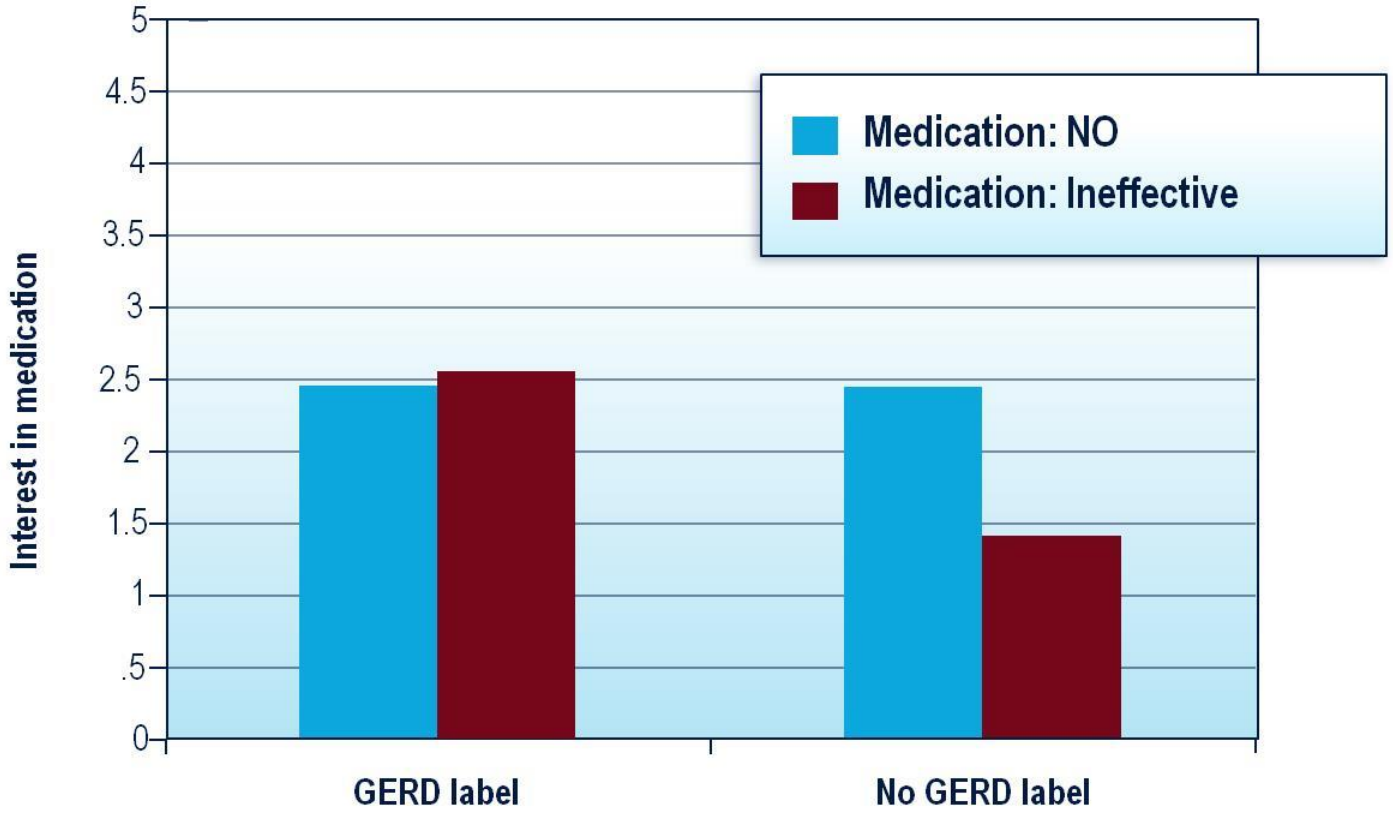
- Minimal evidence supports the contention that acid reflux may cause irritability in infants
- Variations in parental perception of excessive crying/sleep disturbance complicate interpretation



Rudolph C et al. *J Pediatr Gastroenterol Nutr* 2001;32:S1-31.
Feranchak AP et al. *Clin Pediatr* 1994;33:654-62.
Chadwick LM et al. *J Paediatr Child Health* 1997;33:388-93.
Heine RG et al. *Arch Dis Child* 1995;73:121-5.

Photo courtesy of Susan R. Orenstein, MD.

Influence of "GERD" Label on Parents' Decision to Medicate Infants



Scherer LD et al. *Pediatrics* 2013;131;839.

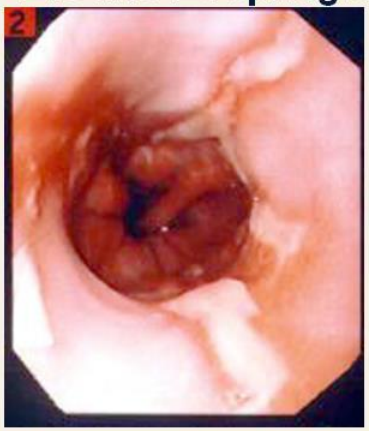
Insufficient Evidence to Associate GERD with a Number of Other Conditions

- Pathological apnea
- Acute life threatening events (ALTE)

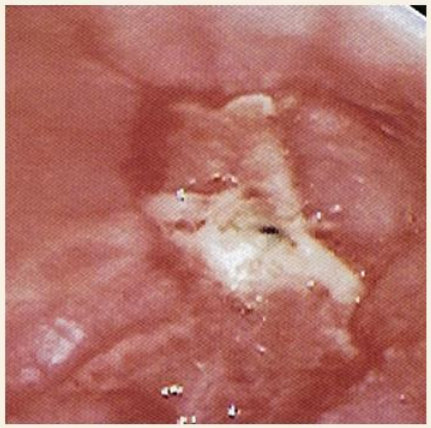
Smits M et al. *Neurogastroenterol Motil* 2014:11:1527-1538.

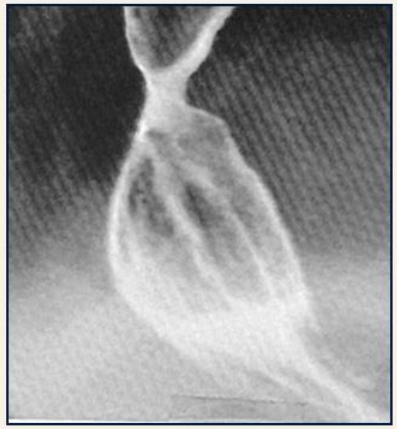
GERD-Related Complications

Erosive Esophagitis

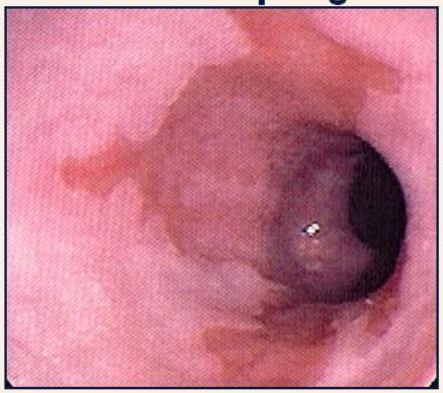


Stricture

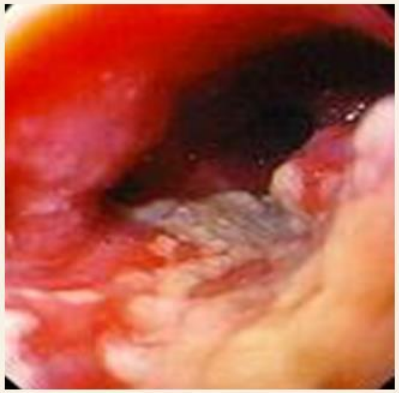




Barrett's Esophagus



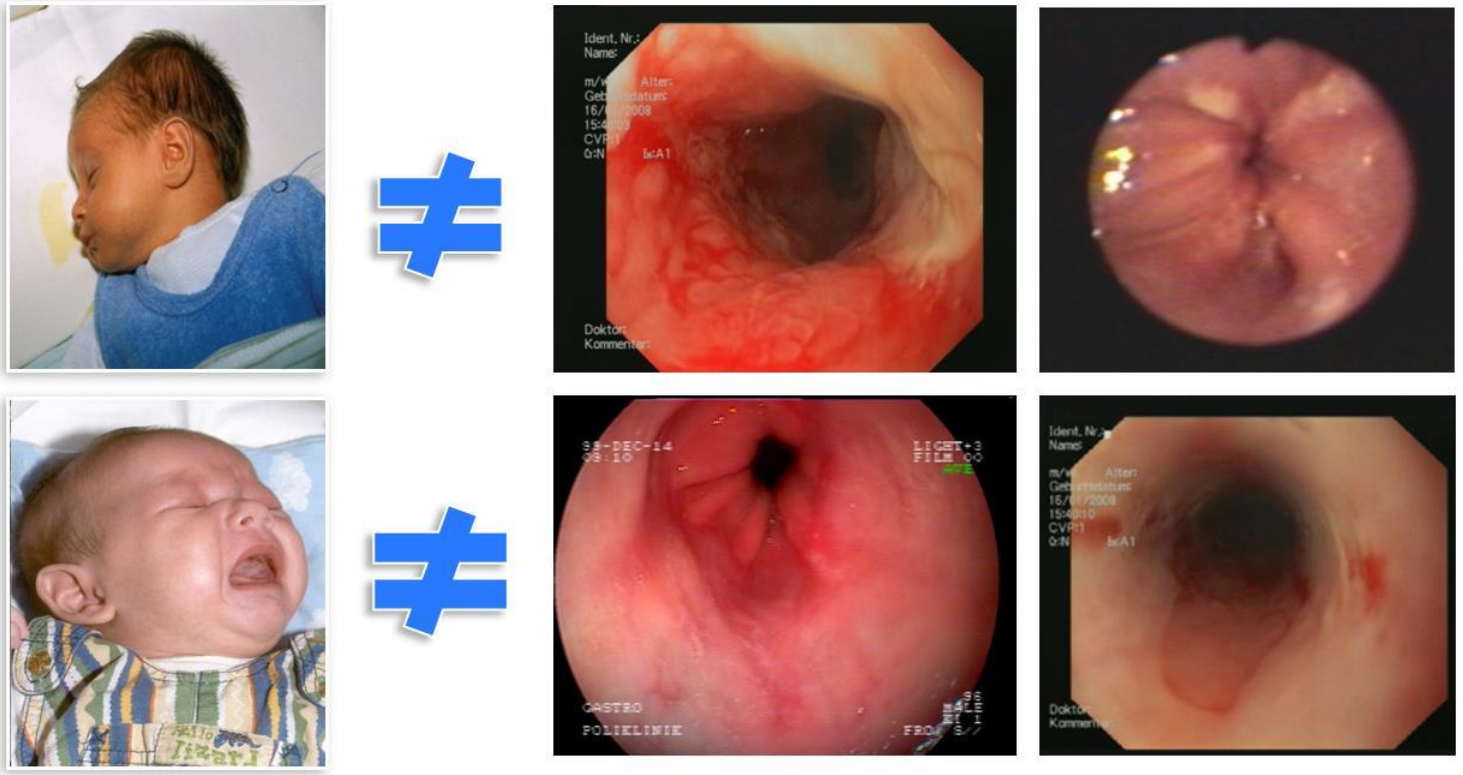
Adenocarcinoma



Endoscopic views courtesy of Benjamin D. Gold, MD.

Correlation of Symptoms and Injury

In infants, symptoms are not reliable to predict the presence or severity of erosive 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.
Endoscopic views courtesy of Benjamin D. Gold, MD.

Efficacy/Safety of Once-Daily Esomeprazole for Treatment of GERD in Neonatal Patients

Objective To evaluate the efficacy and safety of proton pump inhibitors in infants aged <1 year with gastroesophageal reflux disease (GERD).

Study design In this randomized, double-blind, placebo-controlled multicenter study, neonates (premature to 1 month corrected age; n = 52) with signs and symptoms of GERD received esomeprazole 0.5 mg/kg or placebo once daily for up to 14 days. Change from baseline in the total number of GERD symptoms (from video monitoring) and GERD-related signs (from cardiorespiratory monitoring) was assessed with simultaneous esophageal pH, impedance, cardiorespiratory, and 8-hour video monitoring.

Results There were no significant differences between the esomeprazole and placebo groups in the percentage change from baseline in the total number of GERD-related signs and symptoms (−14.7% vs −14.1%, respectively). Mean change from baseline in total number of reflux episodes was not significantly different between esomeprazole and placebo (−7.43 vs −0.2, respectively); however, the percentage of time pH was <4.0 and the number of acidic reflux episodes >5 minutes in duration was significantly decreased with esomeprazole vs placebo (−10.7 vs 2.2 and −5.5 vs 1.0, respectively; $P \leq .0017$). The number of patients with adverse events was similar between treatment groups.

Davidson G et al. *J Pediatr* 2013;163:692-698.

Efficacy/Safety of Once-Daily Esomeprazole for Treatment of GERD in Neonatal Patients

- Signs and symptoms of GERD traditionally attributed to acid reflux in neonates were not significantly altered by esomeprazole treatment
- Esomeprazole was well tolerated and reduced esophageal acid exposure and the number of acid reflux events in neonates

Davidson G et al. *J Pediatr* 2013;163:692-698.

Esomeprazole In Infants with GERD

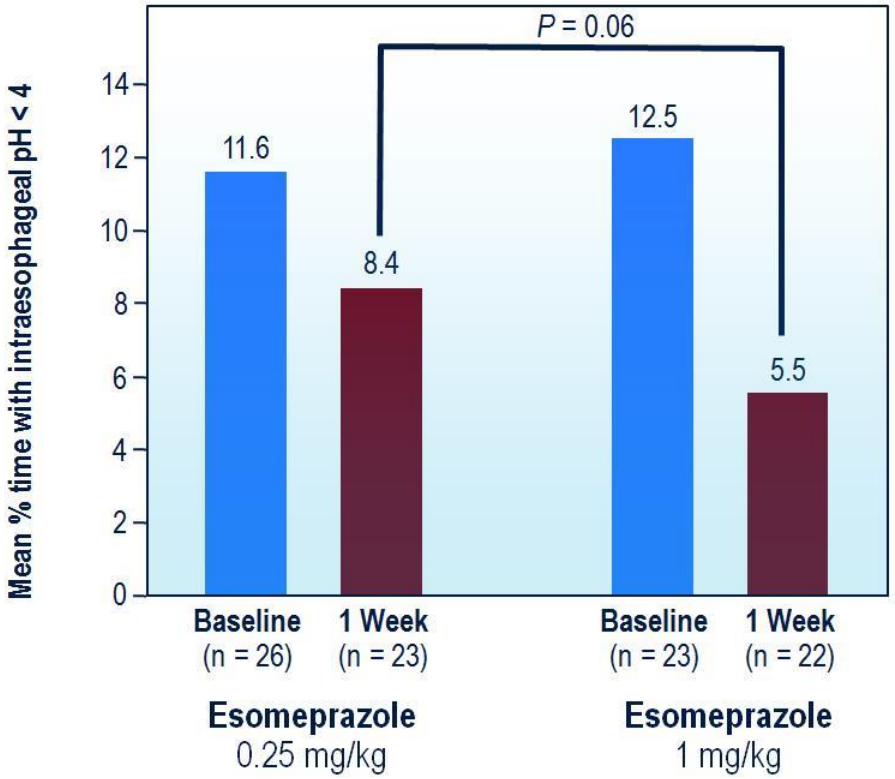


FIG. 2 Mean percentage of time with intraesophageal pH <4 at baseline and after 1 week of oral treatment with esomeprazole in infants with GERD.

Esomeprazole is approved for healing of erosive esophagitis in patients younger than 1 year old and as early as 1 month of age

Omari et al. *J Pediatr Gastroenterol Nutr* 2007;45:530-37.
Winter et al. *J Pediatr Gastroenterol Nutr* 2012;55:14-20.

Managing Infants With Recurrent Vomiting

No warning signals or signs of complicated GER

- History & physical exam generally sufficient
- Parental education
  - warning signals
  - reassurance
- Consider
  - thickened formula
  - hypoallergenic formula
- Pharmacotherapy not recommended
- If no resolution by 18-24 months
  - consider upper GI series or other test
  - consider pediatric GI referral

Rudolph et al. *J Pediatr Gastroenterol Nutr* 2001;32:S1.
Photo courtesy of Alejandro F. Flores, MD.

Allergic Gastroenteropathy in Preterm Infants

- N=25, mean GA 29 weeks and PNA 78 days, all had bx,
- Presentation:
  1. GER (5)
  2. Feeding intolerance (8)
  3. Lower GI bleed (12)

15 responded to hydrolysate formula

10 responded to amino acid based formula

D'Netto MA et al. *J Pediatr* 2000 ;137(4):480-486.

Allergic Gastroenteropathy in Preterm Infants

- Symptoms of cow's milk protein allergy (CMPA) may be identical to GERD
- Risk factors for CMPA include familial history of atopy, infant eczema, symptoms of crying with swallowing
- Initiate 2-week trial with hydrolysate formula

D'Netto MA et al. *J Pediatr* 2000 ;137(4):480-486.

The Effect of Thickened-Feed Interventions on Gastroesophageal Reflux in Infants

mail: hania@ipgate.pl

RESULTS. Fourteen randomized, controlled trials with a parallel or crossover design, some with methodologic limitations, were included. Use of thickened formulas compared with standard formula significantly increased the percentage of infants with no regurgitation, slightly reduced the number of episodes of regurgitation and vomiting per day (assessed jointly or separately), and increased weight gain per day; it had no effect on the reflux index, number of acid gastroesophageal reflux episodes per hour, or number of reflux episodes lasting >5 minutes but significantly reduced the duration of the longest reflux episode of pH < 4. No definitive data showed that one particular thickening agent is more effective than another. No serious adverse effects were noted.

CONCLUSIONS. This meta-analysis shows that thickened food is only moderately effective in treating gastroesophageal reflux in healthy infants. *Pediatrics* 2008;122:e1268–e1277

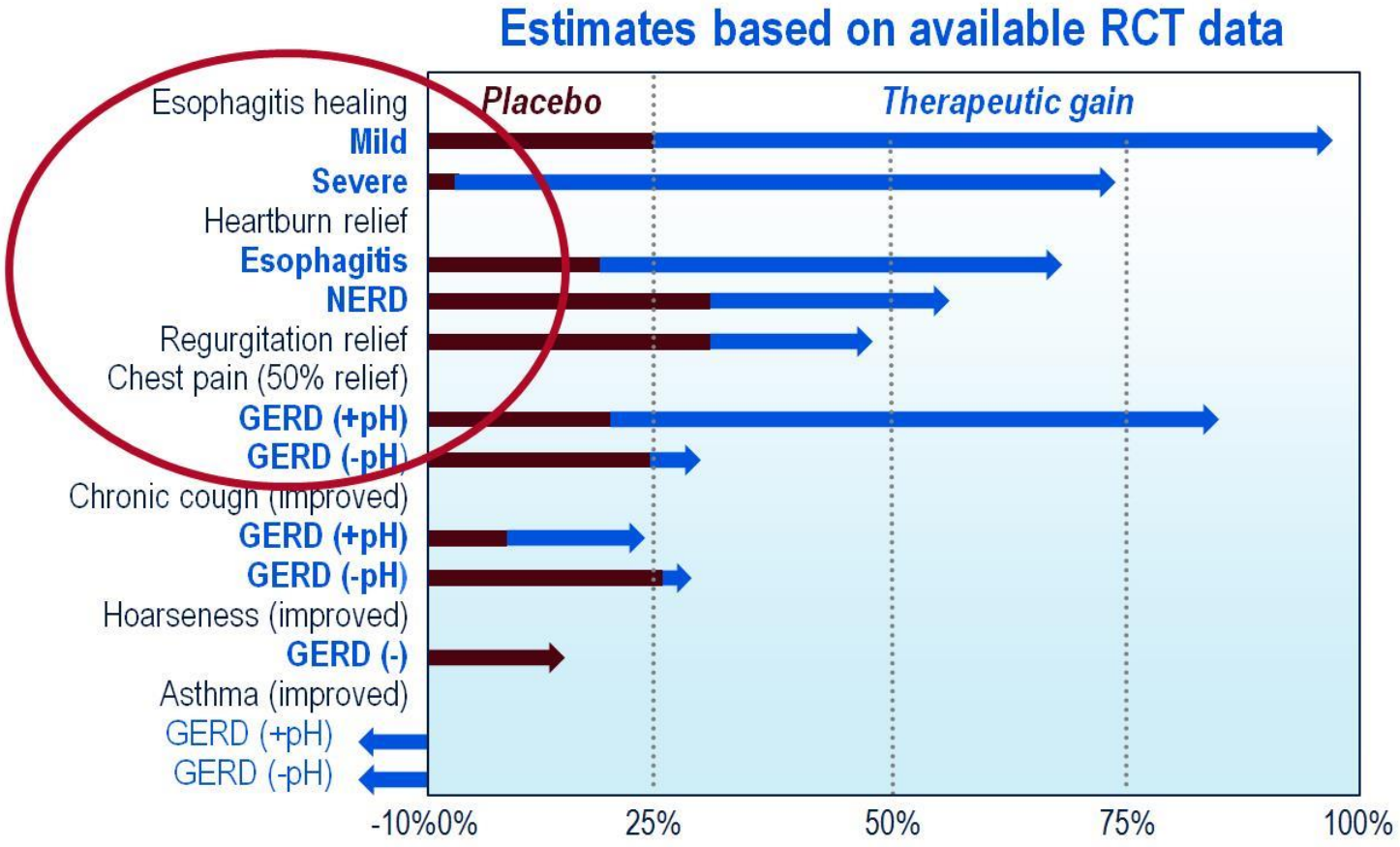
Hovarth et al. *Pediatrics* 2008;122:1268-1277.

Be Aware of Caloric Impact of Thickening Feeds with Rice Cereal

- Thickening a 20 kcal/oz infant formula with:
  - 1 tbsp rice cereal per 2oz ---- 27 kcal/oz
  - 1 tbsp rice cereal per oz ---- 33kcal/oz (1.1Kcal/ml)

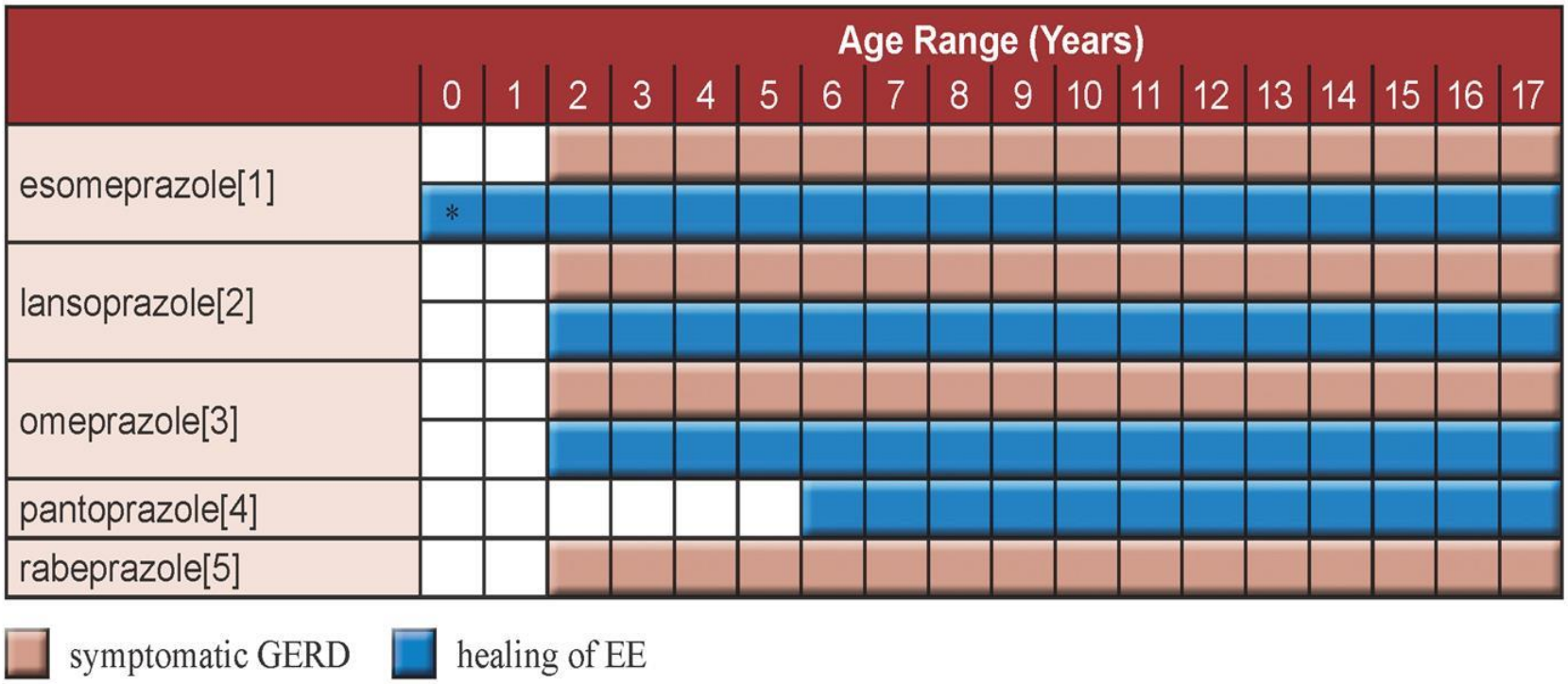
- Change from appropriate macronutrient distribution to one that is not appropriate
  - Fat from 48% to 24% and carbohydrate from 43.5% to 68%.

PPI Efficacy for Potential Manifestations for GERD in Adults



Boeckxstaens G. *Postgrad Med J* 2015;91:46-54.

FDA-Approved Pediatric Age Ranges and Indications for PPIs



* Treatment may begin as early as 1 month of age for this indication.

Current as of October 2015 from https://www.accessdata.fda.gov/drugsatfda_docs

Eosinophilic Esophagitis or PPI-Responsive Esophageal Eosinophilia

- Eosinophilic esophagitis is a clinicopathological diagnosis of an allergic esophagitis characterized by submucosal eosinophilic infiltrates
- At least 1/3 of adult patients with suspected EoE achieve clinical and histological remission on PPI therapy (i.e. PPI-Responsive Esophageal Eosinophilia (PPI-REE))
- The response seems more limited in children as compared to adults
- Treatment for suspected EoE includes high dose PPI for 8 weeks followed by endoscopy and biopsy

Molina-Infante J et al. ***Alimen Pharmacol Ther*** **2013;37:1157-64.**

Esophageal Eosinophilia *Does Not* Equal Eosinophilic Esophagitis

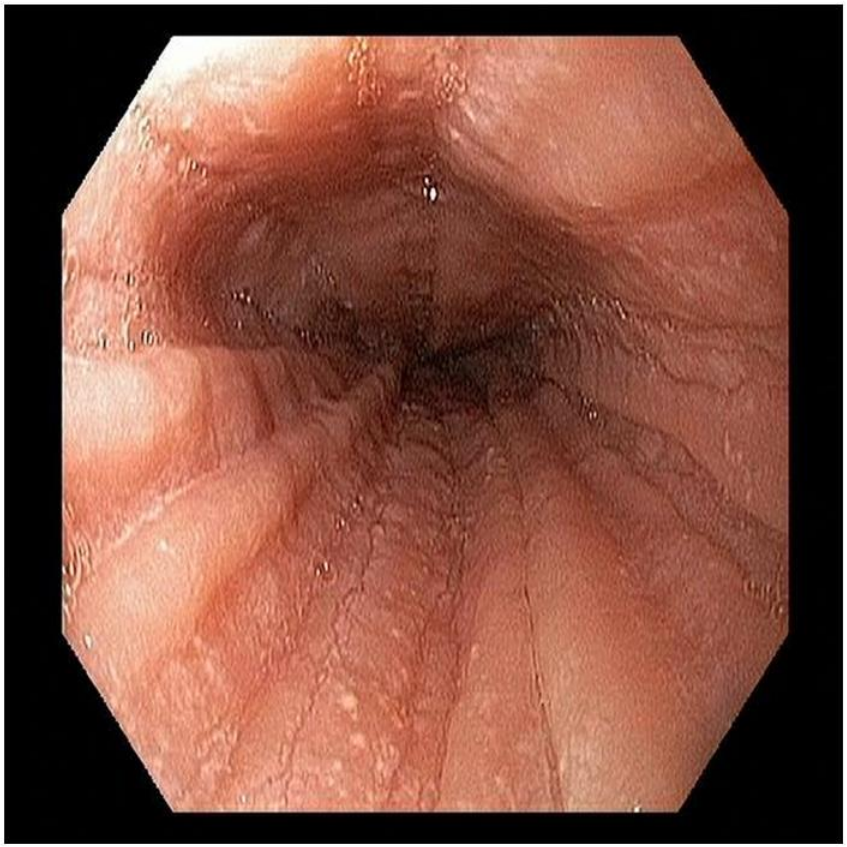


Photo courtesy of Jose M. Garza, MD.

Gastrointestinal Bleeding

- IV PPI is given in almost all instances of upper gastrointestinal bleeding
- Evidence from a Cochrane review suggests PPI therapy in this setting presents no harm and may provide some benefit.

Sreedharan A et al. *Cochrane Database Syst Rev.* 2010:CD005415.

NSAID Prophylaxis

- Patients with poor adherence (<20% PPI coverage) had a significantly increased risk of upper GI complications (OR=1.88) compared with fully adherent patients (≥80% PPI coverage)
- The risk of an event increased by 6% points for every 10% decrease in PPI adherence

Jonassan C et al. *Eur J Gastroenterol Hepatol* 2013;25:531-8.

Treatment

PPIs Should Be Used for…

Indication	PPI Treatment Regimen
PPI-REE	High dose (q.d. or b.i.d.) for 8 weeks followed by endoscopy and biopsy[4,5]
Erosive Esophagitis	Standard dose q.d. for 3 months followed by trials of tapering the dose towards final withdrawal of therapy [1]
NSAID	Standard dose q.d. prophylaxis concurrent with NSAID therapy[2]
Bleeding	IV 1 mg/kg/ q.d. or 0.5 mg/kg b.i.d.[3]
H. pylori	Standard dose b.i.d. (as part of a quadruple or triple regimen) for 10 to 14 days[6]

1. Hassall E et al. *J Pediatr* 2000;137:800-7.
2. Rostom A et al. *Cochrane Review* 2002;15:CD002296.
3. Colle I et al. *Acta Gastroenterol Belg* 2011;74:46-66.
4. Dellon ES et al. *Am J Gastroenterol* 2013;108:679-692.
5. Molina-Infante J et al. *Aliment Pharmacol Ther* 2013;37:1157-64.
6. Koletzko S et al. *J Pediat Gastroenterol Nutr* 2011;53:230-43.

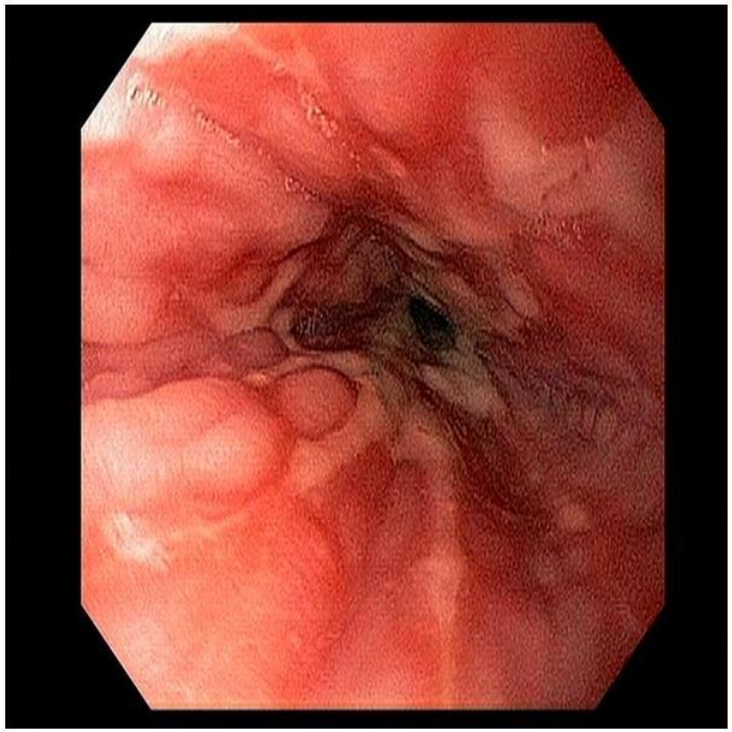
BEFORE **PPI** AFTER

Therapeutic Challenge

Therapeutic Challenge

Mucosal Healing

Managing ulcers, erosive esophagitis, recurrent strictures with antacids and H_2RAs antagonists



BEFORE

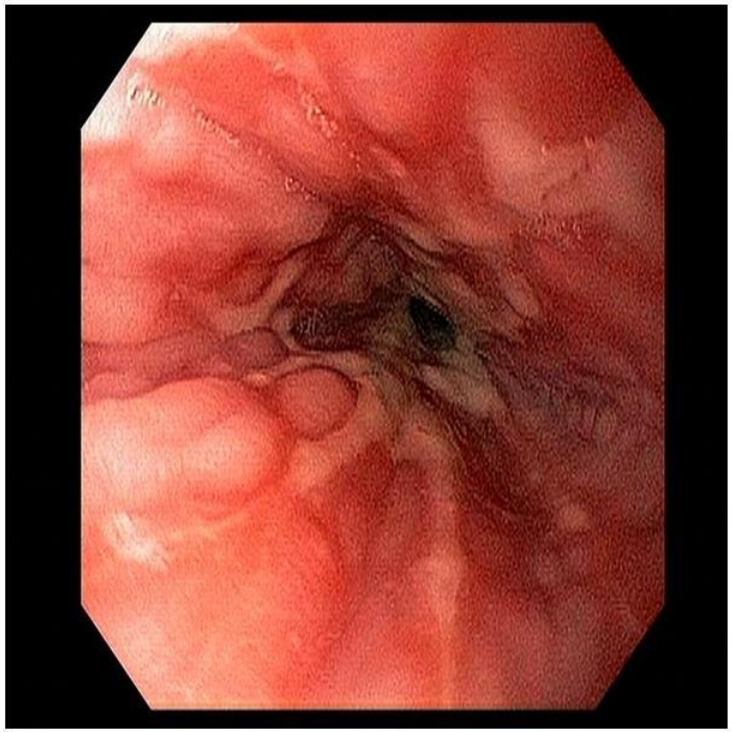
PPI

AFTER

Therapeutic Challenge

Mucosal Healing

Managing ulcers, erosive esophagitis, recurrent strictures with antacids and H_2RAs antagonists



Therapeutic Challenge

Refractory Symptoms

Problem of refractory symptoms blossomed and the list of symptoms and syndromes potentially attributable to GERD expanded

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What to do When PPIs *Don't* Work?

- Assess for treatment compliance
  - Lack of efficacy of PPIs in gastric acid secretion is extremely rare
- Make sure the patient is taking the PPI on an empty stomach and at least 30 to 60 minutes before a meal
- Trial of b.i.d. dosing
- Add an H_2RA at night (tachyphylaxis)
- Make sure the diagnosis is correct

Summary: Indications for PPIs

- PPIs **do not**
  - reduce GER symptoms in infants or decrease infant crying and irritability
- PPIs are **indicated in**
  - GERD, NSAID prophylaxis, bleeding, PPI-REE, and H. pylori eradication
  - **Specific course of treatment**
  - **For a defined duration of treatment with a weaning plan in place**

Understanding the Risks of Treatment

CASE

- 9 year-old boy diagnosed with erosive esophagitis when he presented with an episode of hematemesis
- Treated with PPI b.i.d. for 12 months
- Currently asymptomatic
- Parents want to know if and when they can stop treatment

Section Objectives

To understand:

- why to stop treatment
- when to stop treatment
- how to stop treatment
- what happens if you do not stop treatment

When to Stop Treatment

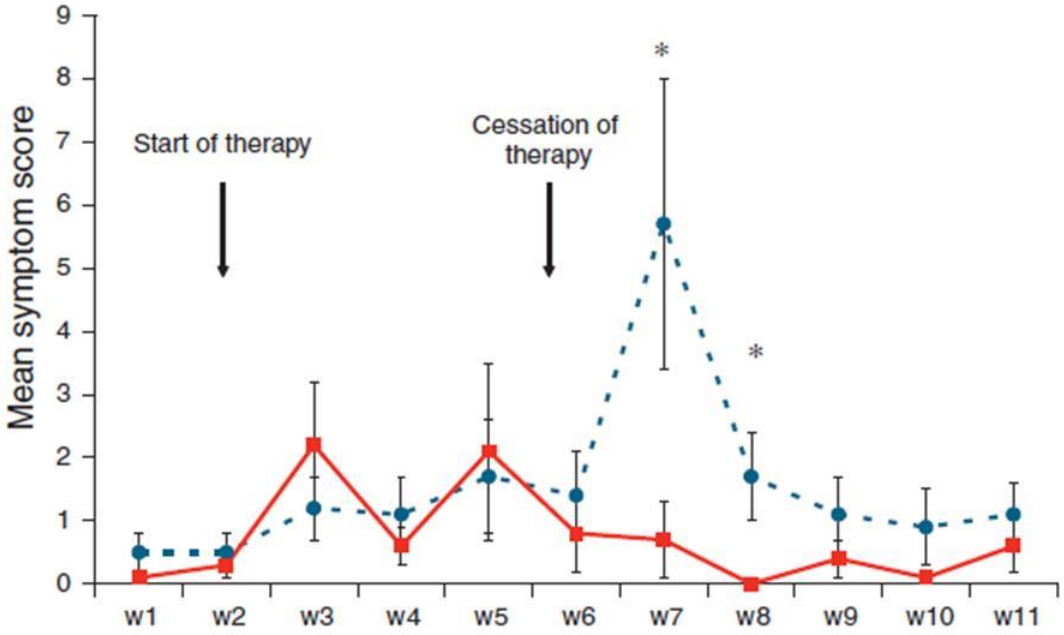
- In otherwise healthy pediatric patients, reflux esophagitis may not be a chronic problem or recur after treatment[1]
  - Of 48 otherwise healthy children with erosive esophagitis who discontinued maintenance treatment, only one had erosive esophagitis recurrence at three months
  - Three of 44 (6.8%) patients reported very mild GERD symptoms within a period of 30 months after maintenance discontinuation

1. Boccia G et al. *Am J Gastroenterol* 2007;102:1291-7.

How to Stop?

Dyspeptic Symptom Development After Discontinuation of a Proton Pump Inhibitor

A Double-Blind Placebo-Controlled Trial



Weekly dyspepsia scores (mean and s.e.m.) in the pantoprazole group (dotted blue lines) and in the placebo group (red lines). Weeks 1-2 = before treatment, weeks 3-6 = during treatment, and weeks 7-12 = after treatment, *P<0.05.

Niklasson A et al. ***Am J Gastroenterol*** **2010;105:1531-7.**

Potential Risks of Prolonged Acid Suppression

- Infections:
  - *C. difficile*
  - Small bowel bacterial overgrowth
  - Other enteric infections
  - Pneumonia and other respiratory infections
- Necrotizing enterocolitis and candidemia
- Effects on vitamins and mineral absorption:
  - Iron
  - Calcium
  - Magnesium
  - Vitamin B12
- Gastric fundic gland polyps
- Interstitial nephritis (rare, idiosyncratic reaction)
- Myocardial infarction and Dementia

Risks of Acid Suppression in Children

Study Author	Type of Study	Age	Location	Medications Investigated	Outcome Assessed
Guillet et al[27]	Retrospective	Neonates	NICU	Ranitidine, famotidine, cimetidine	NEC
Terrin et al[28]	Prospective	Neonates	NICU	Ranitidine	NEC, sepsis, pneumonia, UTI
Beck-Sague et al[29]	Prospective	Neonates	NICU	H_2 antagonists	Bloodstream infection
Rojas et al[30]	Prospective	Neonates	NICU	H_2 antagonists	Nosocomial infection
Graham et al[31]	Retrospective	Neonates	NICU	H_2 antagonists or PPI	Gram-negative bacteremia
Bianconi et al[32]	Retrospective	Neonates	NICU	Ranitidine	Late-onset sepsis
Elward et al[33]	Prospective	≤18 y	PICU	H_2 antagonists	VAP
Yildizdas et al[34]	Prospective	Pediatric, age range not specified	PICU	Omeprazole, ranitidine, sucralfate	VAP
Lopriore et al[35]	Retrospective	Pediatric, age range not specified	PICU	Ranitidine, sucralfate	VAP
Sharma et al[36]	Prospective	1 mo–15 y	PICU	Ranitidine	VAP
Singh-Naz et al[37]	Prospective	Pediatrics, age range not specified	PICU	H_2 antagonists	Nosocomial infection
Canani et al[38]	Prospective	4–36 mo	Pediatric GI centers	Omeprazole and ranitidine	Pneumonia, gastroenteritis
Orenstein et al[6]	Prospective	28 d–12 mo	Primary care centers	Lansoprazole	Lower respiratory tract infection
Turco et al[39]	Retrospective	1–18 y	Hospital	PPI, H_2 antagonist	*C difficile* colitis

Chung EY et al. *Hosp Pediatr* 2013;32:348-54.

Why More Infections?

- Decreased acid barrier
- Altered microbiome
- Attenuation of the immune response
- Direct effects of the bacteria
- Decreased effectiveness of antibiotics

Stark CM et al. *J Pediatr* 2016;168:16-22.

Clostridium Difficile

- A retrospective study in children found those treated with a PPI had an increased odds ratio of 4.52 for *C. difficile* infection [1]
- The risk is further increased by concomitant use of antibiotics with a PPI; H_2RAs may be less harmful [2]
- Multivariate analyses suggest H_2RA and once daily PPI treatment increase the risk by 1.5 whereas ***frequent*** PPI therapy can increase the risk by up to 2.9 times [3]
- FDA safety information 2012: *C. difficile* associated diarrhea can be associated with gastric acid reducing drugs [4]

1. Turco R et al. *Aliment Pharmacol Ther* 2010;31:754-9.
2. Kwok CL et al. *Am J Gastroenterol* 2012;107:1011-9.
3. Howell MD et al. *Ann Intern Med* 2010;170:784-90.
4. FDA. http://www.fda.gov/drugs/drugsafety/ucm290510.htm *Ann Intern Med* 2010170.

Respiratory Infections

- In patients with asthma the addition of lansoprazole compared with placebo [1]
  - improved neither symptoms nor lung function
  - was associated with an increase in respiratory infections
- Prenatal exposure to both PPIs and H_2RAs was associated with an increased risk of asthma [2]
  - However this may be explained by a maternal underlying condition

1. Holbrook JT et al. *JAMA* 2012;307:373-81.
2. Andersen AB et al. *Aliment Pharmacol Ther* 2012;35:1190-8.

Minerals and Vitamins

Association Between Proton Pump Inhibitor Use and Anemia

A Retrospective Cohort Study

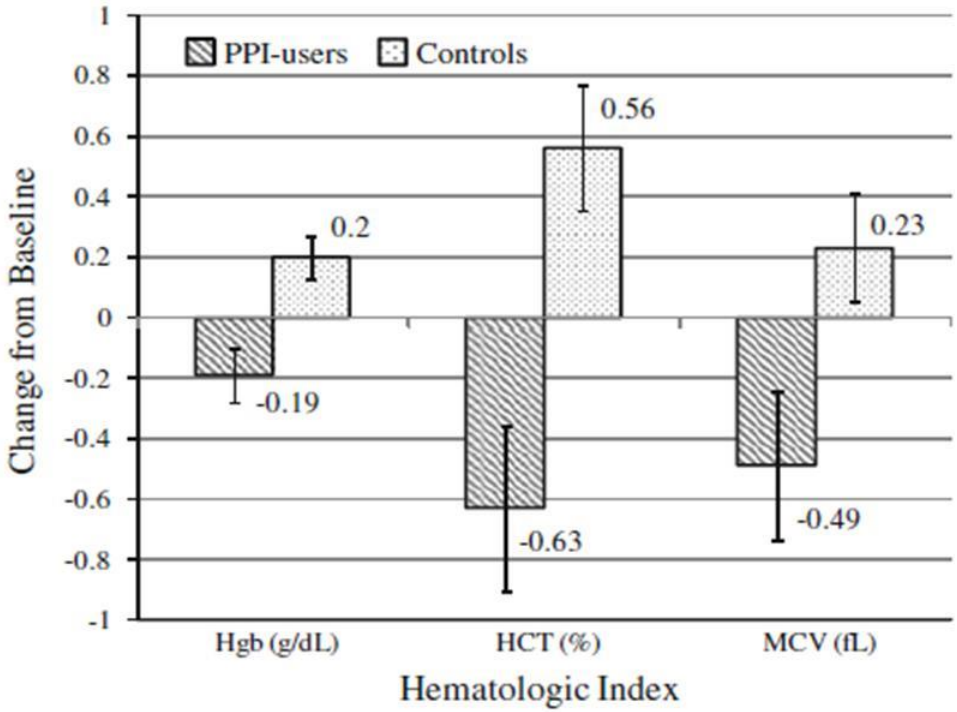


Fig. 2 Change in hematologic indices (± SEM) in patients before and after initiating proton pump inhibitor (PPI) therapy, compared with patients not receiving PPI therapy. *SEM* standard error of mean

Sarzynski E et al. *Dig Dis Sci* 2011;56:2349-53.

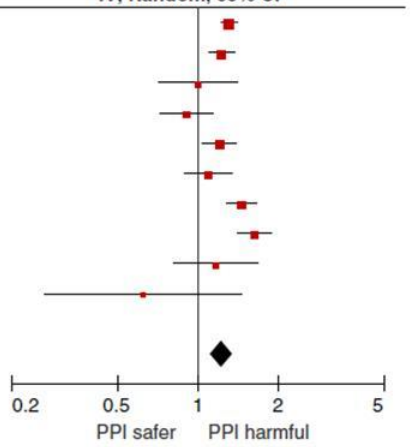
Risk of Hip Fracture

PPI

Study or Subgroup	Weight	Odds Ratio IV, Random, 95% CI
Corley 2010	15.9%	1.30 [1.21, 1.39]
De Vries 2009	14.2%	1.22 [1.09, 1.36]
Gray 2010	5.8%	1.00 [0.71, 1.40]
Kaye 2008	9.2%	0.90 [0.72, 1.13]
Pouwels 2010	12.5%	1.20 [1.03, 1.39]
Targownik 2008	9.8%	1.09 [0.88, 1.35]
Vestergaard 2006	13.5%	1.45 [1.28, 1.65]
Yang 2006	12.6%	1.62 [1.40, 1.88]
Yu 2008a	5.2%	1.16 [0.80, 1.68]
Yu 2008b	1.3%	0.62 [0.26, 1.46]
Total (95% CI)	100.0%	1.23 [1.11, 1.36]

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 31.93$, df = 9 (P = 0.0002); $I^2 = 72\%$

Test for overall effect: Z = 3.97 (P < 0.0001)

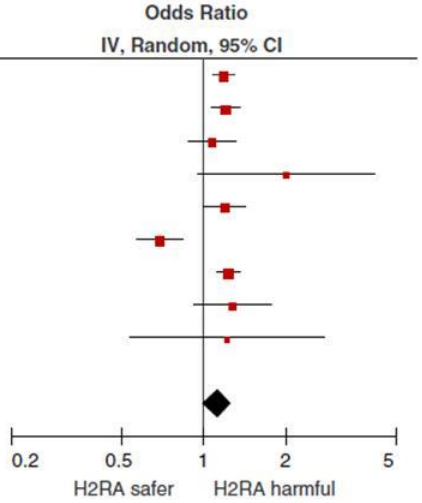


H2RA

Study or Subgroup	Weight	Odds Ratio IV, Random, 95% CI
Corley 2010	16.9%	1.18 [1.08, 1.29]
De Vries 2009	15.9%	1.20 [1.07, 1.35]
Gray 2010	12.3%	1.07 [0.88, 1.31]
Grisso 1997	2.3%	2.00 [0.95, 4.20]
Pouwels 2010	13.4%	1.19 [1.00, 1.42]
Vestergaard 2006	12.6%	0.69 [0.57, 0.84]
Yang 2006	16.6%	1.23 [1.11, 1.36]
Yu 2008a	8.0%	1.27 [0.92, 1.75]
Yu 2008b	2.0%	1.22 [0.54, 2.76]
Total (95% CI)	100.0%	1.12 [0.99, 1.27]

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 32.43$, df = 8 (P < 0.0001); $I^2 = 75\%$

Test for overall effect: Z = 1.88 (P = 0.06)



Kwok CS et al. *Bone* 2011;48:768-76.

Risk of Hip Fracture

PPI

Study or Subgroup	Weight	Odds Ratio IV, Random, 95% CI
Corley 2010	15.9%	1.30 [1.21, 1.39]
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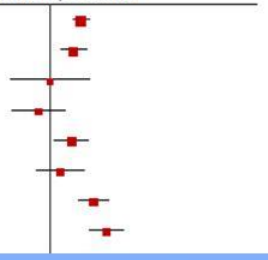

But no correlation with duration of use, many PPI users had lower BMD at baseline, conflicting more recent evidence…

Corley 2010	16.9%	1.18 [1.08, 1.29]
De Vries 2009	15.9%	1.20 [1.07, 1.35]
Gray 2010	12.3%	1.07 [0.88, 1.31]
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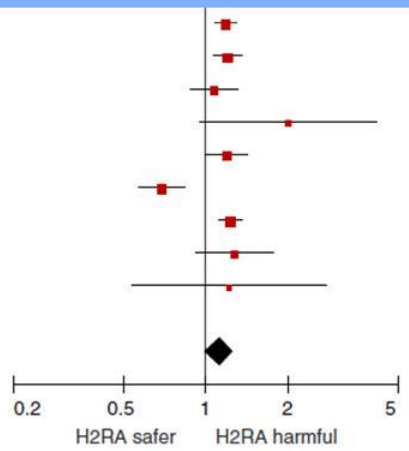
Test for overall effect: $Z = 1.88$ ($P = 0.06$)



Kwok CS et al. *Bone* 2011;48:768-76.

Risk Factors for Fractures in Children

Conclusions: "PPI use was associated with fracture in young adults, but overall evidence did not support a PPI-fracture relationship in children"

Table 2 Dose and total exposure relationship between proton pump inhibitors and fracture among subjects <18 years old

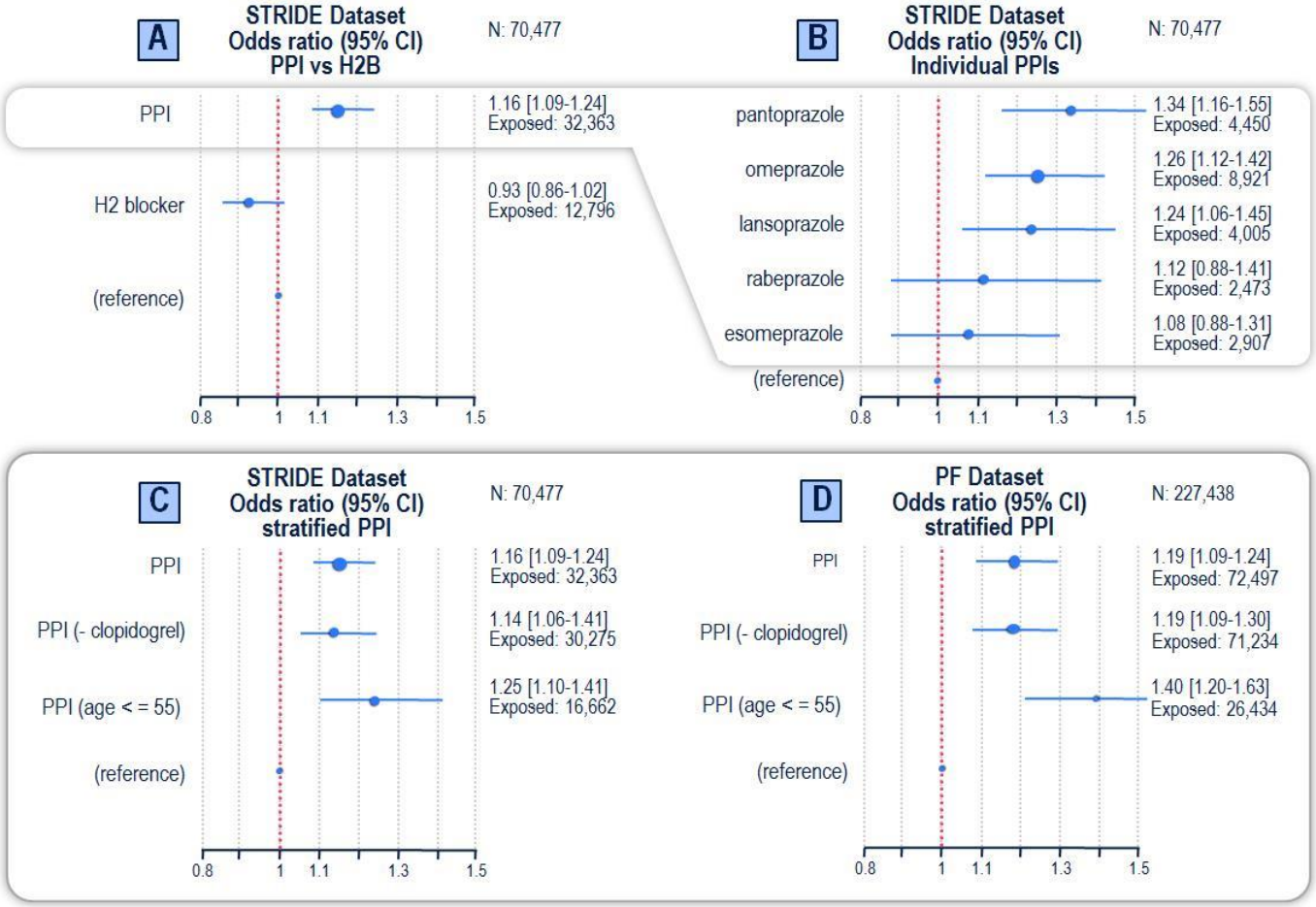
Proton pump inhibitors	Cases	Controls	Crude OR (95 % CI)	Adjusted OR[a] (95 % CI)
Maximal dose		Total:	1.16 (0.94 to 1.43)	1.13 (0.92 to 1.39)
None	86,578	422,162	Reference	Reference
Daily or less	424	1651	1.25 (1.12–1.40)	1.22 (1.09–1.36)
>Daily	69	253	1.33 (1.00–1.74)	1.30 (1.00–1.70)
Cumulative exposure				
None	86,578	422,162	Reference	Reference
1–179 doses	379	1427	1.30 (1.15–1.45)	1.26 (1.12–1.41)
180–720 doses	61	278	1.07 (0.78–1.42)	1.03 (0.78–1.37)
>720 doses	53	199	1.30 (0.94–1.77)	1.29 (0.95–1.74)

OR odds ratio, *CI* confidence interval, *IQR* interquartile range

[a] Adjusted for prior use of histamine-2 receptor antagonists, anti-epileptic drugs, opiates, and oral glucocorticoids

Freedberg DE et al. *Osteoporos Int* 2015;26:2501-7.

PPI Use is Associated with an Increased Risk for MI, Regardless of Age or Clopidogrel Use



Shah NH et al. *PLoS ONE* 2015;10:e0124653.

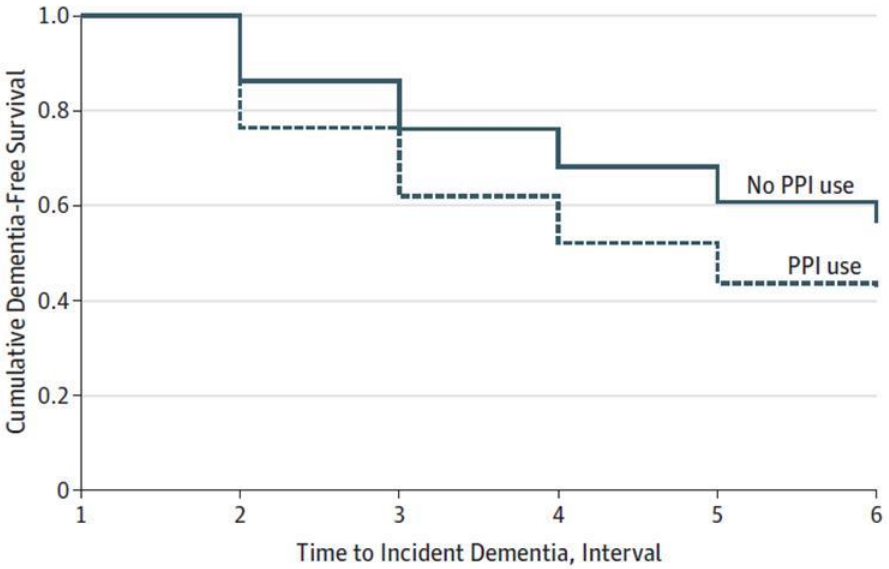
But…

- Data mining exercise (queried over 16 million clinical documents on 2.9 million individuals)
- Modest absolute increased risk: for every 4,000 patients treated with PPIs only one would develop an MI
- There are other features of GERD patients who take PPIs that may explain the association (obesity, smoke)
- No dose or duration effect

Dementia

- 73,679 participants >75 y/o and free of dementia at baseline.
- Patients receiving regular PPI medication (n = 2950) were found to have a significantly increased risk of incident dementia compared with the patients not receiving PPI medication (n = 70,729)

Figure 2. Dementia-Free Survival by Use of Proton Pump Inhibitors (PPIs)



Gomm W et al. *JAMA Neurol* 2016;published online Feb 15.

Dementia and PPI

- Unclear mechanism:
  1) Modulation of brain enzymes by PPIs?
  2) Enhancement of β-amyloid (Aβ) levels in the brain (PPI inhibit degradation enzymes)?
  3) Decreased level of Vit B12 affecting cognition?
- Age, stroke, depression, diabetes, and polypharmacy also all significantly elevated the risk of dementia
- PPI Data not controlled for diet, lifestyle, and education
- Different etiologies of dementia not clarified
- So far this report suggests association, no evidence for causation

Gomm W et al. *JAMA Neurol* 2016;published online Feb 15.

Summary: Understanding the Risks of Treatment

- Prolonged acid suppression should be used **only** when indicated
- Ongoing management should include strategies for treatment discontinuation
- In children there is evidence of an increased risk of infection, particularly *C. difficile* for those treated with a PPI
- Other risks demonstrated in adults have not been yet confirmed in children

Aerodigestive Conditions and Associations with Reflux

Case

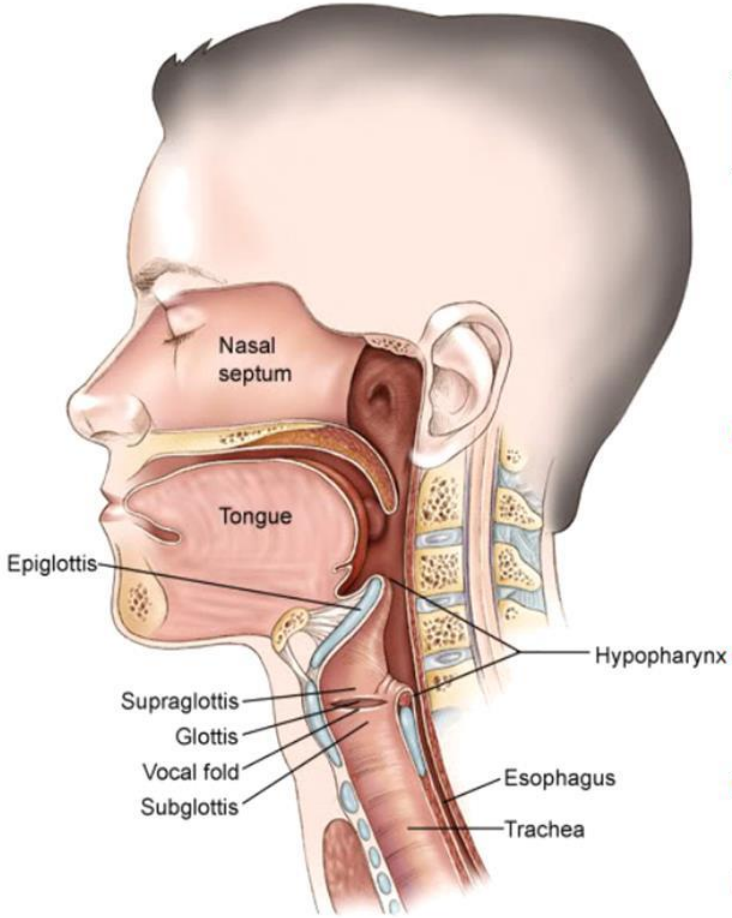
- 6 ½ year-old with persistent cough, day and night
- Patient has had noticeable increase in wheezing episodes over the past year
- Past medical history significant for GERD as an infant, diagnosed after patient presented with an ALTE
- Currently using PPI therapy one time/day

Section Objectives

To understand “aerodigestive” diseases

- A family of conditions which may represent extra-esophageal manifestations of acid reflux
- The pathophysiology and biological plausibility for their association with acid reflux
- When there is a current evidence-basis to use PPI to treat aerodigestive disease

Airway Protective Mechanisms



ESOPHAGEAL DISTENTION → UES contracts

↓

→ **Vagal reflexes**
- Vocal cords close
- Central apnea occurs
- UES relaxes

Hypopharynx → Refluxate enters pharynx

→ Swallowing clears pharynx

→ Respiration resumes

Image: Adapted from Robert Morreale / *Visual Explanations*, LCC

Jadcherla SR et al. *Am J Gastroenterol* 2009;104:2572-82.
Jadcherla SR et al. *J Pediatr Gastroenterol Nutr* 2009;48:186-92.

Respiratory Disease and Reflux

Have they met the burden of proof for causality?

Asthma

- Asthma is a reversible obstructive lung disease
  - Caused by increased reaction of the airways to various stimuli
  - Chronic disease prone to acute exacerbations
  - Can be life-threatening if not managed appropriately
- One of the most common chronic inflammatory diseases in childhood
  - Currently affecting an estimated 7.1 million children under 18 years

Lang JE et al. *J Allergy Clin Immunol Pract* 2013;1(2):172-180.
Usta Guc B et al. *Clin Respir J* 2014;8(3):330-337.
Karabel M et al. *Clin Respir J* 2014; 8(2): 152-159.
Pirogowicz I et al. *Adv Exp Med Biol* 2013;788:161-166.
Blake K et al. *Curr Opin Pulm Med* 2013;19(1):24-29.

Asthma and GER; Association or Causation?

- Proposed mechanisms by which reflux aggravates asthma are:
  - Direct production of airway inflammation
  - Airway hyper-responsiveness
  - Vagally-mediated bronchial or laryngeal spasm
  - Neuronal-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 intra-thoracic pressure

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

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.)

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 subgroup with a positive pH study, no treatment effect for lansoprazole vs placebo was observed for any asthma outcome. Children treated with lansoprazole reported more respiratory infections (relative risk, 1.3 [95% CI, 1.1-1.6]).

Conclusion In this trial of children with poorly controlled asthma without symptoms of GER who were using inhaled corticosteroids, the addition of lansoprazole, compared with placebo, improved neither symptoms nor lung function but was associated with increased adverse events.

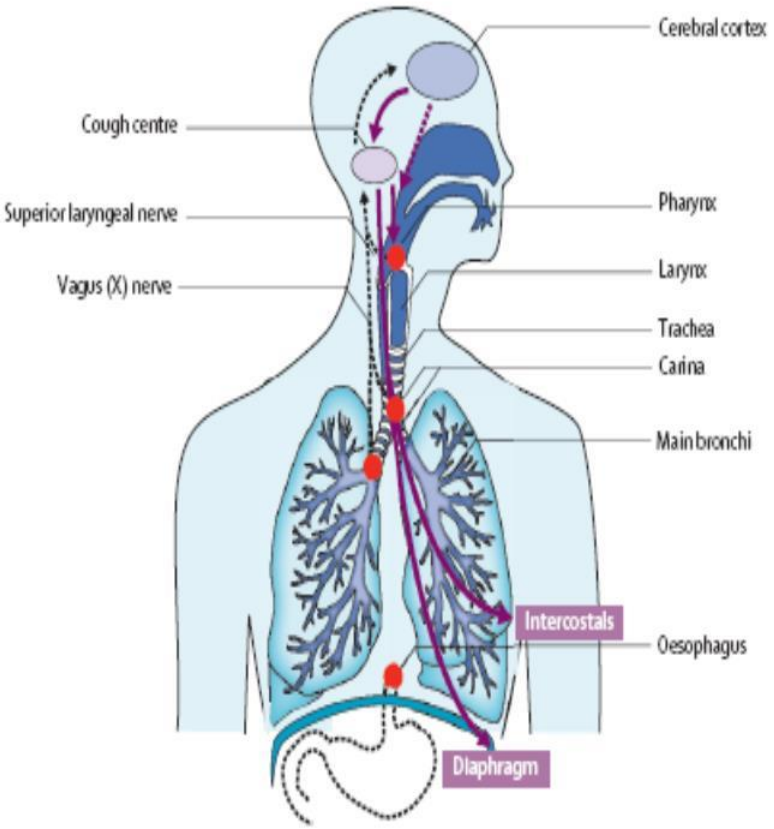
Mastonarde JG et al. *N Engl J Med* 2009;160:1487-99.
Holbrook JT et al. *JAMA* 2012;307:373-80.

GER and Asthma…the Saga Continues

- Biological plausibility — ☑ YES
- Causality — ? Not definitively characterize
- What effect will a PPI have on asthma symptoms, severity (i.e. some patients benefit)? — ? Not clear who will benefit, more research needed

Neurophysiology of Cough

- Not every child who coughs or wheezes has ***asthma***
- Not every child who coughs or wheezes has ***reflux***
- Other etiologies for cough include dysphagia and aspiration syndromes; habitual cough, etc.



Lang J. E et al. *J Allergy Clin Immunol Pract* 2013;1:172-180.
Usta Guc B et al. *Clin Respir J* 2014;8:330-337.
Karabel M et al. *Clin Respir J* 2014;8:152-9.
Pirogowicz I et al. *Adv Exp Med Biol* 2013;788:161-6.
Blake K et al. *Curr Opin Pulm Med* 2013;19:24-29.

Persistent Cough and Reflux

- Intraesophageal Pressure Recording (IEPR) is very sensitive at detecting cough
- Parental and patient symptom recording in children is inadequate for making the diagnosis of reflux-related lung disease
- IEPR may represent a new standard for clinical practice

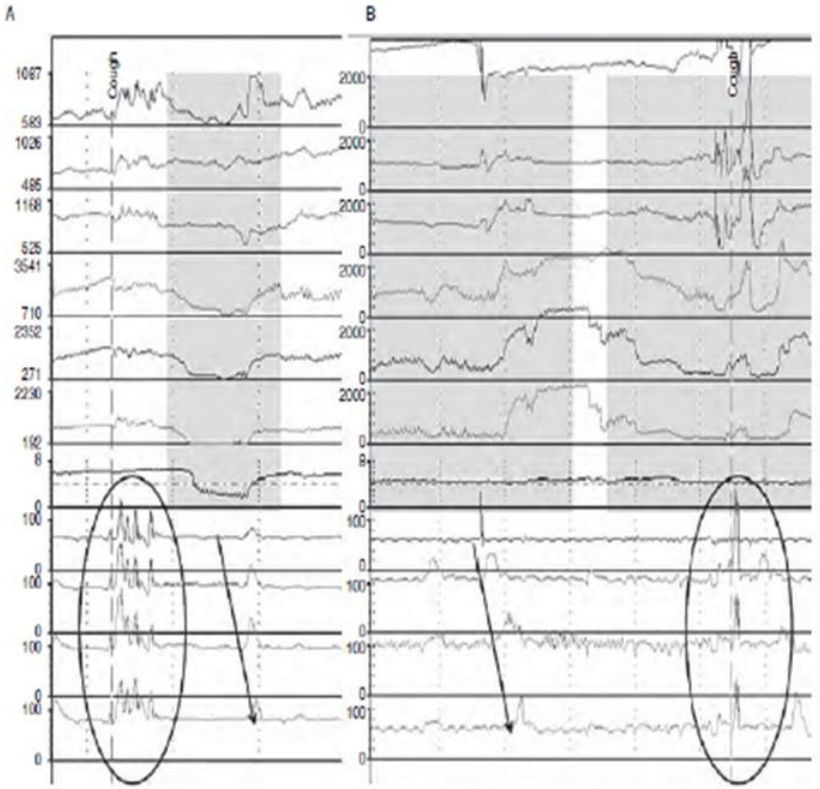


FIGURE 1. Tracing of a cough preceding reflux (A) and reflux preceding cough (B). Intraesophageal pressure recording coughs, seen as high amplitude, simultaneous pressure spikes, are shown in the circles. Reflux episodes are shaded gray. The arrow highlights normal, propagating esophageal peristalsis, in contrast to simultaneous pressure spikes with cough.

Rosen R et al. *J Pediatr Gastroenterol Nutr* 2014;58:22-26.
Lang JE et al. *J Allergy Clin Immunol Pract* 2013;1:172-80.
Usta Guc B et al. *Clin Respir J* 2014;8:330-37.
Karabel M et al. *Clin Respir J* 2014;8:152-59.

Cough and Reflux…a Possibility

Biological plausibility	☑ YES
Causality	☑ Likely multi-factorial
Is there a role for a PPI	☑ Yes, in select individuals

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Signs You Could Have 'Silent Reflux'

That chronic cough may not be what it seems.

People who suffer from this reflux disease may frequently clear their throat or have trouble swallowing.

By Chai Woodham | April 30, 2015 | 10:57 a.m. EDT + More

The Washington Post

By Jamie Koufman December 8, 2014

Opinions

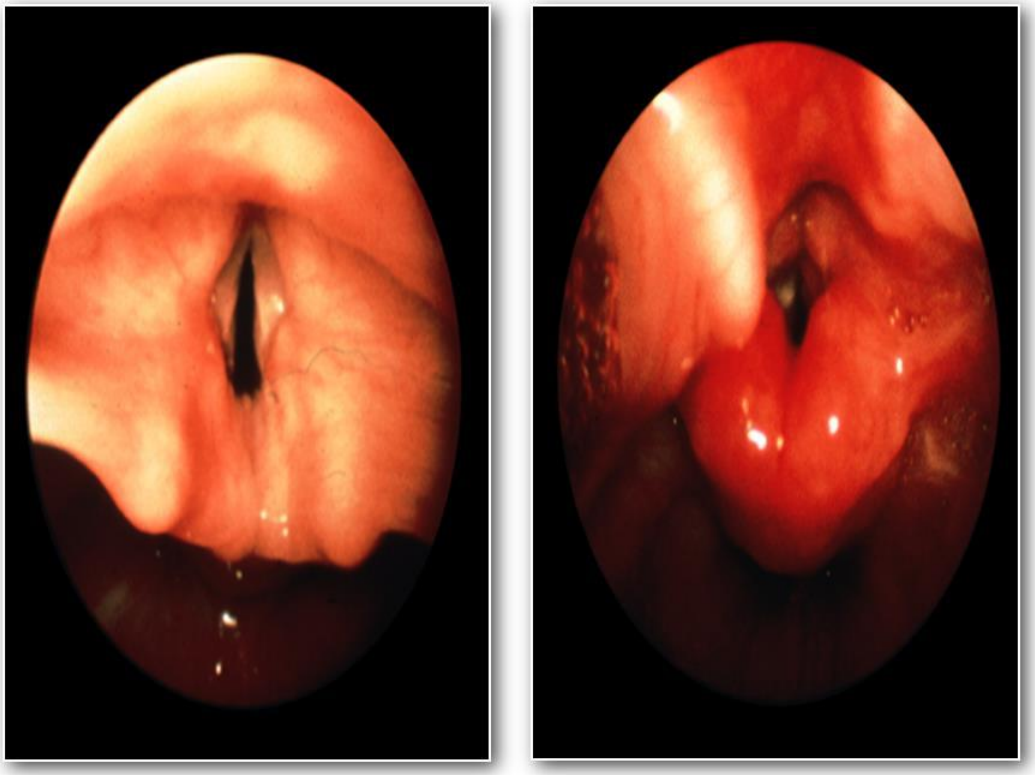
Obama's acid reflux may help others receive proper diagnosis and treatment

ENT Manifestations of GERD

Have they met the burden of proof for causality?

Laryngeal: Normal vs. Erythema

Not all red in the airways = reflux!



Johansson H et al. *Thorax* 2015;70:57-63.
Pearson JP et al. *Aliment Pharmacol Ther* 2011;33(sup 1):1-71.
Venkatesan NN et al. *Pediatr Clin Nor Amer* 2013;60:865-78.

Laryngeal-pharyngeal Pathology and Reflux

- The sensitivity of laryngoscopic findings to identify laryngeal-pharyngeal disease related to reflux (LPR) is poor
- Newly validated, adult-based LPR outcome tool that shows improvement with therapy that may help identify
  - *Responder Definition of a Patient-Reported Outcome Instrument for Laryngopharyngeal Reflux Based on the US FDA Guidance*
- Clinical improvement followed by recurrence off acid-suppression treatment and/or life-style changes suggests an association with GER
- There is insufficient evidence to recommend for ***OR*** against the use of acid suppression therapy

Chang AB et al. *Otolaryngol Clin North Am* 2010;43:181-98.
Lien HC et al *Value Health* 2015;18:396-403.
Vandenplas Y et al. *J Pediatr Gastroenterol Nutr* 2009;49:498-547.
Sherman P et al. *Am J Gastroenterol* 2009;104:1278-95.
Kahrilis P et al. *Gastroenterology* 2008;135:1392-1413.
Patel D et al. *Curr Gastroenterol Rep* 2016;18:12-20.

Laryngeal-pharyngeal Pathology and Reflux

REZA BAND, a Noninvasive Device for Laryngopharyngeal Reflux, FDA OK'ed

MARCH 13TH, 2015 EDITORS GI, MEDICINE

Sleep Review
THE JOURNAL FOR SLEEP SPECIALISTS

Oral Appliances Side-by-Side Comparison Guide (December 2015)
Compare 17 oral appliances for obstructive sleep apnea side-by-side. The guide compares features such as warranty, indications, type, how it...

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CLINICAL TRIALS

Clinical Study Shows MedCline As Effective Treatment for Silent Reflux

Published on December 8, 2015

Chang AB et al. *Otolaryngol Clin North Am* 2010;43:181-98.
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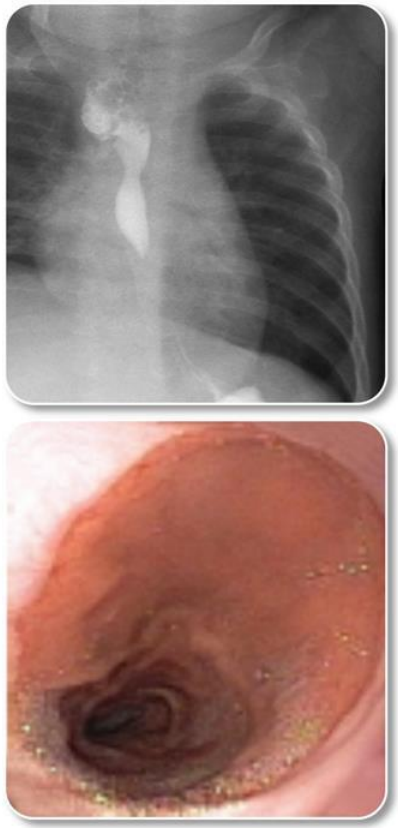
Kahrilis P et al. *Gastroenterology* 2008;135:1392-1413.
Patel, D et al. *Curr Gastroenterol Rep* 2016;18:12-20.

ENT Manifestations of GERD

Biological plausibility	☑ YES
Causality	☑ Not at present, more research needed
Is there a role for PPIs?	☑ Maybe

Esophageal Atresia (EA) / Tracheal-Esophageal Fistulae (TEF) and Reflux Disease

- Symptoms can include coughing with feeding, recurrent pneumonia, and episodic cyanosis concerning for ALTE
- H-type TEF prone to delay in diagnosis
  - May not be identified on fluoroscopy
  - May require bronchoscopy with methylene blue
- Predisposed to reflux
  - Abnormal motility prevents adequate acid clearance
  - Hiatal hernia created during repair changes the position of the LES and diaphragm
- Long term high-risk for esophageal cancer



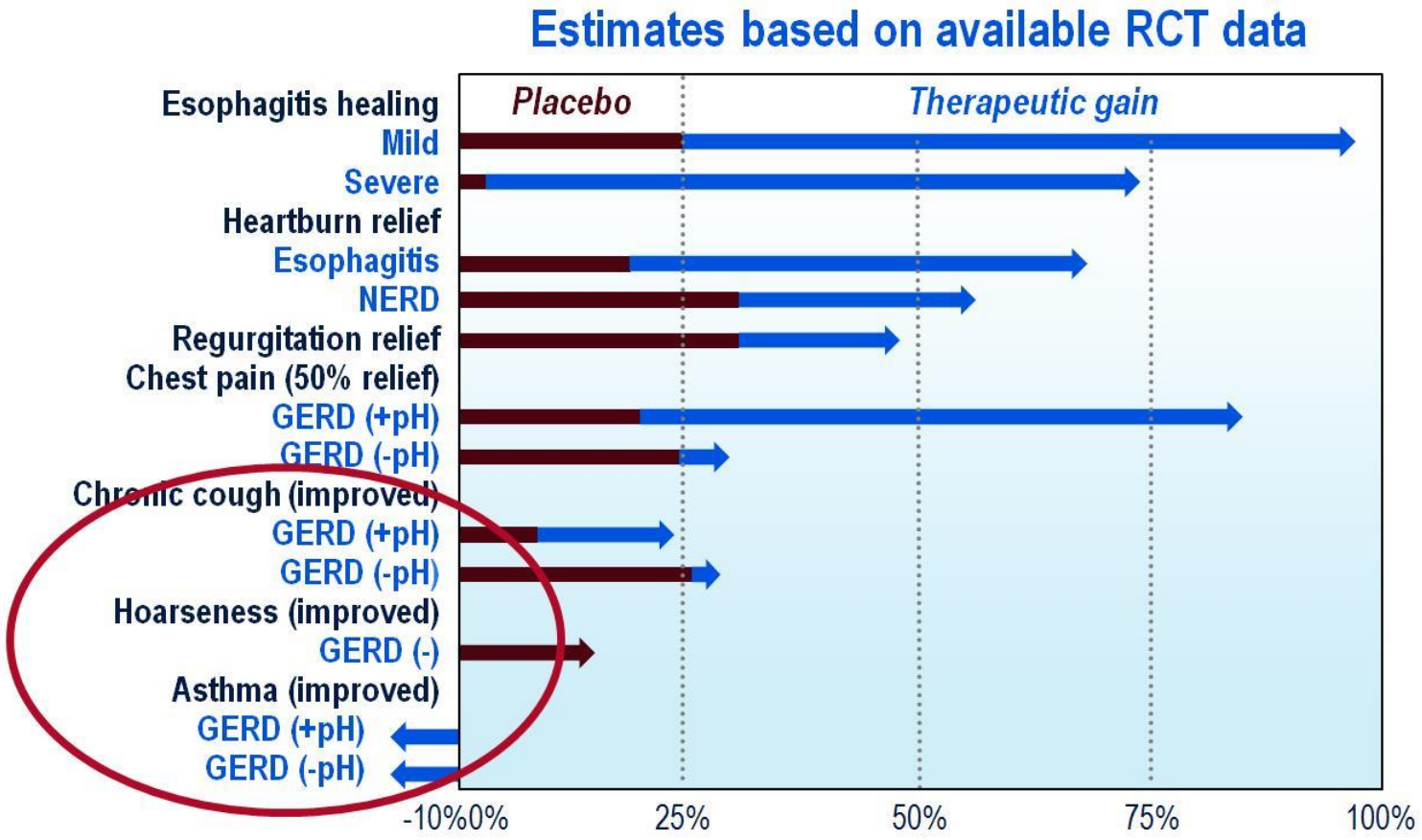
Levesque D et al. *Dis Esophagus* 2013;26:382-87.
Sistonen SJ et al. *Pediatr Surg Int* 2011;27:1141-9.
Rintala RJ et al. *J Pediatr Gastroenterol Nutr* 2011;52:S35-6.
Sistonen SJ et al. *Pediatr Surg* 2008;43:602-5.
http://www.we-are-eat.org

Esophageal Atresia/ Tracheal-Esophageal Fistulae and GERD

Biological plausibility	☑ YES
Causality	☑ YES
Is there a role for PPIs?	☑ YES

http://www.we-are-eat.org

PPI Efficacy for Potential Manifestations for GERD in Adults



Boeckxstaens G. *Postgrad Med J* 2015;91:46-54.

Summary: Aerodigestive Disease – Reflux Related?

- GER causality not yet satisfied for asthma, cough, and laryngeal disease
- Research is needed in childhood asthmatics
  - Identification of children with asthma responsive to acid suppression
- Possible role for PPI in cough and select laryngeal pharyngeal reflux patients
  - Studies to validate adult-based patient-reported outcome tool in children
- Clearly a role for the PPI in infants and children with EA/TEF

Naik RD et al. *Expert Rev Gastroenterol Hepatol* 2015;9:969-82.
Kostovski A et al. *J Pediatr Gastroenterol Nutr* 2015;61:527.
Silvia CE et al. *Int Arch Otorhinolaryngol* 2015;19:234-7.
Connor MJ et al. *Am J Surg* 2015;209:47-759.

Beyond Erosive-reflux Disease (ERD) to NERD

Case

- 13 year-old with epigastric and chest pain
- History of 3 years of PPI use
  - Initially with complete symptom resolution but now with only partial relief with symptoms multiple times per day
- Has had endoscopy performed twice (3 years ago and repeated last week)
  - Both times suggesting no evidence of mucosal breaks and normal biopsies in the duodenum, stomach and the esophagus

Section Objectives

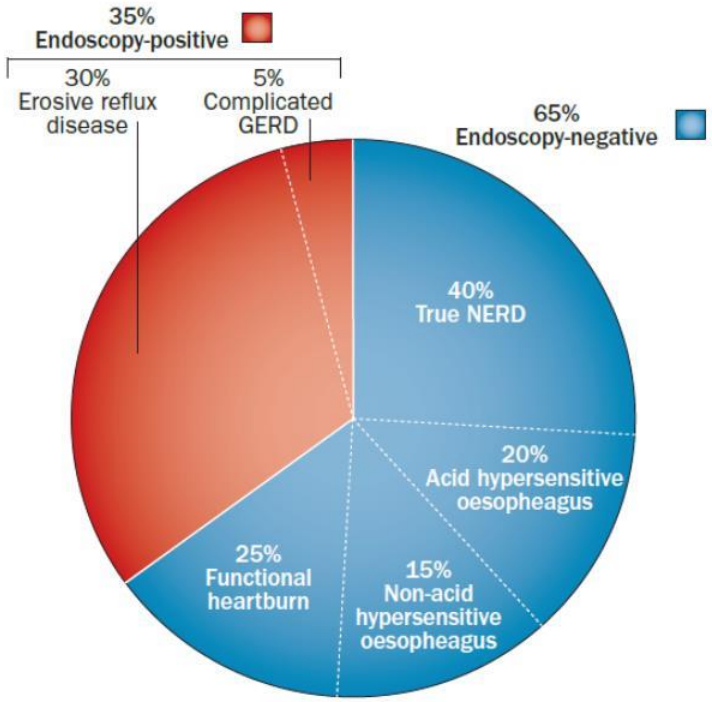
To review:

- An expanding understanding of acid mediated disease at the cellular level that includes non-erosive reflux disease (NERD) vs. erosive reflux disease (ERD)
- How to clinically differentiate NERD from ERD, functional heartburn and hypersensitive esophagus
- An evidence-basis for treating ERD and NERD ***versus*** **not** for treating functional heartburn or hypersensitive esophagus with PPI

Differentiating Between Various Reflux Related Disorders

	Typical Symptoms	Erosions by Endoscopy	Abnormal acid reflux on pH-MII testing	Symptom association with acid or non-acid reflux
ERD	+	+	+	+/-
NERD	+	-	+	+/-
Hypersensitive Esophagus	+	-	-	+
Functional Heartburn	+	-	-	-

Incidence of Reflux Disease Subtypes in Adults



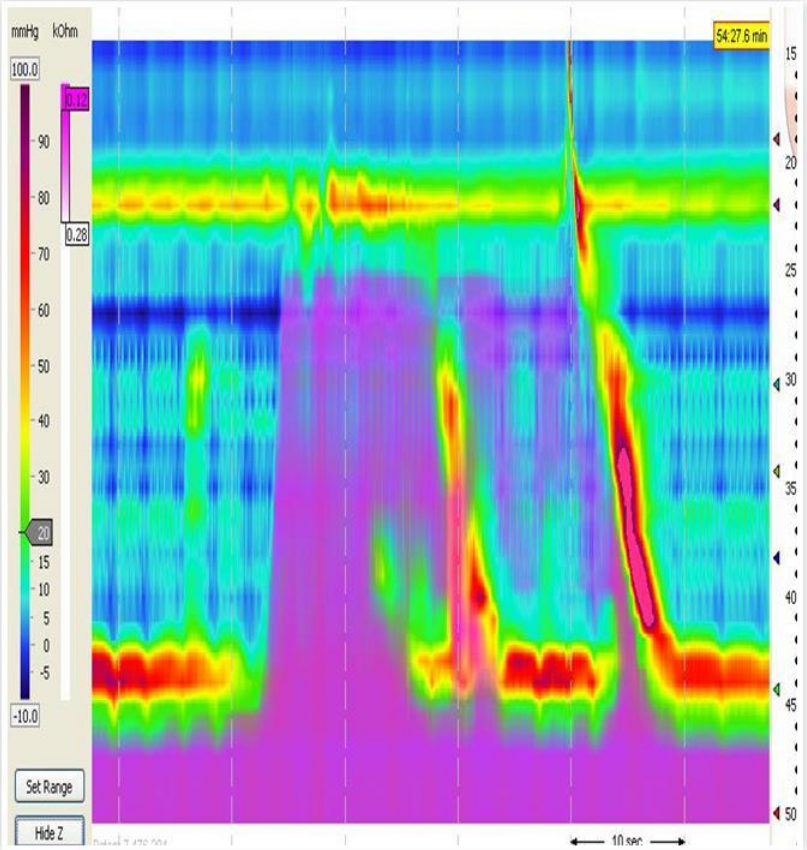
Reprinted by permission from Macmillan Publishers Ltd. [1]

- 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

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

The Mechanisms

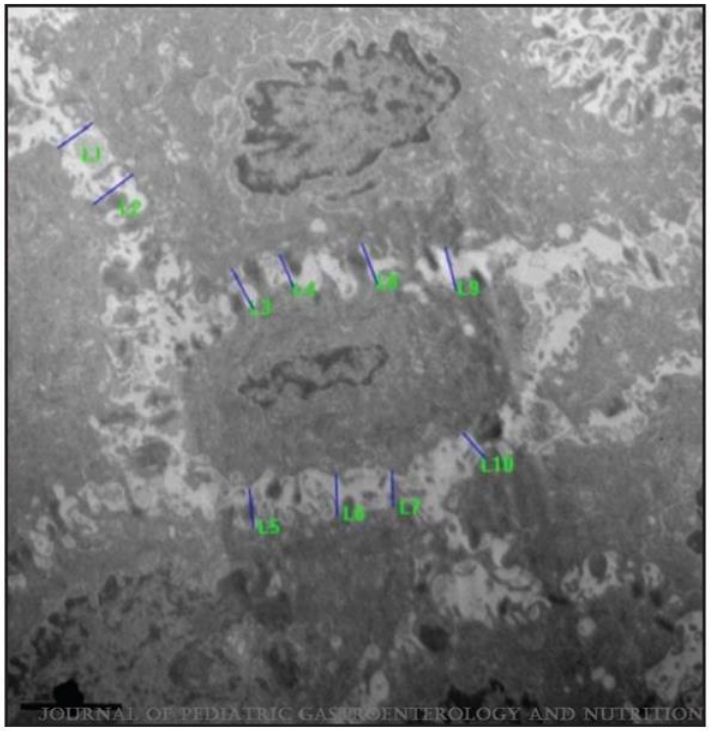
- The mechanism of reflux in NERD patients is transient lower esophageal sphincter relaxations (TLSERs)[1]
- Patients with NERD have similar symptom severity to those with ERD [2]
- Visceral hypersensitivity is similar in patients with NERD and ERD [3]



1. Ribolsi M et al. *Clin Gastroenterol Hepatol* 2014;12:52-7.
2. Weijenborg PW et al. *Am J Pysiol Gastrointest Liver Physiol* 2014;307:G323-9.
3. Thoua NM et al. *Aliment Pharmacol Ther* 2008;27:396-403.

Diagnosing NERD

- Heartburn, regurgitation, epigastric pain or discomfort, and dyspepsia **ARE NOT USEFUL** to differentiate NERD and ERD [1,2,3]
- ERD and NERD adult patients respond similarly to a PPI trial [4]
- The microscopic presentation of ERD and NERD is similar; both with microscopic inflammation and dilated intracellular spaces [5,6]

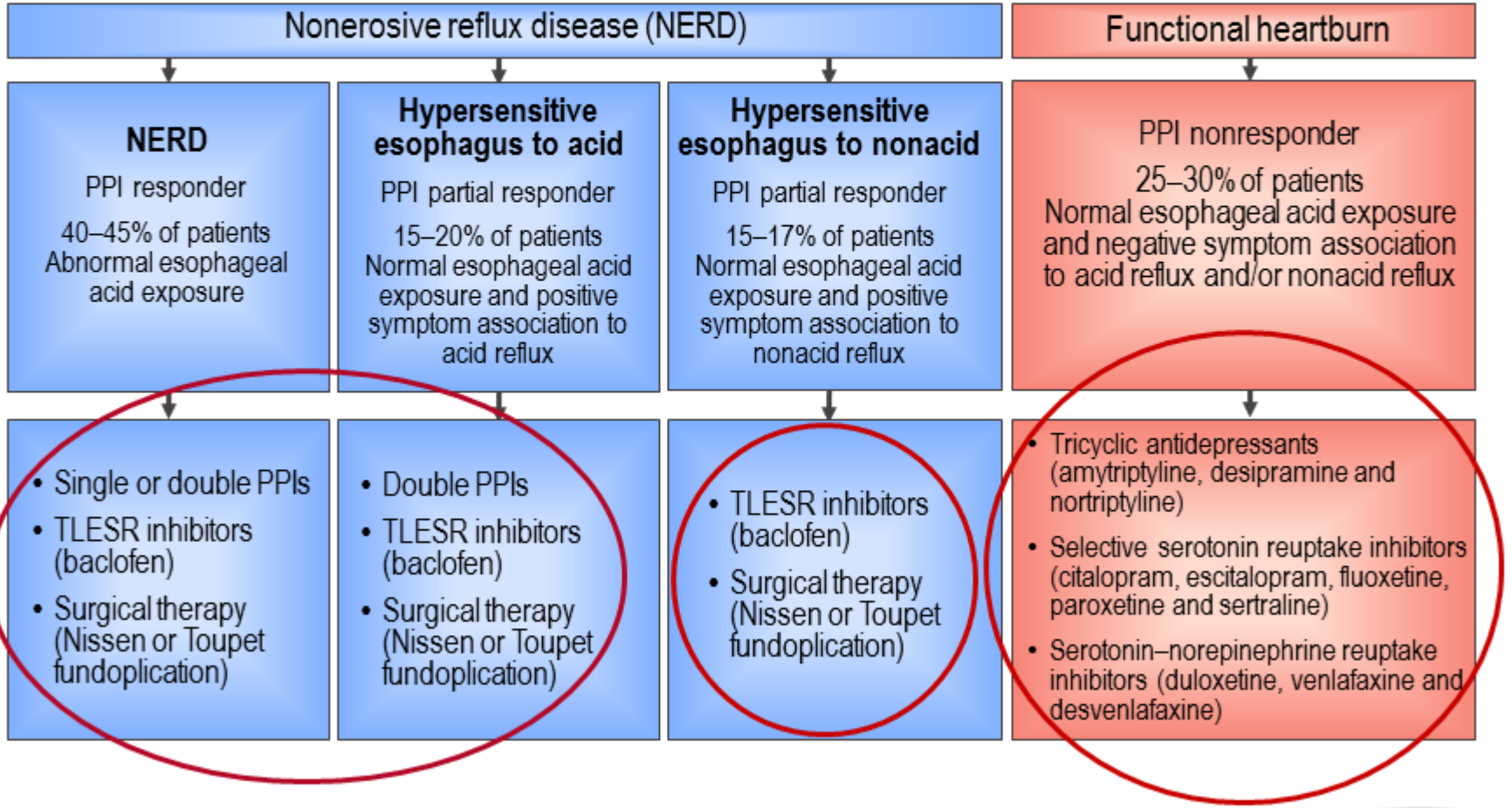


Microscopic view of dilated intracellular spaces
Reprinted by permission from Wolters Kluwer Health, Inc.
J Ped Gastroenterol Nutr, Altaf MA et al. 2014

1. Kandulski A et al. *Aliment Pharmacol Ther* 2013;38:643-51.
2. Savarino E et al. *Gut* 2009;58:1185-91.
3. Nelson SP et al. *Arch Pediatr Adolesc Med* 2000;154;150-4.
4. Bytzer P et al. *Clin Gastroenterol Hepatol* 2012;10:1360-6.
5. Kandulski A et al. *Aliment Pharmacol Ther* 2013;38:643-51.
6. Borrelli O et al. *Neurogastoenterol Motil* 2012;24:828-e394.

Why do we Care About the Names?

Treatments may be Different, at least in Adults



Savarino E et al. *Nat Rev Gastroenterol* 2013;10:371-80.

Case Work-Up and Outcome

- Impedance results off therapy:
  - 45 total reflux episodes, 27 acid, 18 nonacid
  - pH<4 for 4.6% of the time (normal is 10%)
  - 6/6 chest pain episodes associated with reflux
- Diagnosis: hypersensitive esophagus
- Outcome:
  - Twice a day acid suppression continued due to partial response with lessening of symptom severity
  - Citalopram started with reduction in pain frequency and severity

Summary: Functional Heartburn or NERD

- Definitions of NERD, ERD and other reflux related conditions are changing
- Critical to understand the potential for response, and non-response of NERD and other conditions to therapies
- One of the primary indications of pH-Multichannel Intraluminal Impedence testing (pH-MII) may be to differentiate NERD from functional heartburn
  - Should be performed off-therapy
- Acid suppression has a role in NERD and hypersensitive esophagus **but not** in functional heartburn

Closing Thoughts

PPI, to Use, or Not to Use ...Is that the Right Question?

- Answer: Not really…
- Perhaps more important questions are:
  - Is treatment with PPIs indicated and evidence-based?
  - For how long will treatment continue?

Take Home Messages

- PPIs have no role in extremely common infant GER
  - Should be used when indicated in infants with GERD
- PPIs have a role in NERD and hypersensitive esophagus
  - Not in functional heartburn
- Limited evidence for using PPI in some aerodigestive diseases
- PPIs are indicated and can be very effectively used in ERD, NSAID prophylaxis, bleeding, PPI-REE, and *H. pylori* eradication
  - For a defined period of time
- Ongoing management should include a plan for treatment discontinuation
  - In consideration of risks associated with PPI therapy

Questions?

Additional Slides

Evidence-Based Indications for Treatment with PPIs

CME

A Global, Evidence-Based Consensus on the Definition of Gastroesophageal Reflux Disease in the Pediatric Population

Philip M. Sherman, MD[1], Eric Hassall, MD[2], Ulysses Fagundes-Neto, MD[3], Benjamin D. Gold, MD[4], Seiichi Kato, MD[5], Sibylle Koletzko, MD[6], Susan Orenstein, MD[7], Colin Rudolph, MD[8], Nimish Vakil, MD[9,10] and Yvan Vandenplas, MD[11]

OBJECTIVES: **We sought to develop an international consensus on the definition of gastroesophageal reflux disease (GERD) in the pediatric population.**

METHODS: **Using the Delphi process, a set of statements was developed and voted on by an international panel of eight pediatric gastroenterologists. Statements were based on systematic literature searches using Medline, EMBASE, and CINAHL. Voting was conducted using a six-point scale, with consensus defined *a priori* as agreement in 75% of the group. The strength of each statement was assessed using the GRADE system.**

RESULTS: **There were four rounds of voting. In the final vote, consensus was reached on 98% of the 59 statements. In this vote, 95% of the statements were accepted by seven of eight voters. Consensus items of particular note are: (i) GERD is present when reflux of gastric contents causes troublesome symptoms and/or complications, but this definition is complicated by unreliable reporting of symptoms in children under the age of ~8 years; (ii) histology has limited use in establishing or excluding a diagnosis of GERD; its primary role is to exclude other conditions; (iii) Barrett's esophagus should be defined as esophageal metaplasia that is intestinal metaplasia, positive or negative; and (iv) extraesophageal conditions may be associated with GERD, but for most of these conditions causality remains to be established.**

CONCLUSIONS: **The consensus statements that comprise the Definition of GERD in the Pediatric Population were developed through a rigorous process. These statements are intended to be used for the development of future clinical practice guidelines and as a basis for clinical trials.**

Am J Gastroenterol 2009; 104:1278–1295; doi:10.1038/ajg.2009.129; published online 7 April 2009

Sherman PM et al. *Am J Gastroenterol* 2009;104:1278-1295.

Case Reports of Infants with Infantile Spasms Misdiagnosed as GERD

ACTA PÆDIATRICA
NURTURING THE CHILD

Acta Pædiatrica ISSN 0803–5253

SHORT COMMUNICATION

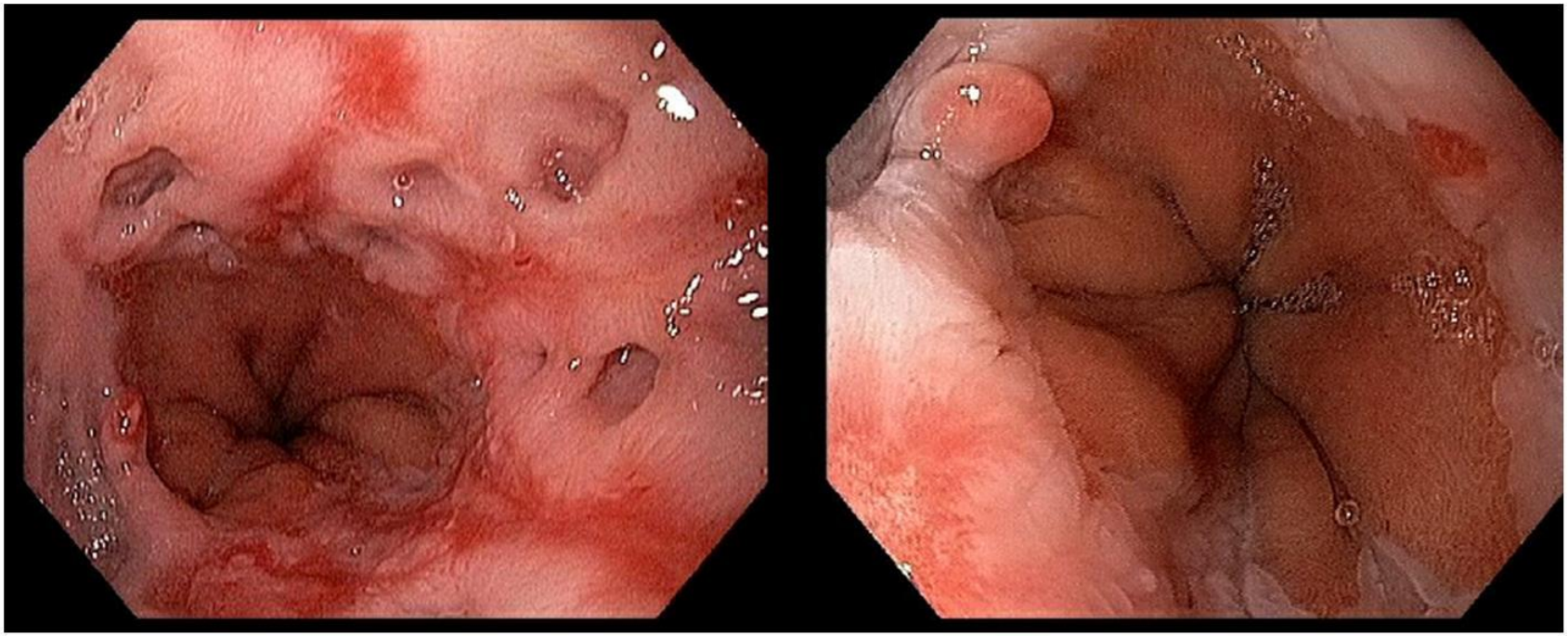
Gastroesophageal reflux disease at any cost: a dangerous paediatric attitude

Andrea Taddio (ataddio@yahoo.it)[1], Chiara Bersanini[2], Lucio Basile[3], Massimo Fontana[2], Alessandro Ventura[1]

1.Department of Pediatrics, Institute of Child Health IRCCS Burlo Garofolo, University of Trieste, Trieste, Italy
2.SCO Pediatria, Ospedale dei Bambini "V. Buzzi", Milan, Italy
3.A.S.L. 105; Pescara, Italy

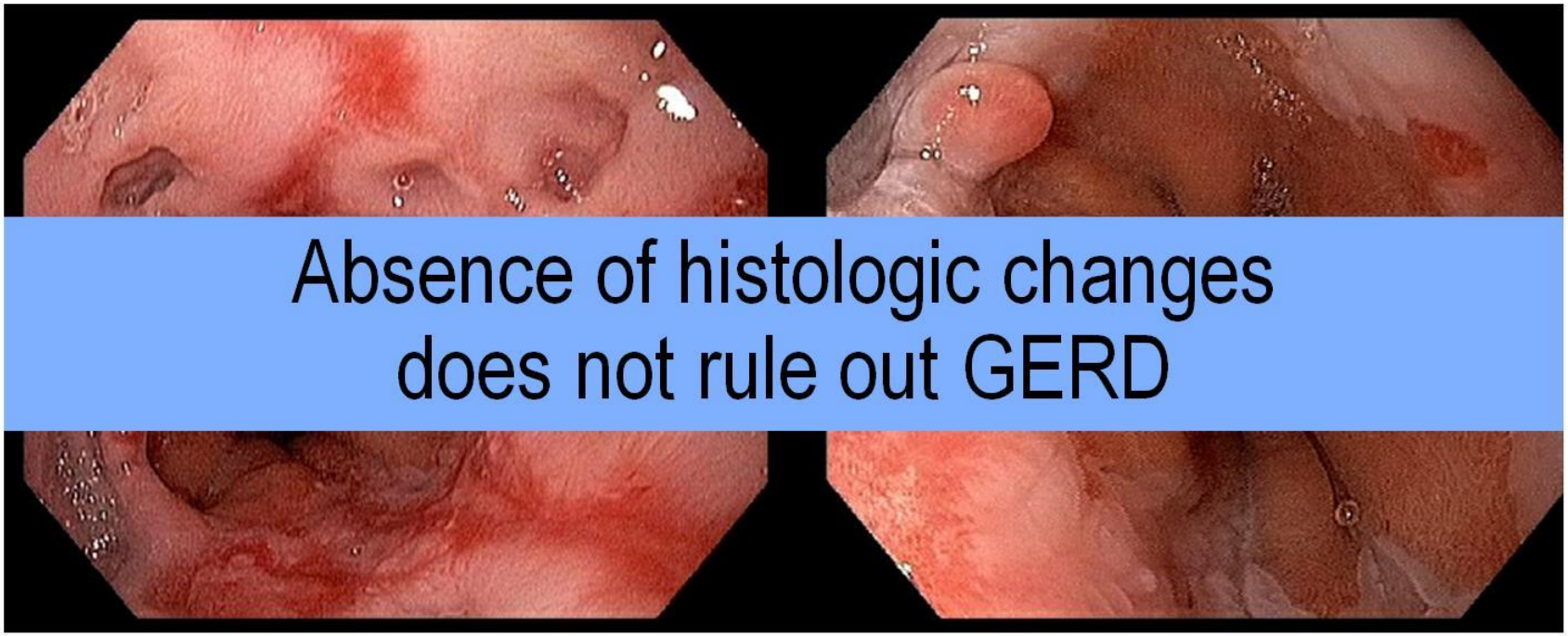
Taddio a et al. *Acta Paediatr* 2011;100:e178-180.

Endoscopically Visible Breaks in the Distal Esophageal Mucosa are the Most Reliable Evidence of Reflux Esophagitis



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

Endoscopically Visible Breaks in the Distal Esophageal Mucosa are the Most Reliable Evidence of Reflux Esophagitis



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

Assessing the Efficacy and Safety of Proton Pump Inhibitor Lansoprazole in Infants with Symptoms of GERD

Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial Assessing the Efficacy and Safety of Proton Pump Inhibitor Lansoprazole in Infants with Symptoms of Gastroesophageal Reflux Disease

SUSAN R. ORENSTEIN, MD, ERIC HASSALL, MBCHB, FRCPC, WANDA FURMAGA-JABLONSKA, MD, PHD, STUART ATKINSON, MBCHB, AND MARSHA RAANAN, MS

Objective To assess the efficacy and safety of lansoprazole in treating infants with symptoms attributed to gastroesophageal reflux disease (GERD) that have persisted despite a ≥ 1-week course of nonpharmacologic management.

Study design This multicenter, double-blind, parallel-group study randomized infants with persisting symptoms attributed to GERD to treatment with lansoprazole or placebo for 4 weeks. Symptoms were tracked through daily diaries and weekly visits. Efficacy was defined primarily by a ≥ 50% reduction in measures of feeding-related crying and secondarily by changes in other symptoms and global assessments. Safety was assessed based on the occurrence of adverse events (AEs) and clinical/laboratory data.

Results Of the 216 infants screened, 162 met the inclusion/exclusion criteria and were randomized. Of those, 44/81 infants (54%) in each group were responders—identical for lansoprazole and placebo. No significant lansoprazole–placebo differences were detected in any secondary measures or analyses of efficacy. During double-blind treatment, 62% of lansoprazole-treated subjects experienced 1 or more treatment-emergent AEs, versus 46% of placebo recipients ($P = .058$). Serious AEs (SAEs), particularly lower respiratory tract infections, occurred in 12 infants, significantly more frequently in the lansoprazole group compared with the placebo group (10 vs 2: $P = .032$).

Conclusions This study detected no difference in efficacy between lansoprazole and placebo for symptoms attributed to GERD in infants age 1 to 12 months. SAEs, particularly lower respiratory tract infections, occurred more frequently with lansoprazole than with placebo. *(J Pediatr 2009;154:514-20)*

See editorial, p 475

From the University of Pittsburgh School of Medicine, Pittsburgh, PA (S.O.); Division of

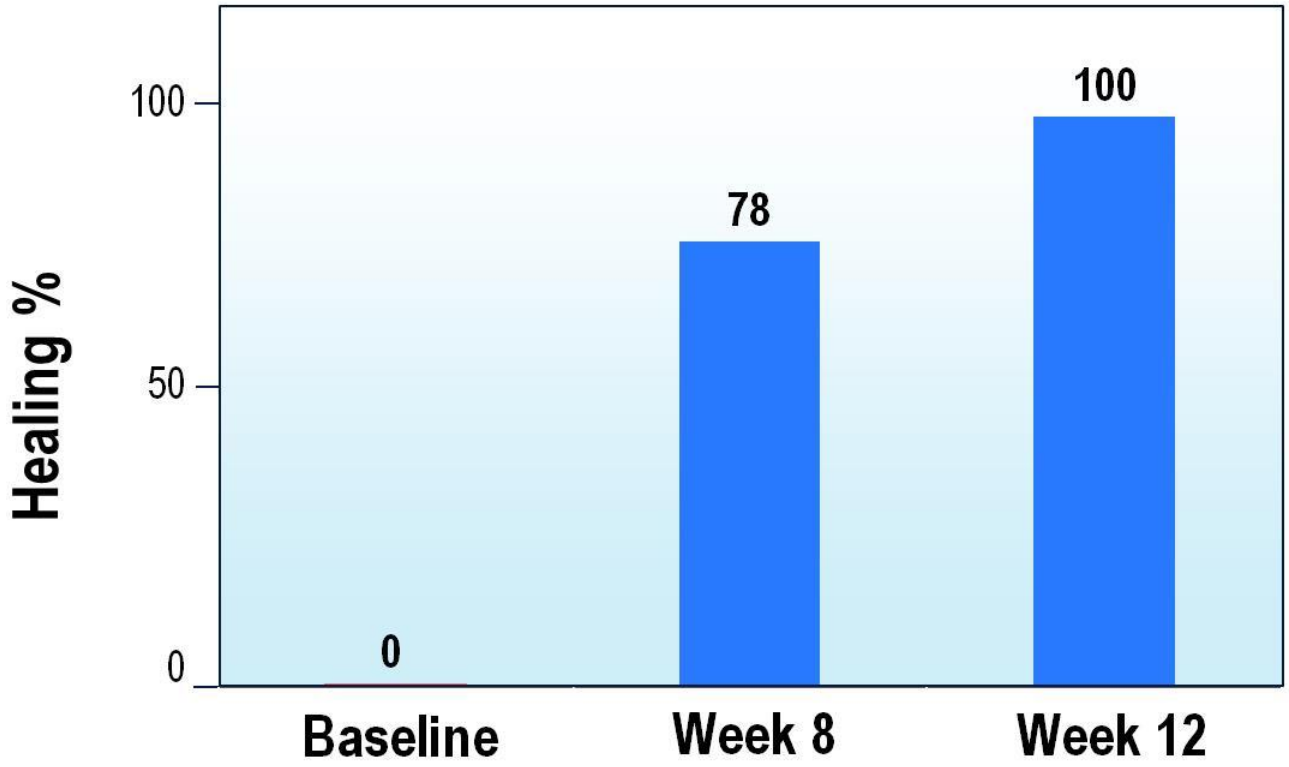
Orensten S et al. *J Pediatr* 2009;154:514-520.

Assessing the Efficacy and Safety of Proton Pump Inhibitor Lansoprazole in Infants with Symptoms of GERD

- No difference in efficacy between lansoprazole and placebo for symptoms attributed to GERD in infants 1 to 12 months

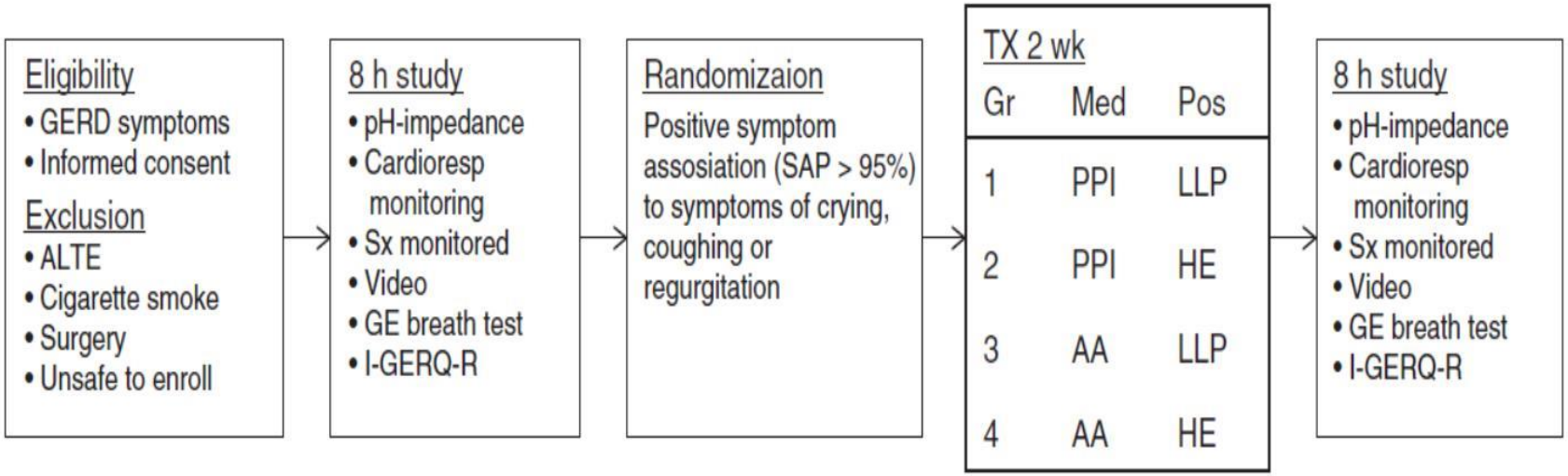
Orensten S et al. *J Pediatr* 2009;154:514-520.

Effect of Lansoprazole on Erosive Esophagitis in Children (12 months–11 yrs)



Tolia V et al. *J Pediatr Gastroenterol Nutr* 2002;35:S308-18.

Body Positioning and Medical Therapy for Infantile Gastroesophageal Reflux Symptoms



Loots C et al. *J Pediatr Gastroenterol Nutr* 2014;59(2):237-43.

ACTA PÆDIATRICA
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Acta Pædiatrica ISSN 0803-5253

REGULAR ARTICLE

Extensive protein hydrolysate formula effectively reduces regurgitation in infants with positive and negative challenge tests for cow's milk allergy

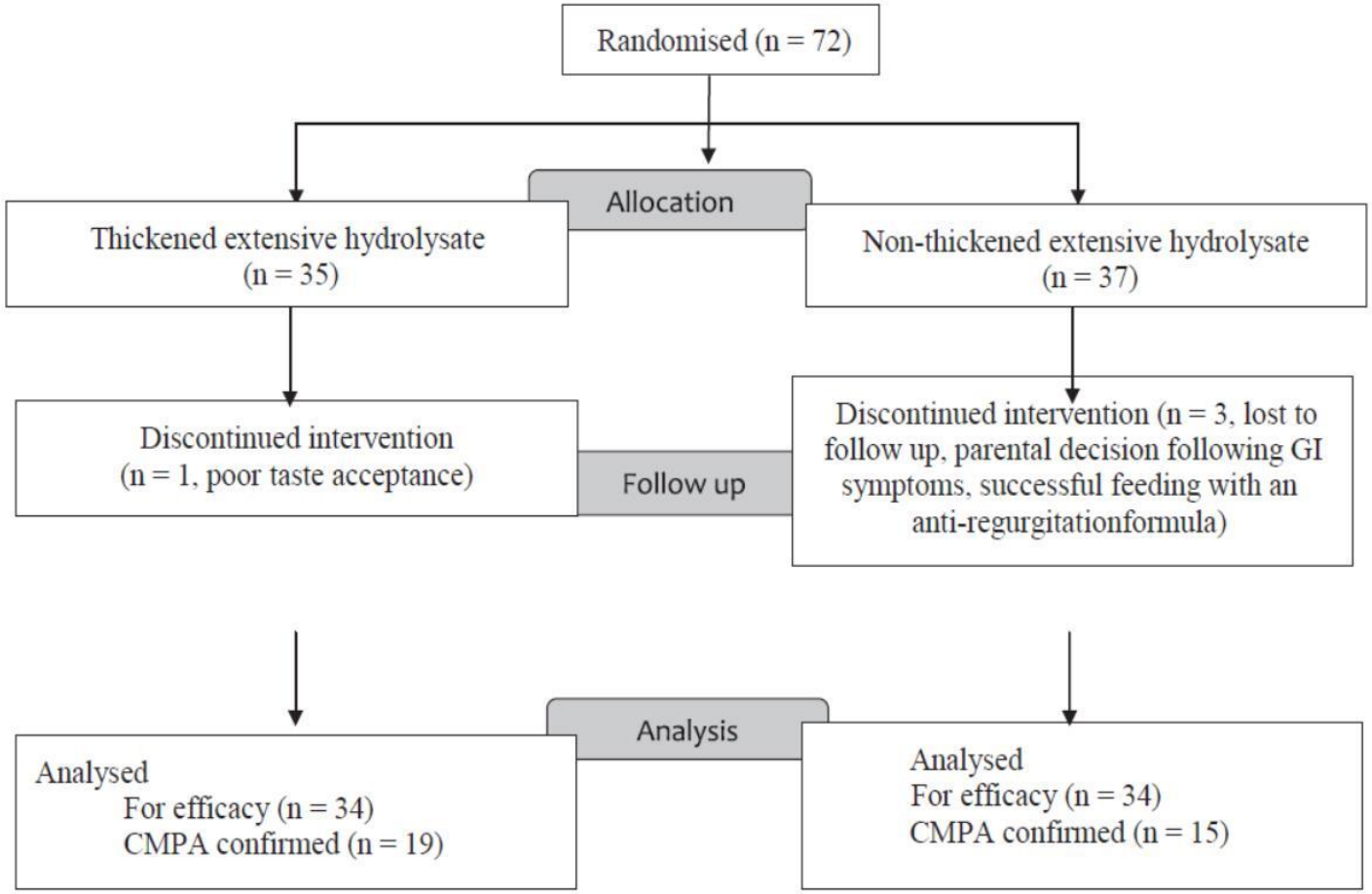
Y. Vandenplas (yvan.vandenplas@uzbrussel.be), E. De Greef, ALLAR study group†

Department of Paediatrics, UZ Brussel, Vrije Universiteit Brussel, Brussels, Belgium

- Prospective, randomized, double-blind
- 72 infants
- < 6 months of age with symptoms evaluated at inclusion and at 1 month:
  - General discomfort
  - GI symptoms (regurgitation, vomiting, diarrhea, constipation, blood in stools)
  - Respiratory symptoms (runny nose, cugh, wheezing)
  - Dermatological symptoms

Vandenplas Y et al. *Acta Paediatr* 2014 Jun; 103(6): e243–e250.

Protein Hydrolysate Formula Effectively Reduces Regurgitation in Infants *continued*



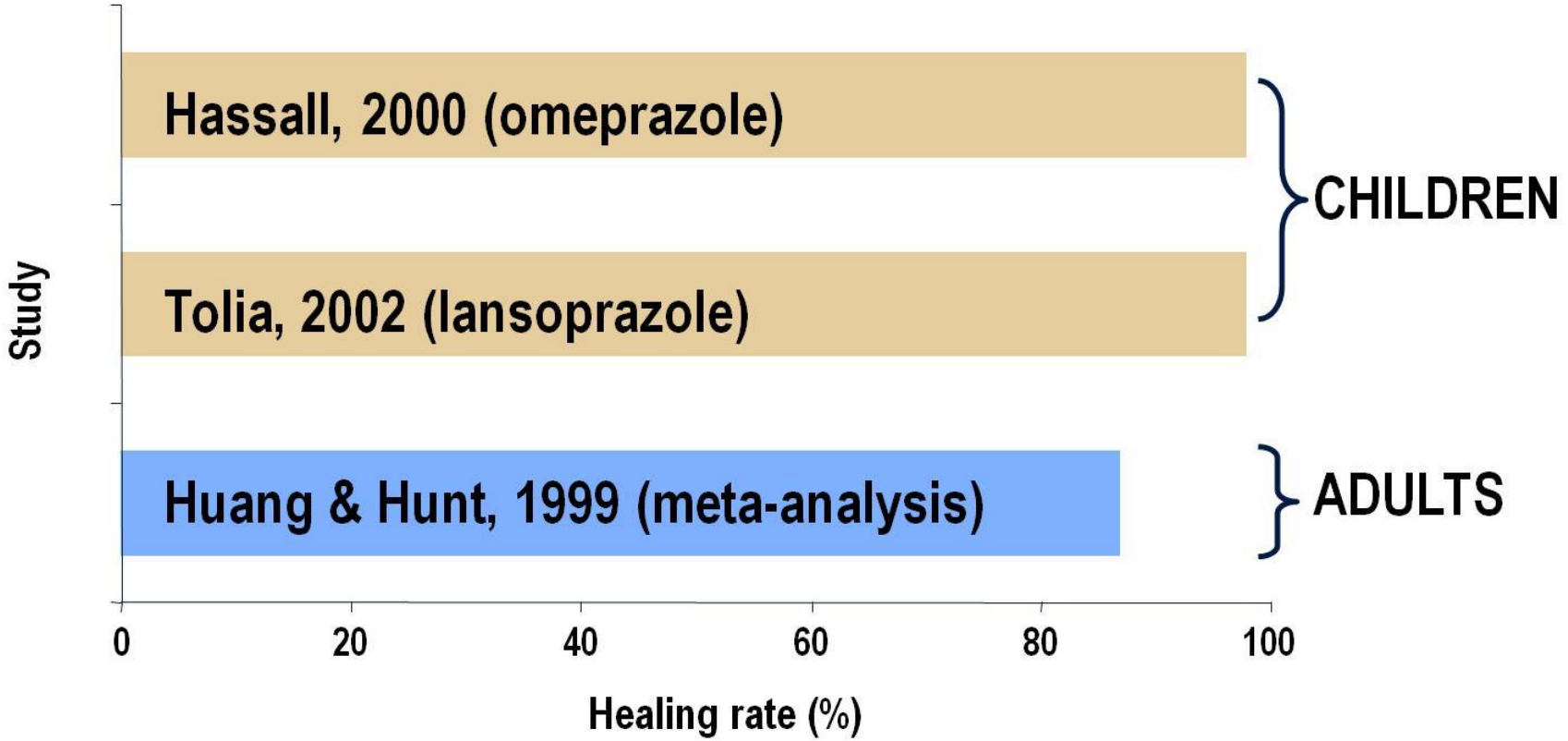
Vandenplas Y et al. *Acta Paediatr* 2014 Jun; 103(6): e243–e250.

Protein Hydrolysate Formula Effectively Reduces Regurgitation in Infants *continued*

- Regurgitation reduced in all infants, but more so with thickened formula, within a month
- Highest reduction in symptoms was in those with confirmed CMPA

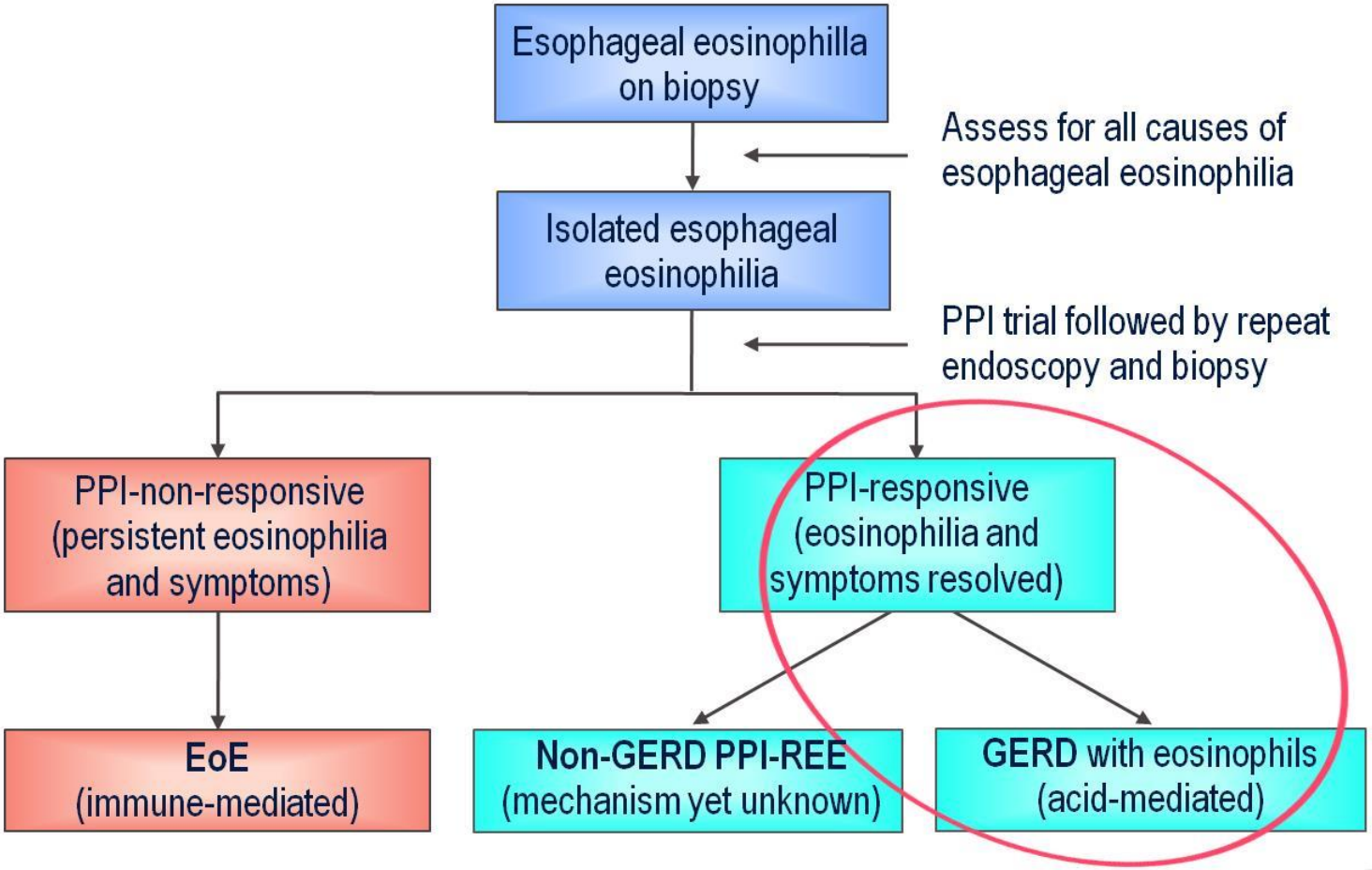
Vandenplas Y et al. *Acta Paediatr* 2014 Jun; 103(6): e243–e250.

Similar PPI Healing Rates in Adults and Children



Hassall E et al. *J Pediatr* 2000;137:800-7.
Tolia V et al. *J Pediatr Gastroenterol Nutr* 2002;35:S308-18.
Huang JQ et al. *Gut* 1999;45:P513.

Diagnosis and Management of Eosinophilia and EoE



Dellon ES et al. *Am J Gastroenterol* 2013;108:679-92.

Understanding the Risks of Treatment

Other Infections

- PPI treated patients had an increased rate of infection (after prescription for PPI) of 1.46 for *Campylobacter* and 1.2 for *Salmonella* , compared with baseline [1]
- Acid suppression resulted in gastric bacterial overgrowth, in particular with organisms that cause pharyngeal and laryngeal disease [2]
  - Could acid suppression for GERD result in, exacerbate, or worsen the very same extra-esophageal disease it was used to treat?

1. Brophy S et al. *Am J Gastroenterol* 2013;108:1094-100.
2. Rosen R et al. *JAMA Pediatr* 2014;168:932-7.

Ranitidine is Associated With Infections, Necrotizing Enterocolitis, and Fatal Outcome in Newborns

WHAT'S KNOWN ON THIS SUBJECT: Although still off-label for newborns, the use of inhibitors of gastric acid secretion continues to increase. Acid-suppressive drugs could facilitate the onset of infections in adults and children. Evidence for efficacy is weak in newborns, particularly if preterm.

WHAT THIS STUDY ADDS: This is the first prospective study demonstrating an association between the use of ranitidine and infections, necrotizing enterocolitis, and fatal outcome in very low birth weight newborns. Caution is advocated in using ranitidine in newborns.

AUTHORS: Gianluca Terrin, MD, PhD,[a] Annalisa Passariello, MD, PhD,[b,c] Mario De Curtis, MD, PhD,[d] Francesco Manguso, MD, PhD,[e] Gennaro Salvia, MD,[f] Laura Lega, MD,[g] Francesco Messina, MD,[h] Roberto Paludetto, MD,[b] and Roberto Berni Canani, MD, PhD[b,i]

[a]Department of Women's Health and Territorial Medicine, University La Sapienza, Rome, Italy; [b]Department of Pediatrics, University Federico II, Naples, Italy; [c]Neonatology Unit, Monaldi Hospital, Naples, Italy; [d]Department of Pediatrics, University La Sapienza, Rome, Italy; [e]Gastroenterology Unit, Cardarelli Hospital, Naples, Italy; [f]Neonatology Unit, Fatebenefratelli Hospital, Naples, Italy; [g]Neonatology Unit, Meyer Pediatric Hospital, Florence, Italy; [h]Neonatology Unit, V. Betania Evangelic Hospital, Naples, Italy; and

TABLE 2 Rate of Patients Presenting Infections During the Study Period

	Not exposed to Ranitidine (n = 183)	Exposed to Ranitidine (n = 91)	P
Overall infections, n (%)	18 (9.8)	34 (37.4)	<.001
Sepsis, n (%)	16 (8.7)	23 (25.3)	<.001
Pneumonia, n (%)	1 (0.5)	4 (4.4)	.043
Urinary tract infections, n (%)	1 (0.5)	7 (7.7)	.002

Terrin G et al. *Pediatrics* 2012;129:e40-45.

Abdominal Pain Due to Onset of Bacterial Overgrowth in Children Treated with a PPI

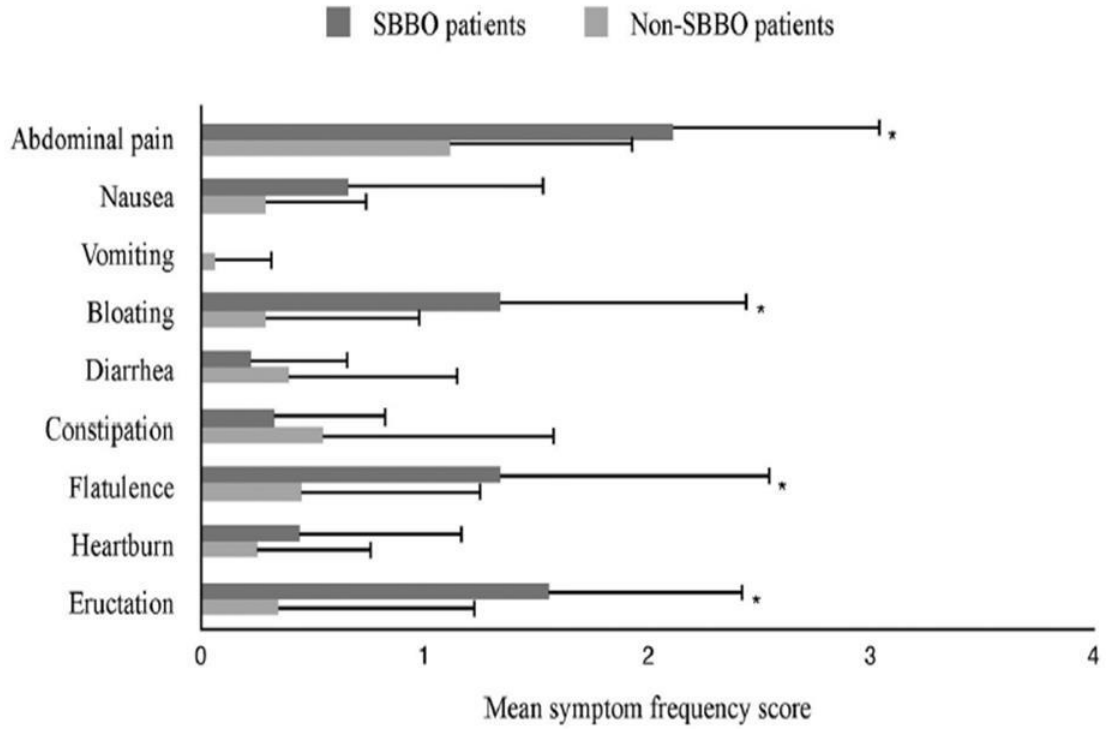


Figure. Mean symptom frequency score after PPI treatment in patients with and without SBBO. $^{*}P < .05$.

Sieczkowska A et al. *J Pediatr* 2015;166:1310-2.

Aerodigestive Conditions and Associations with Reflux

Persistent Cough and Reflux

Clinical Gastroenterology and Hepatology 2016;14:378–384

Airway Hypersensitivity, Reflux, and Phonation Contribute to Chronic Cough

David O. Francis,[*,‡] James C. Slaughter,[§] Fehmi Ates,[‖] Tina Higginbotham,[‖] Kristin L. Stevens,[¶] C. Gaelyn Garrett,[*] and Michael F. Vaezi[‖]

*Vanderbilt Voice Center, ‡Center for Surgical Quality and Outcomes Research, §Department of Biostatistics, ‖Division of Gastroenterology, Hepatology, and Nutrition, and ¶Vanderbilt University Medical School, Vanderbilt University Medical Center, Nashville, Tennessee

CONCLUSIONS: Antecedent phonation and reflux increased the rate of cough events in patients with idiopathic chronic cough. Reflux events were more strongly associated with increased rate of coughing. Our findings support the concept that airway hypersensitivity is a cause of chronic cough, and that the vocal folds may be an effector in chronic cough ClinicalTrials.gov number: NCT01263626.

Rosen R et al. J Pediatr Gastroenterol Nutr 2014;58:22-26.
Lang JE et al. J Allergy Clin Immunol Pract 2013;1:172-80.
Usta Guc B et al. Clin Respir J 2014;8:330-37.
Karabel M et al. Clin Respir J 2014;8:152-59.

Laryngeal-pharyngeal Pathology and Reflux

REZA BAND, a Noninvasive Device for Laryngopharyngeal Reflux, FDA OK'ed

MARCH 13TH, 2015 EDITORS GI, MEDICINE

Sleep Review
THE JOURNAL FOR SLEEP SPECIALISTS

Oral Appliances Side-by-Side Comparison Guide (December 2015)
Compare 17 oral appliances for obstructive sleep apnea side-by-side. The guide compares features such as warranty, indications, type, how it...

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CLINICAL TRIALS

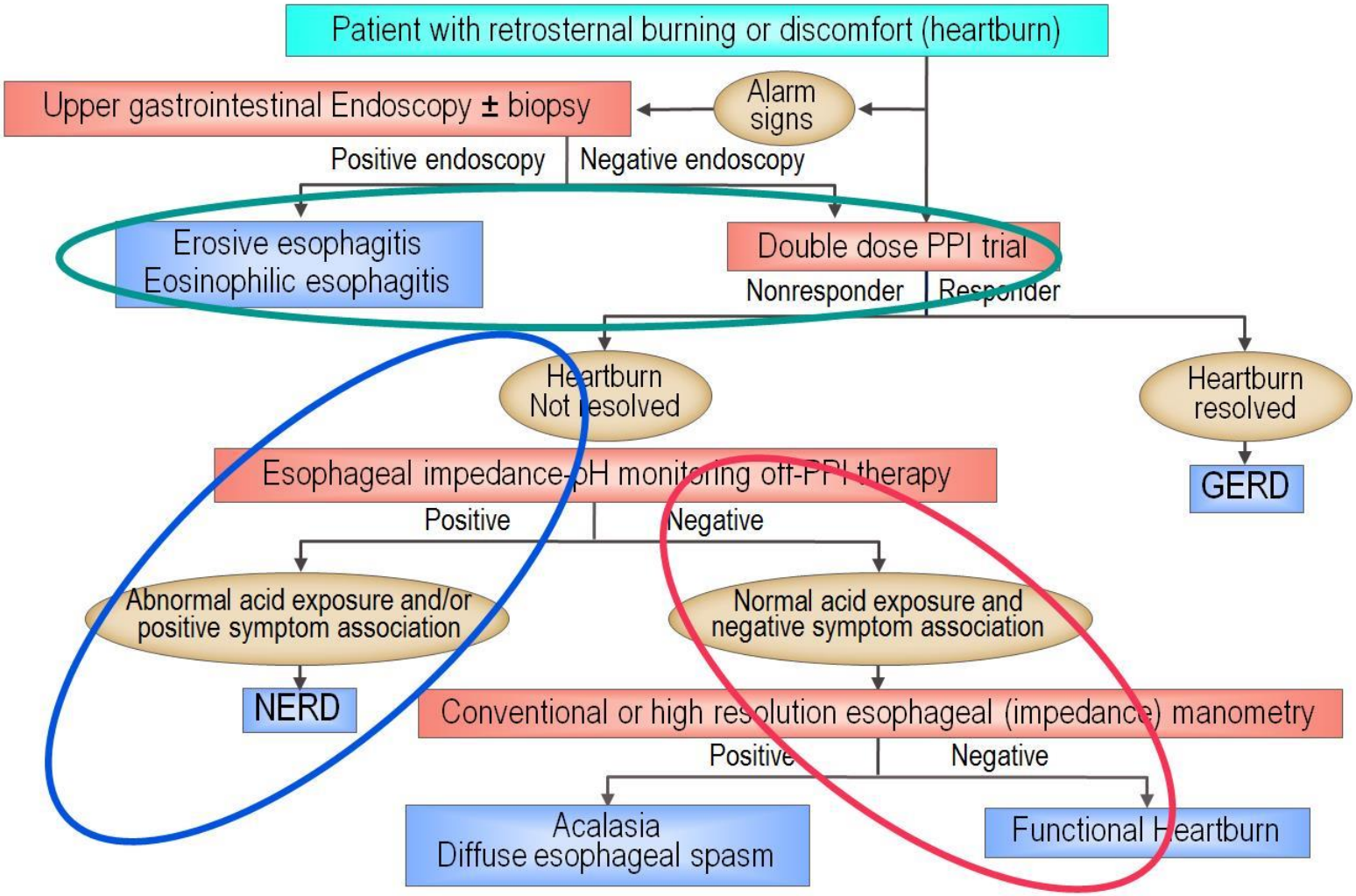
Clinical Study Shows MedCline As Effective Treatment for Silent Reflux

Published on December 8, 2015

Chang AB et al. *Otolaryngol Clin North Am* 2010;43:181-98.
Lien HC et al *Value Health* 2015;18:396-403.
Vandenplas Y et al. *J Pediatr Gastroenterol Nutr* 2009;49:498-547.
Sherman P et al. *Am J Gastroenterol* 2009;104:1278-95.
Kahrilis P et al. *Gastroenterology* 2008;135:1392-1413.
Patel, D et al. *Curr Gastroenterol Rep* 2016;18:12-20.

Beyond Erosive-reflux Disease (ERD) to NERD

NERD Management Algorithm



Savarino E et al. *Nat Rev Gastroenterol* 2013;10:371-80.