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

Moderated by:

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Introduction

- There has been a tremendous rise in use of proton pump inhibitors (PPIs) in children over past 15 years¹
 - Particularly an issue in infants <12 months of age²
- Preponderance of evidence that PPIs **do not**
 - reduce GER symptoms in infants^{3, 4} or
 - decrease infant crying and irritability⁵

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. Gieruszczak-Bialek D et al. *J Pediatr* 2015;166:767-70.

Introduction

- PPIs are extremely effective at acid suppression¹
 - Preferred treatment for a number of acid related disorders ²
 - Relatively safe medications ³
- However, there are growing concerns with the risk of 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

- Objective of this webinar is to discuss evidence-basis for using, vs. not using, PPIs in children
 - Due to time constraints this will be a high level discussion
 - Intended for pediatric gastroenterologists

Learning Objectives

1. To differentiate Non-Erosive Reflux Disease (NERD) from Erosive Reflux Disease (ERD), Functional Heartburn and Hypersensitive Esophagus
2. To understand the pathophysiology for extra-esophageal associations with reflux disease
3. To understand indications for when PPIs should be prescribed, as well as what to do when PPIs don't work
4. To discuss the risks of treatment, why, when, and how to stop treatment

Agenda

Introduction	Jenifer Lightdale
NERD and Beyond	Rachel Rosen
Aerodigestive Conditions and Associations with Reflux	Benjamin D. Gold
Evidence-Based Indications for Treatment with PPIs	Jose Garza
Understanding the Risks of Treatment	Carlo Di Lorenzo
Conclusion	Jenifer Lightdale
Q & A	Panel

NERD and Beyond

Rachel Rosen, MD, MPH

Assistant Professor of Pediatrics

Director, Aerodigestive Center

Harvard Medical School

Boston, MA

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
- Endoscopy 3 years ago, repeated last week, was normal with biopsies in the duodenum, stomach and at 3 esophageal levels

Section Objectives

To understand:

- how to differentiate NERD from ERD, functional heartburn and hypersensitive esophagus
- how to diagnose NERD
- how to treat NERD

Defining NERD

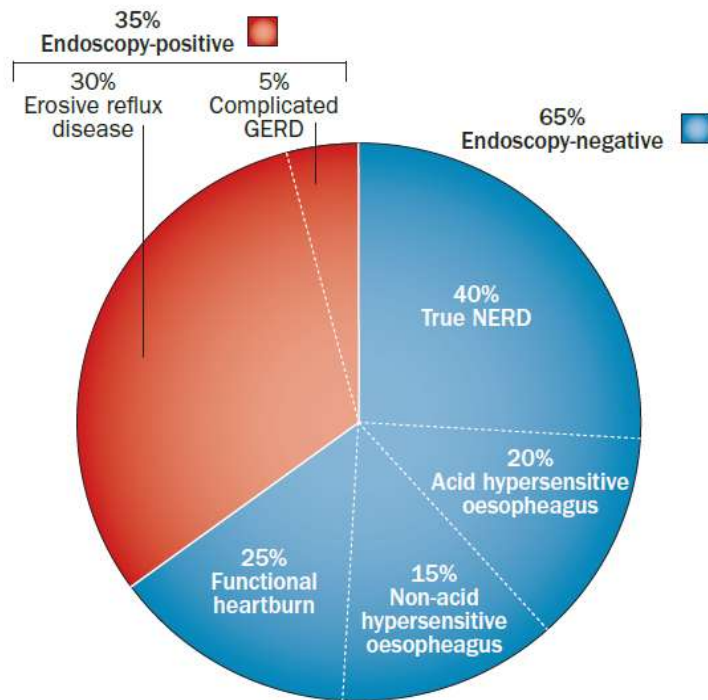
The Old

- No erosions, abnormal acid reflux by pH, classic reflux symptoms of heartburn

The New

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

Incidence of Reflux Disease Subtypes in Adults



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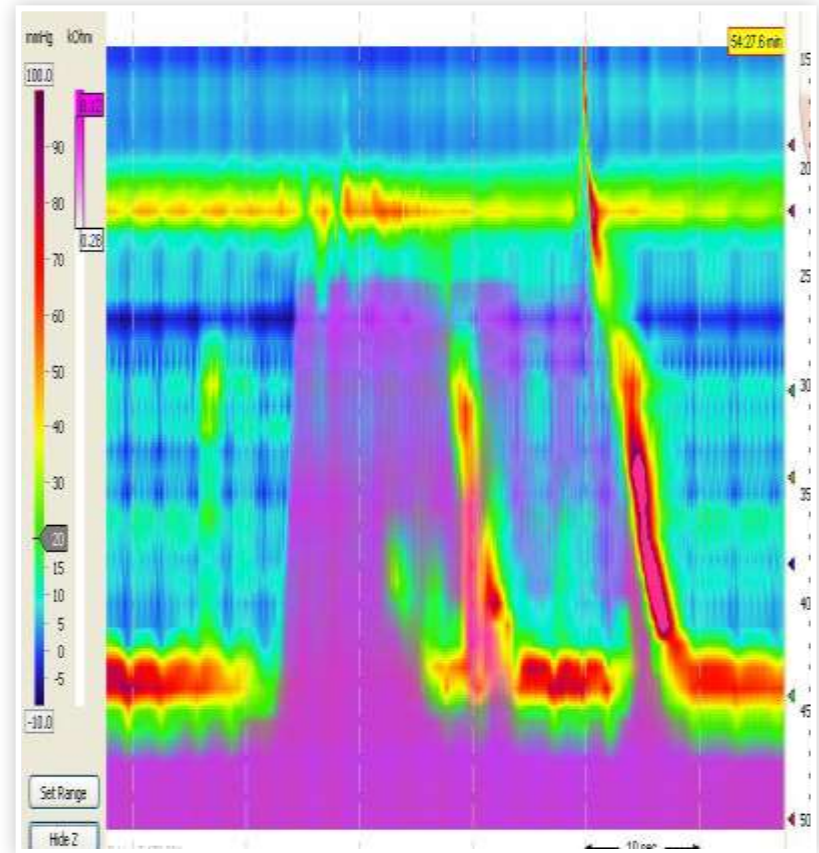
- In 221 adult patients, 54% did not have a diagnosis that would respond to PPI therapy ²
- There are no pediatric studies that systematically address this

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

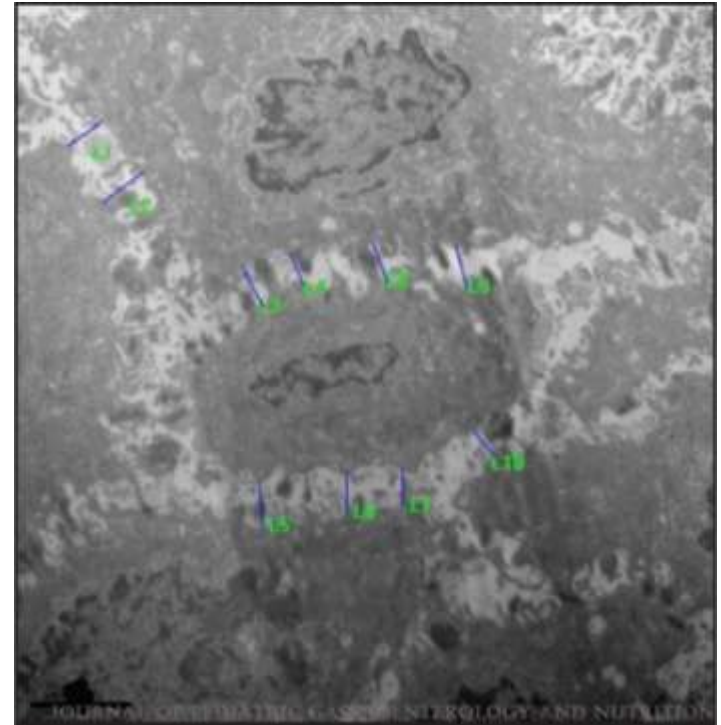
- The mechanism of reflux in NERD patients is transient lower esophageal sphincter relaxations (TLSEs)¹
- Patients with NERD have similar symptom severity to those with ERD²
- Visceral hypersensitivity is similar in patients with NERD and ERD³



1. Ribolsi M et al. *Clin Gastroenterol Hepatol* 2014;12:52-7.
2. Weijenborg PW et al. *Am J Physiol 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}



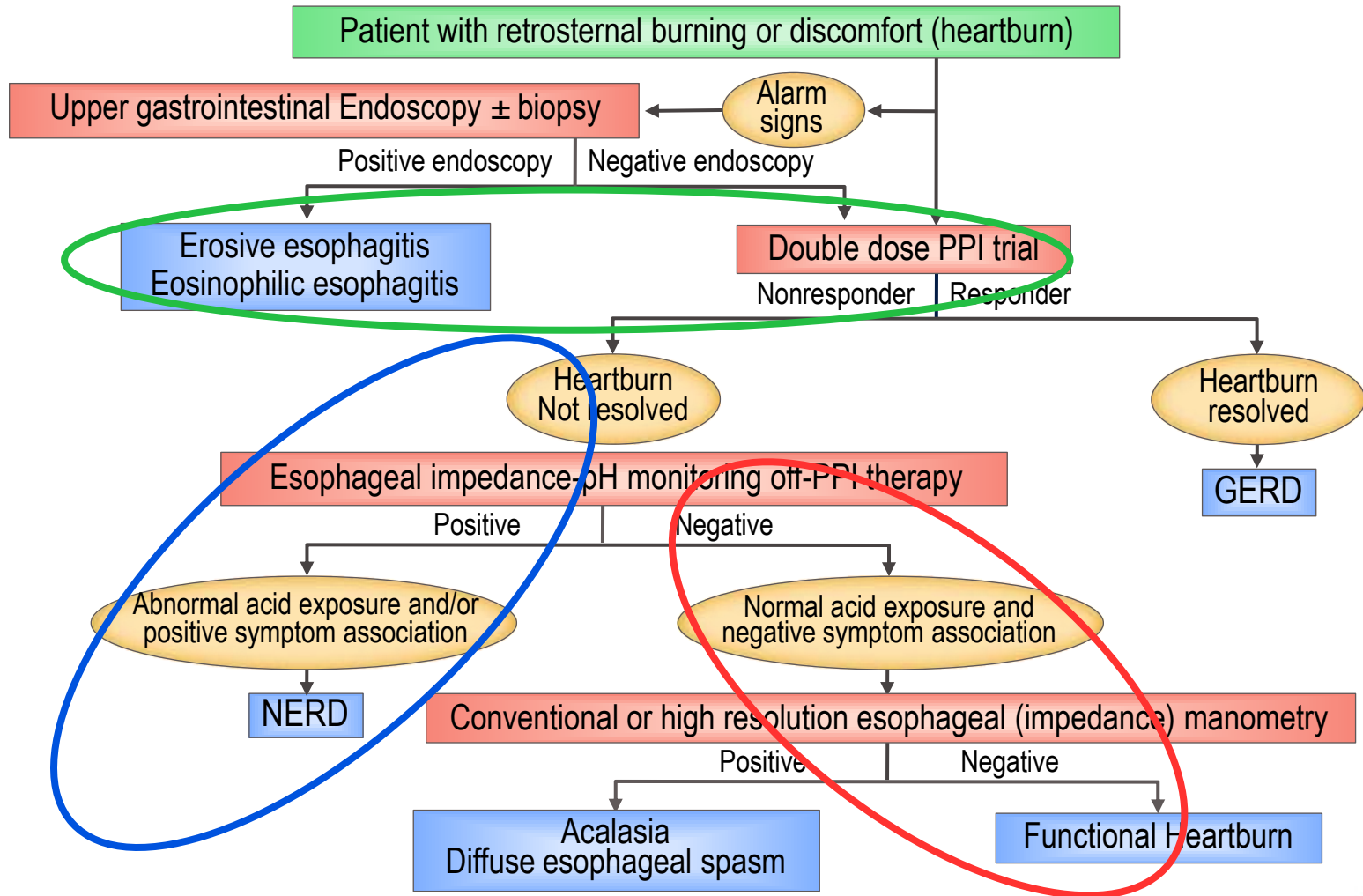
Microscopic view of dilated intracellular spaces

Reprinted by permission from Wolters Kluwer Health, Inc.

J Ped Gastroenterol Nutr, Altam MA et al. 2014

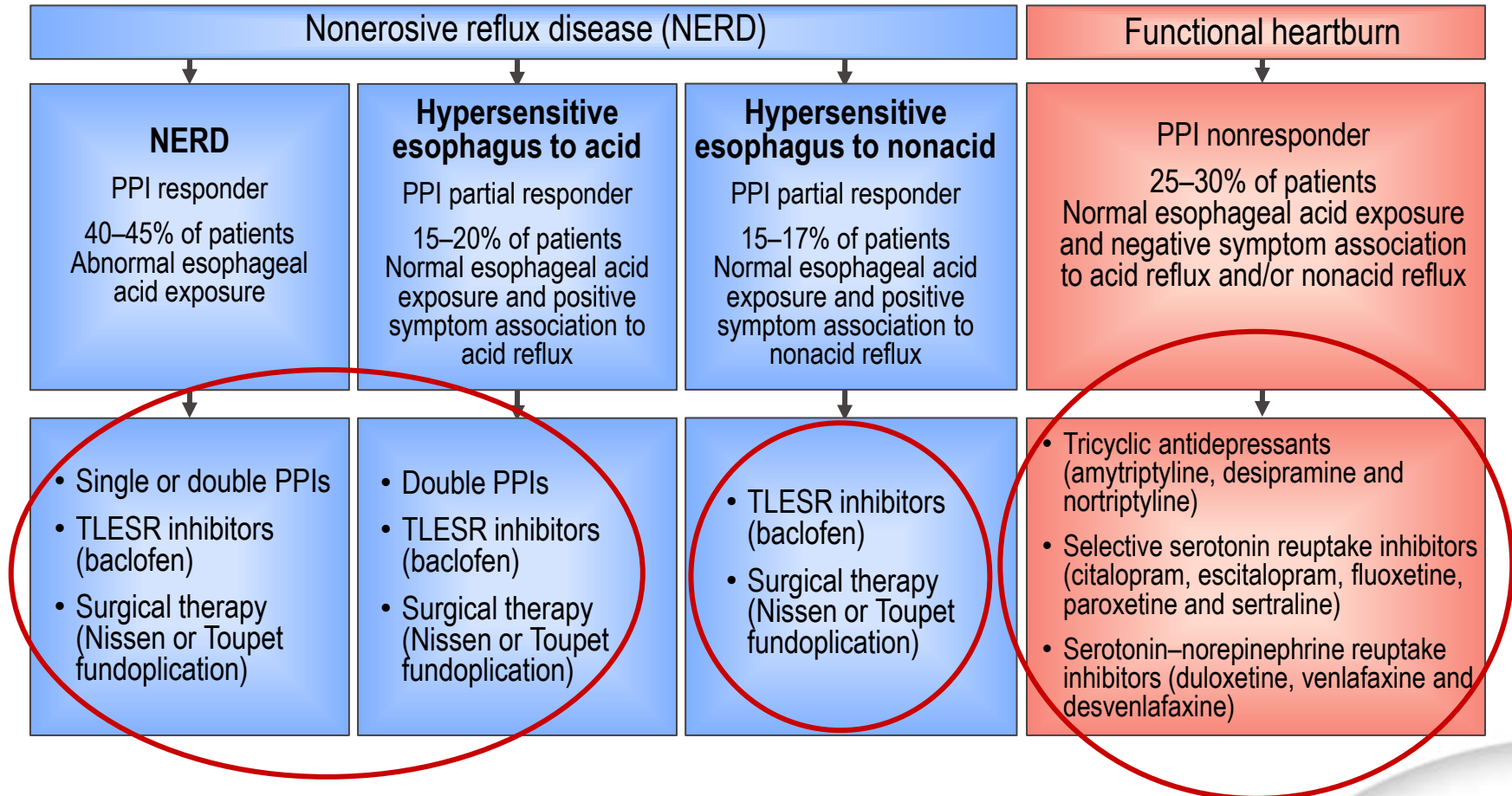
1. Kandulski A et al. *Aliment Pharmacol Ther* 2013;38:643-51.
2. Savarino E et al. *Gut* 2009;58:1185-91.
3. Nelson SP et al. *Arch Pediatr Adolesc Med* 2000;154;150-4.
4. Bytzer P et al. *Clin Gastroenterol Hepatol* 2012;10:1360-6.
5. Kandulski A et al. *Aliment Pharmacol Ther* 2013;38:643-51.
6. Borrelli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

NERD Management Algorithm



Why do we Care About the Names?

Treatments may be Different, at least in Adults



Case Review

- Impedance results off therapy:
 - 45 total reflux episodes, 27 acid, 18 nonacid
 - pH<4 for 4.6% of the time
 - 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 conditions are changing and are critical for understanding the potential for response, and non-response, to therapies
- One of the primary indications of pH-Multichannel Intraluminal Impedance testing (pH-MII), off therapy, may be to differentiate NERD from functional heartburn
- Acid suppression has a role in NERD and hypersensitive esophagus **but not** in functional heartburn

Aerodigestive Conditions and Associations with Reflux

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Adjunct Professor of Pediatrics

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Atlanta, GA

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:

- the pathophysiology for common aerodigestive associations with reflux
- a biological plausibility for these associations
- when it might be appropriate to use a PPI for extra-esophageal conditions associated with reflux

Airway Protective Mechanisms

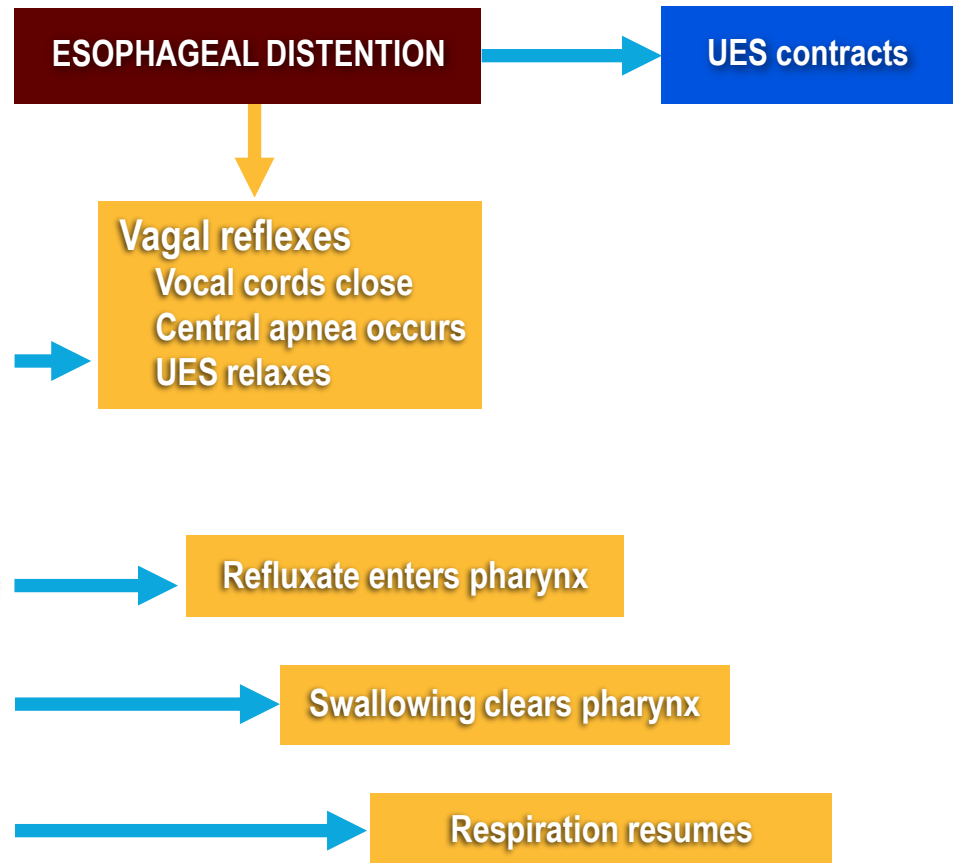
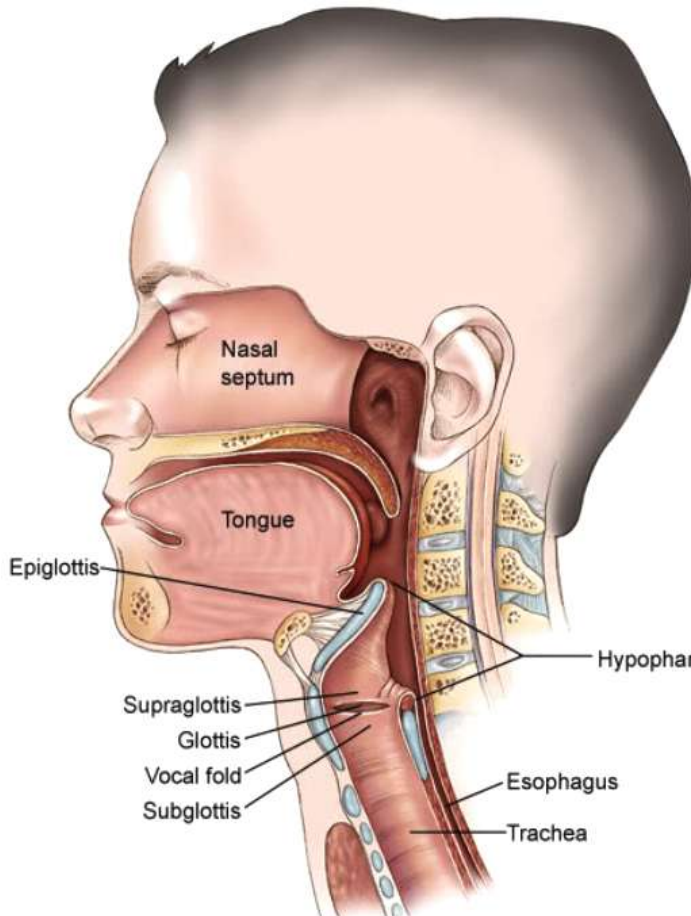


Image: Adapted from Robert Morreale / *Visual Explanations*, LCC ©2003 American Society of Clinical Oncology
Jadcherla SR et al. *Am J Gastroenterol* 2009;104:2572-82.
Jadcherla SR et al. *J Pediatr Gastroenterol Nutr* 2009;48:186-92.

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

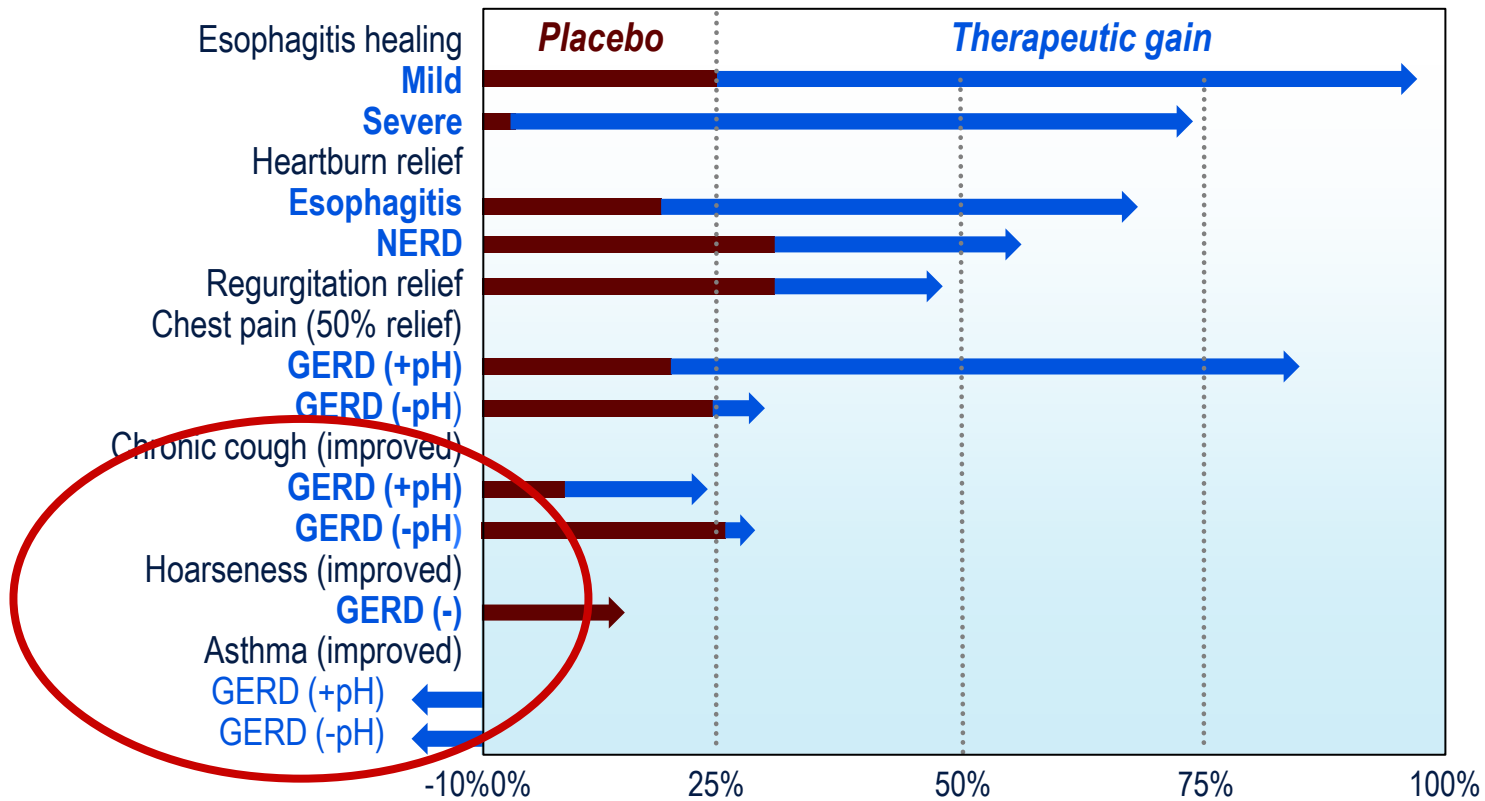
Sherman P et al. *Am J Gastroenterol* 2009;104:1278-95.

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

Field SK. *Chest* 1999;115:848-56.

PPI Efficacy for Potential Manifestations for GERD in Adults

Estimates based on available RCT data



Asthma and GER

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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

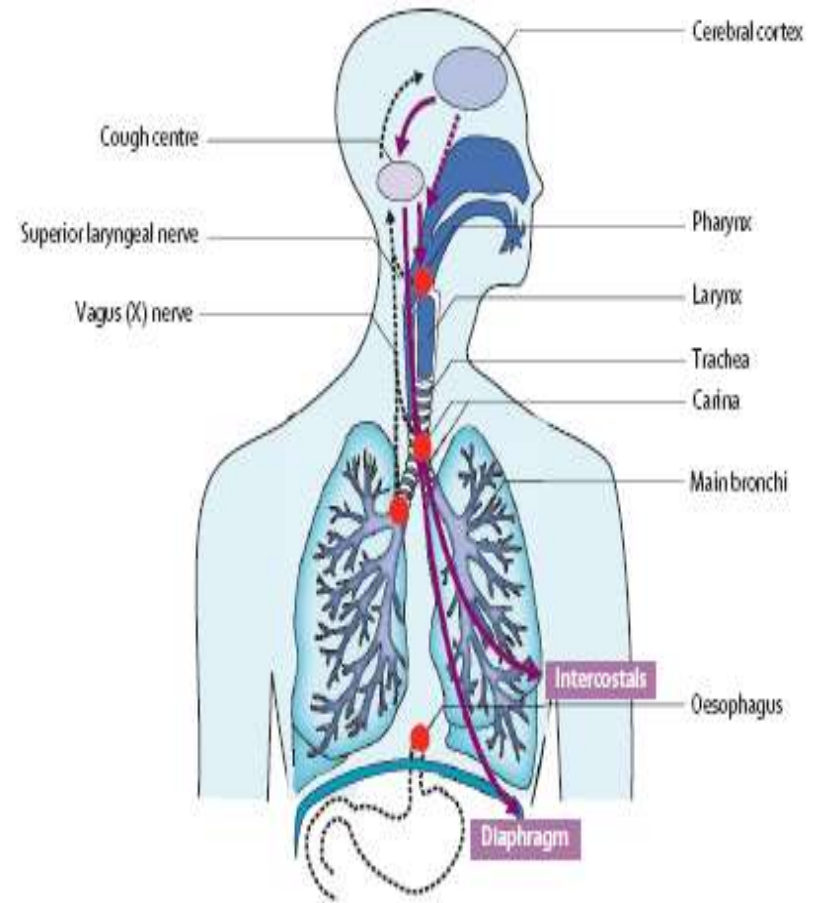
YES

Causality

Not at present,
more research
needed

Neurophysiology of Cough

- Not every child who coughs or wheezes has **asthma**
- Not every child who coughs or wheezes has **reflux**
- Consider dysphagia and aspiration syndromes; other etiologies e.g. habitual cough



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

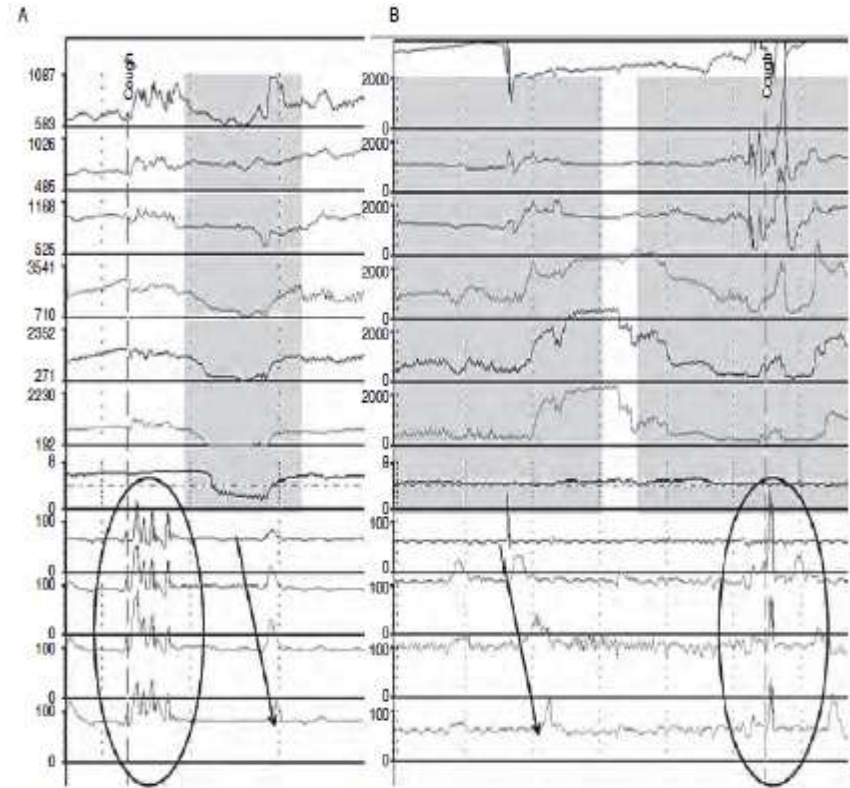


FIGURE 1. Tracing of a cough preceding reflux (A) and reflux preceding cough (B). Intraesophageal pressure recording coughs, seen as high amplitude, simultaneous pressure spikes, are shown in the circles. Reflux episodes are shaded gray. The arrow highlights normal, propagating esophageal peristalsis,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



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



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 reflux disease is poor
- Clinical improvement followed by recurrence off treatment 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.
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.

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)

- 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.

Esophageal Atresia/ Tracheal-Esophageal Fistulae

Biological plausibility

YES

Causality

YES

Is there a role for PPIs?

YES

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
- 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.

Evidence-Based Indications for Treatment with PPIs

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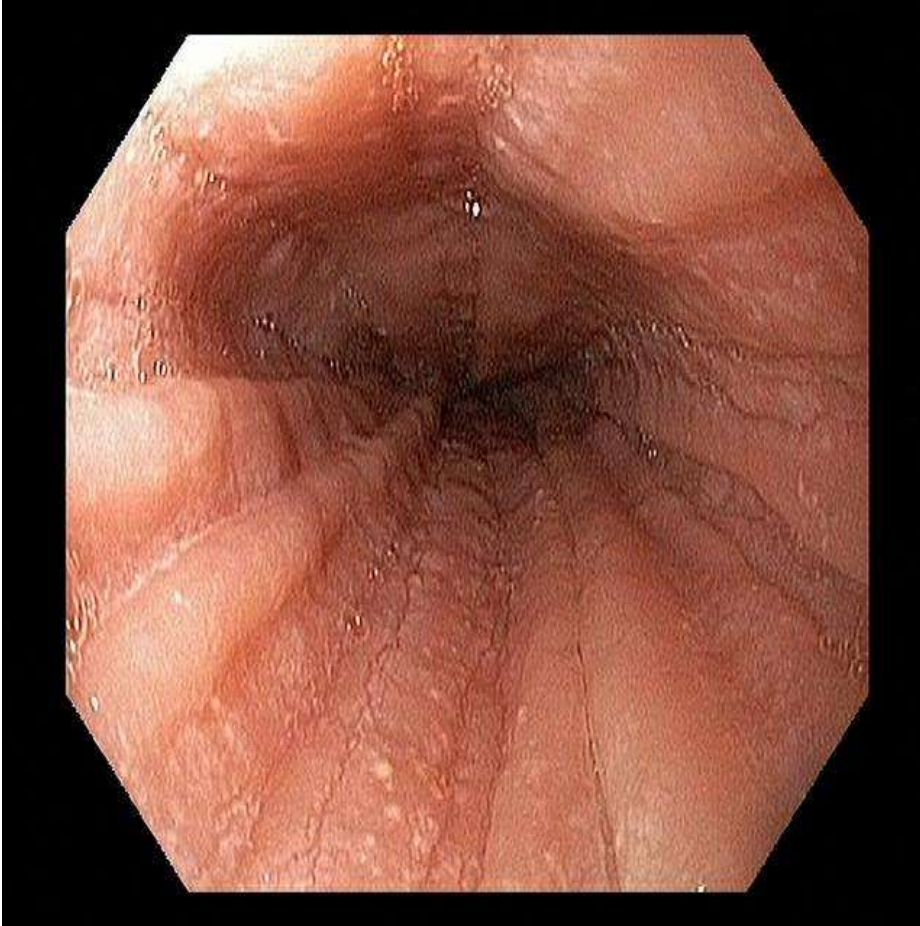
Emory University

Atlanta, GA

CASE

- 12 y/o male 2 year history of intermittent epigastric burning sensation, regurgitation and dysphagia
- Treated with OTC antacid with minimal relief

EGD



Proximal, mid and distal biopsies

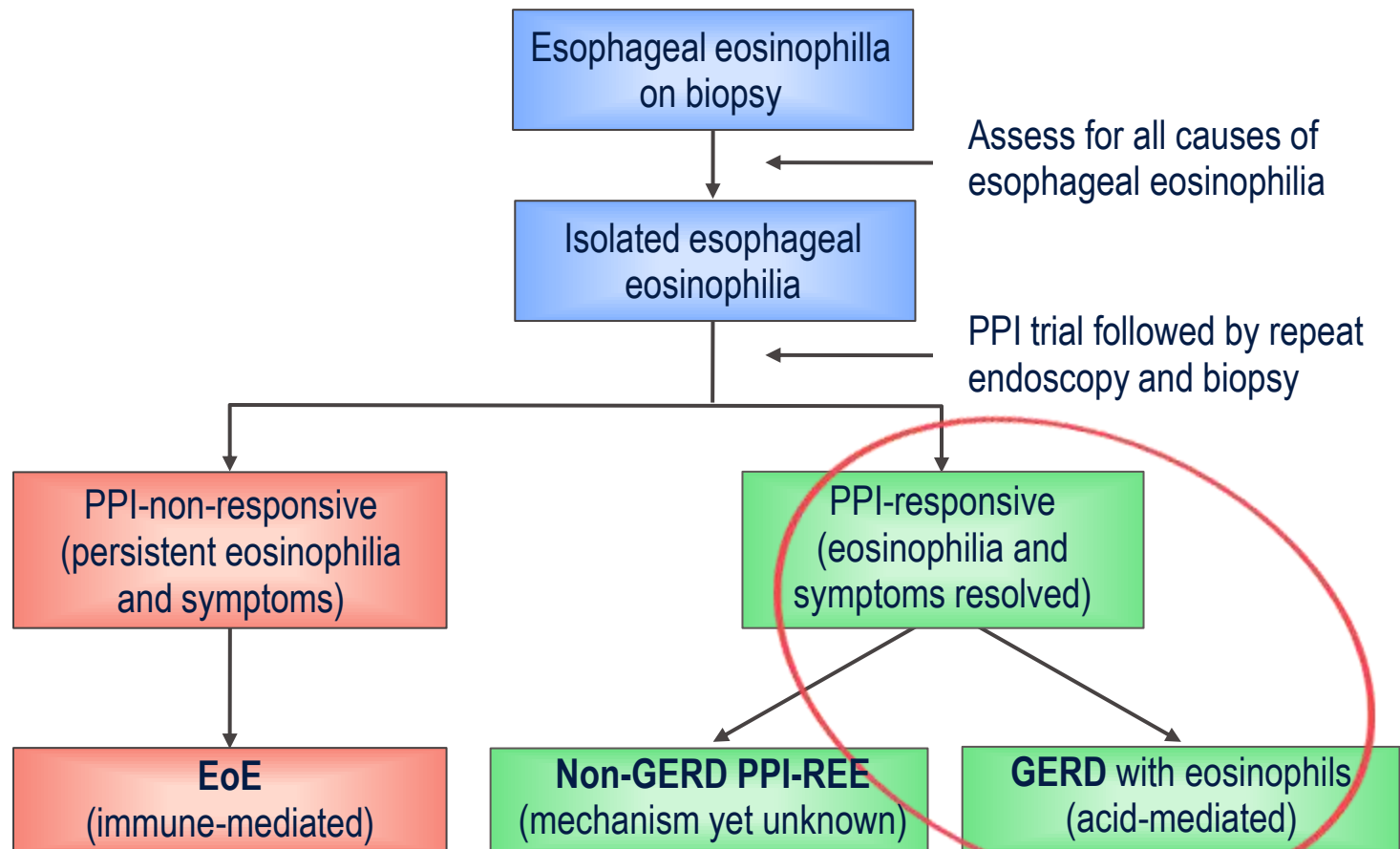
- basal cell hyperplasia
- >15 eosinophils per high power field

Section Objectives

To understand:

- when PPIs should be prescribed
- if eosinophils are found in the esophagus does that indicate EoE?
- which is more indicative of erosive disease, endoscopic or histologic findings?
- what to do when PPIs don't work

Diagnosis and Management of Eosinophilia and EoE



Eosinophilic Esophagitis or PPI-Responsive Esophageal Eosinophilia

- At least 1/3 of adult patients with suspected EoE achieve clinical and histological remission on PPI therapy
- The response seems more limited in children as compared to adults
- Treatment includes high dose PPI for 8 weeks followed by endoscopy and biopsy

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

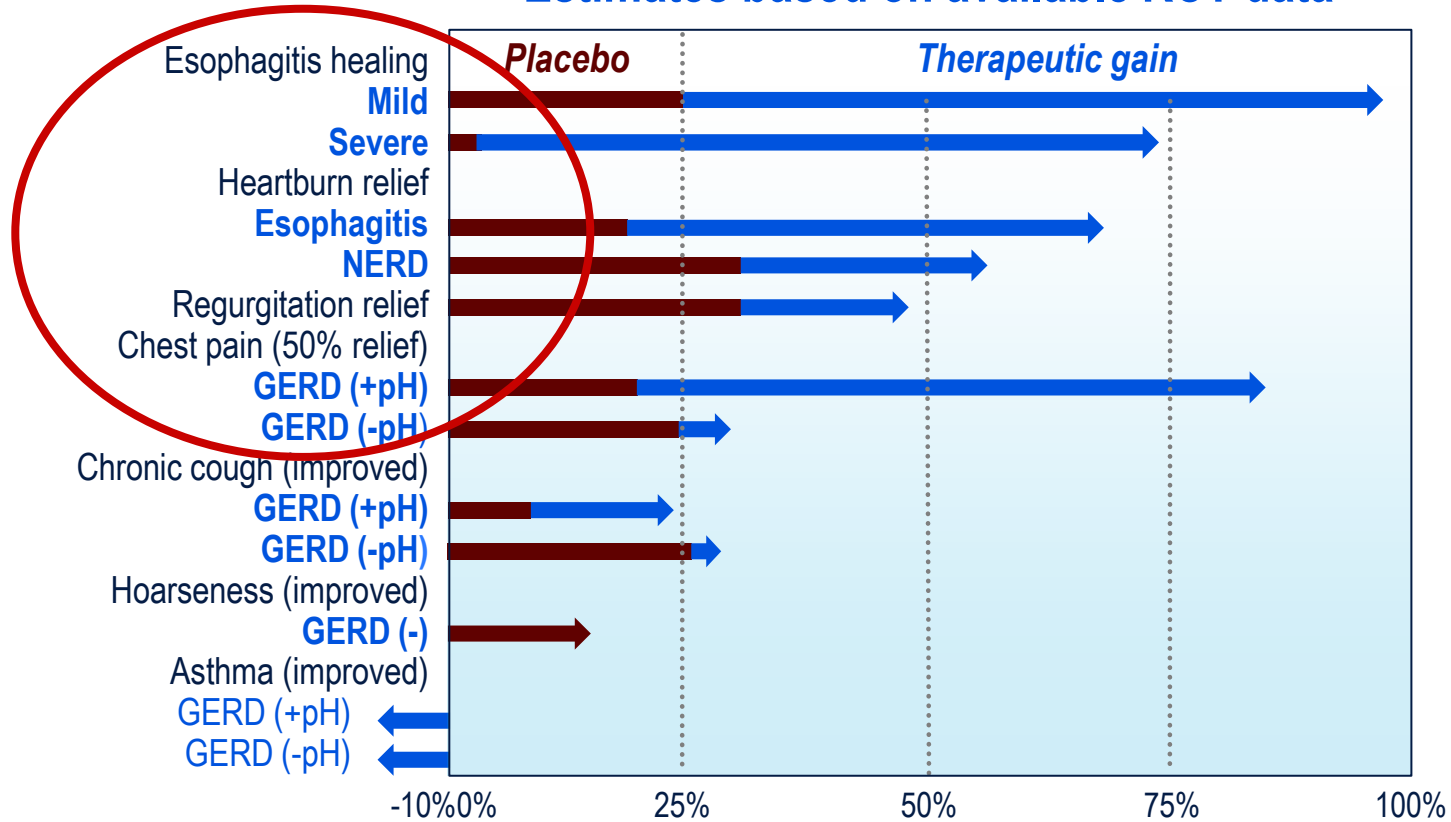


Absence of histologic changes
does not rule out GERD

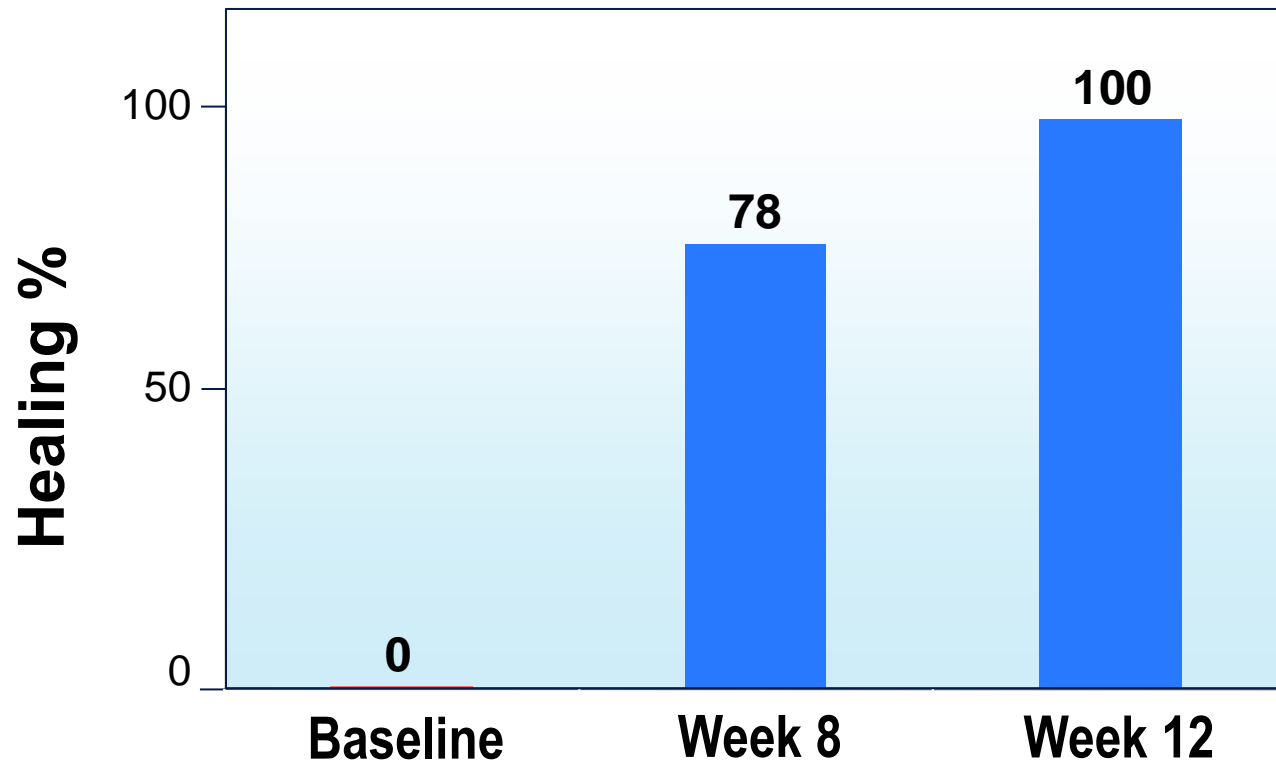
Vandenplas Y et al. *J Pediatr Gastroenterol Nutr* 2009;49:498-547.
Sherman P et al. *Am J Gastroenterol* 2009;104:1278-95.

PPI Efficacy for Potential Manifestations for GERD in Adults

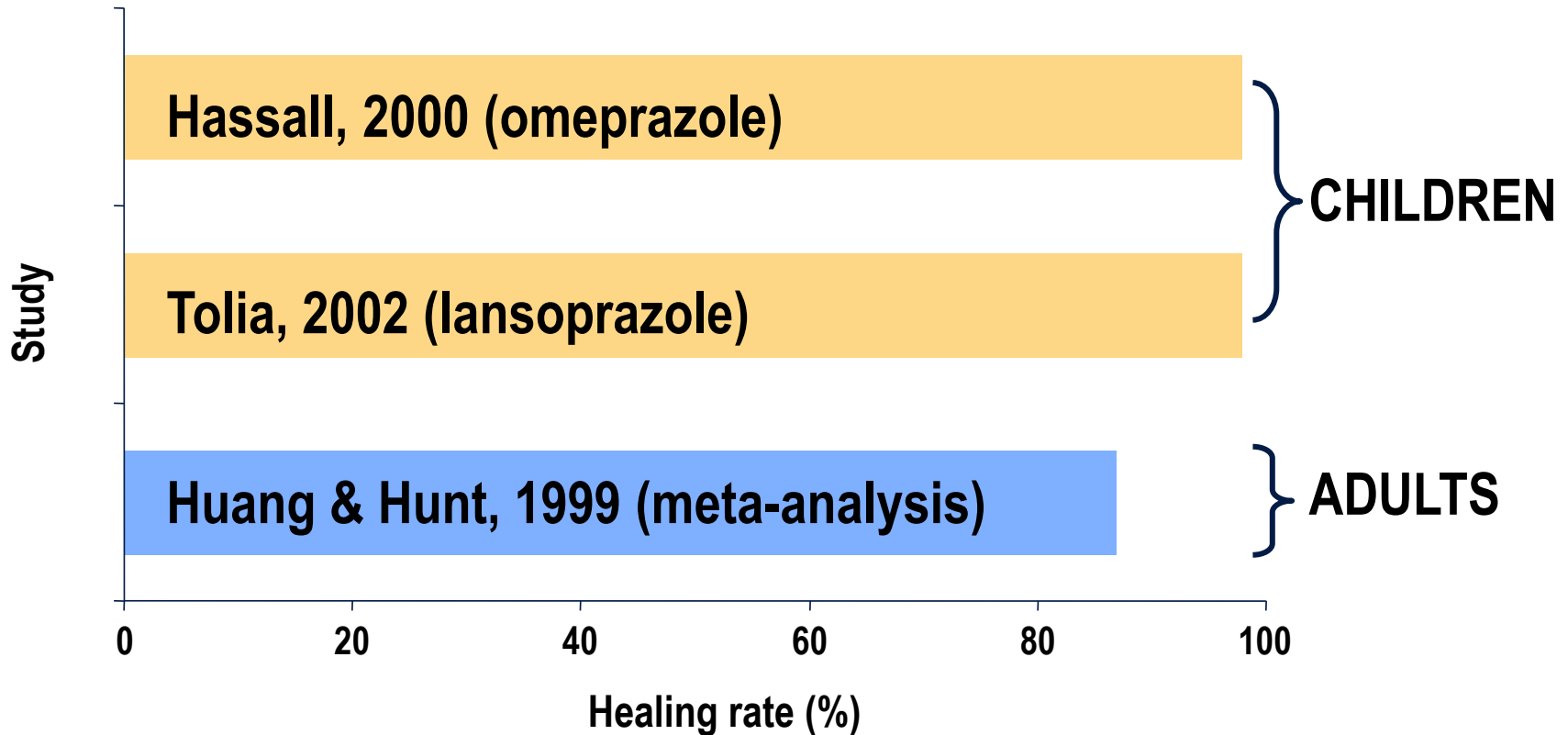
Estimates based on available RCT data



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



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.

Esomeprazole In Infants with GERD

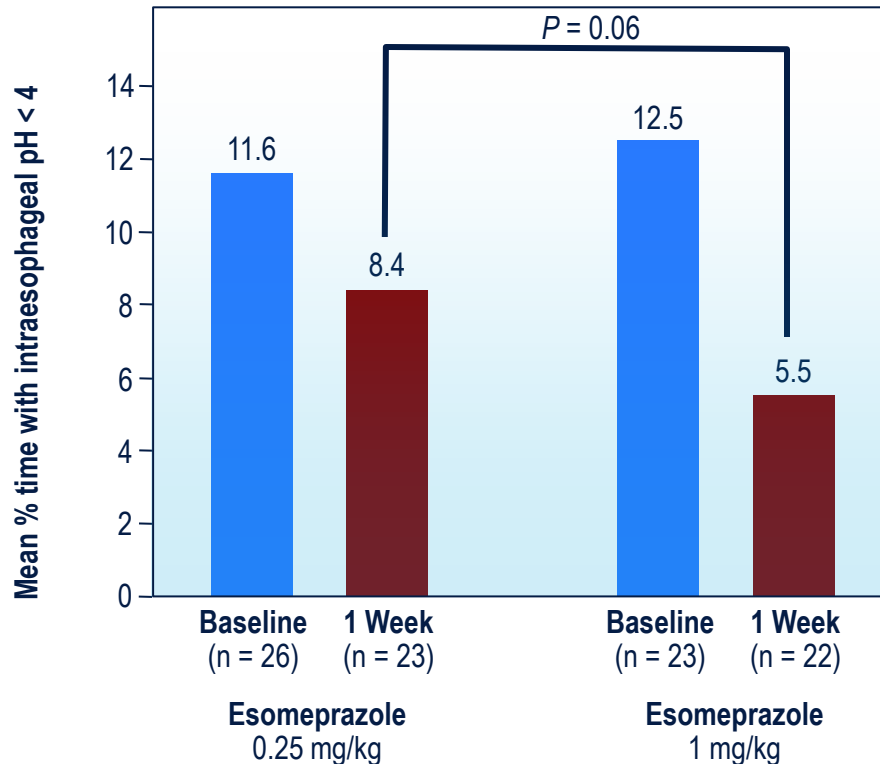


FIG. 2 Mean percentage of time with intraesophageal pH <4 at baseline and after 1 week of oral treatment with esomeprazole in infants with GERD.

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

FDA-Approved Pediatric Age Ranges and Indications for PPIs

	Age Range (Years)																	
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
esomeprazole[1]																		
	*																	
lansoprazole[2]																		
omeprazole[3]																		
pantoprazole[4]																		
rabeprazole[5]																		

symptomatic GERD
 healing of EE

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

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 ($\geq 80\%$ PPI coverage)
- The risk of an event increased by 6% points for every 10% decrease in PPI adherence

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.

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
<i>H. pylori</i>	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 Pediatr Gastroenterol Nutr* 2011;53:230-43.

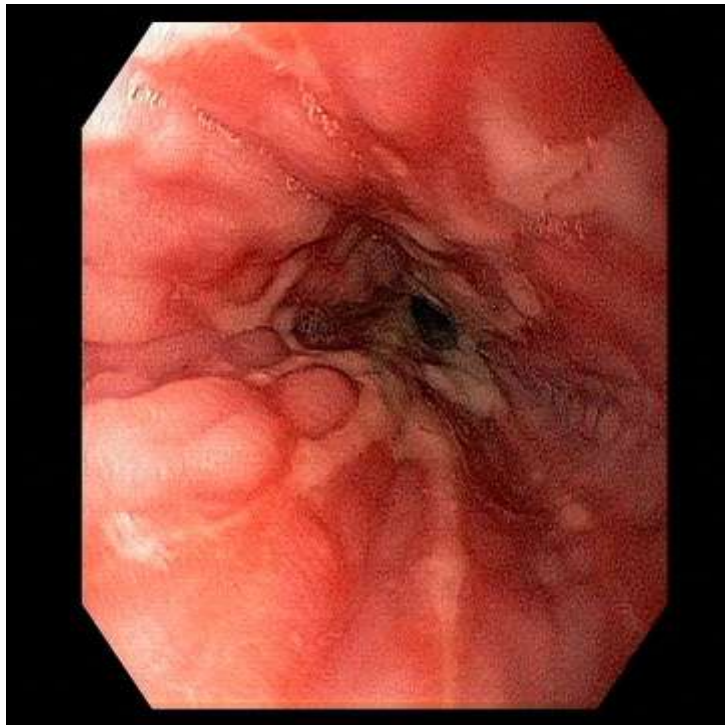


BEFORE

**Therapeutic
Challenge**

Mucosal Healing

Managing ulcers, erosive esophagitis, recurrent strictures with antacids and H₂RA antagonists



PPI



AFTER

**Therapeutic
Challenge**

Refractory Symptoms

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



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 H₂RA at night (tachyphylaxis)
- Make sure the diagnosis is correct

Summary: Indications for PPIs

- 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**
- For Erosive Reflux Disease, ongoing management should include review of a plan for treatment discontinuation

Understanding the Risks of Treatment

Carlo Di Lorenzo, MD

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The Ohio State University

Nationwide Children's Hospital

Columbus, OH

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

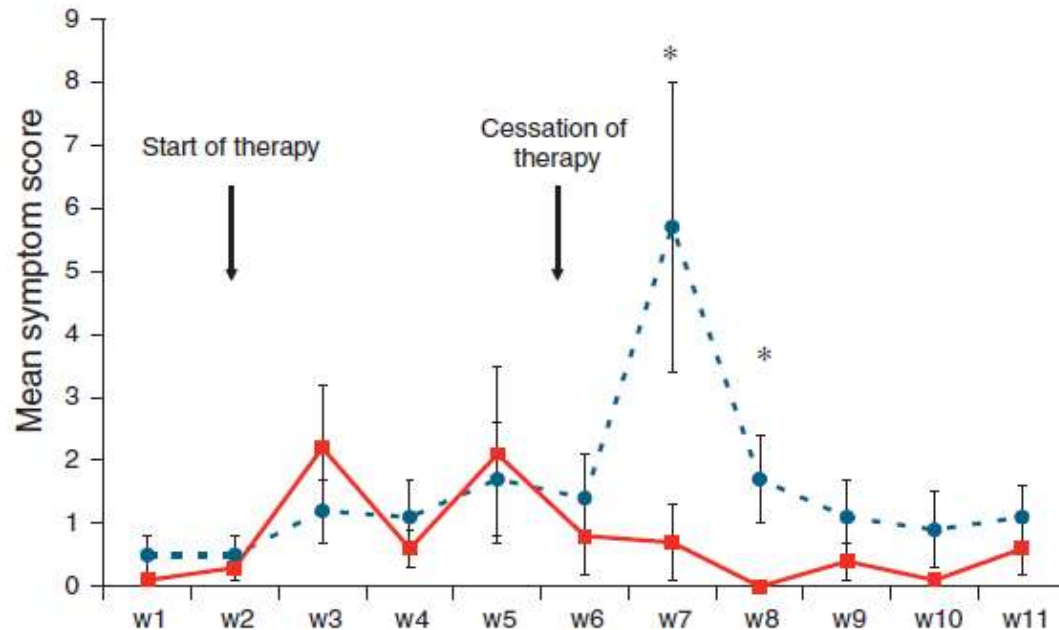
- In otherwise healthy pediatric patients, reflux esophagitis may not be a chronic problem or recur after treatment ¹
 - Of 48 otherwise healthy children with erosive esophagitis who discontinued maintenance treatment, only one had erosive esophagitis recurrence at three months
 - Three of 44 (6.8%) 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.

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

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 ⁹	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	<i>C difficile</i> 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

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; H₂RAs may be less harmful ²
- Multivariate analyses suggest H₂RA 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 2010;170

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.

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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

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

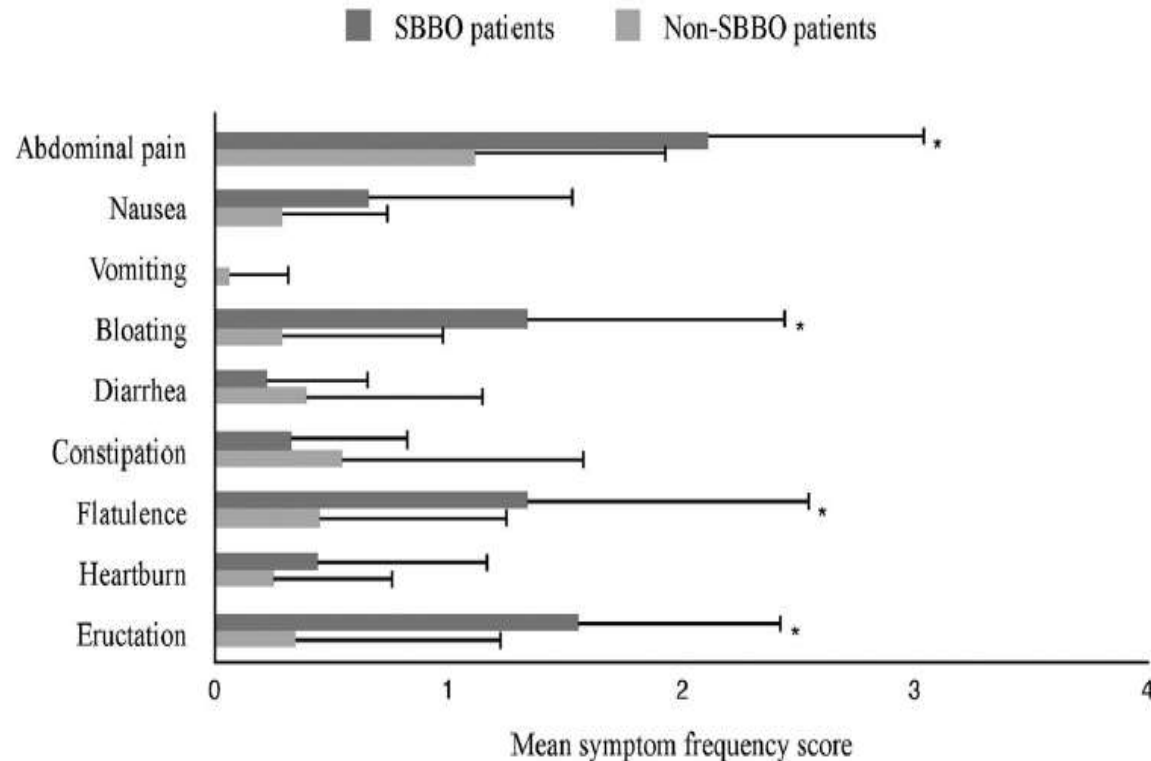


Figure. Mean symptom frequency score after PPI treatment in patients with and without SBBO. * $P < .05$.

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 H₂RAs 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

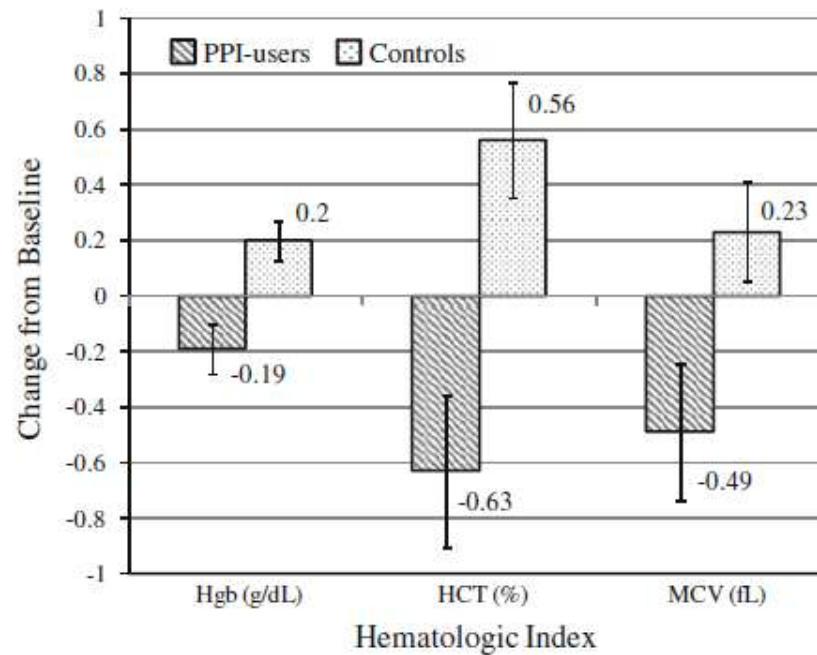
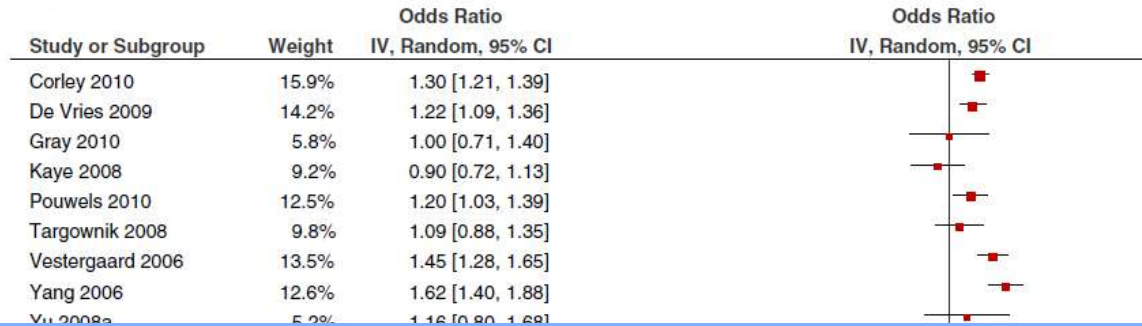


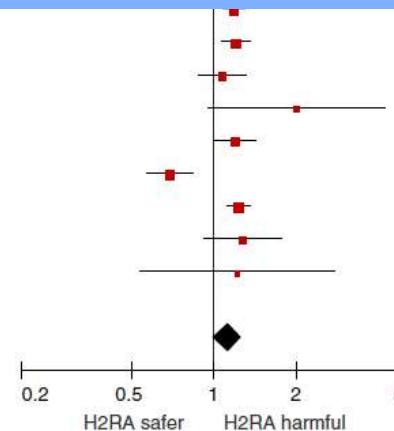
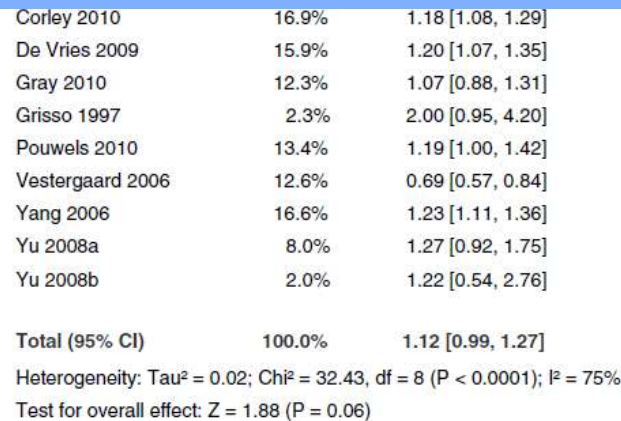
Fig. 2 Change in hematology indices (\pm SEM) in patients before and after initiating proton pump inhibitor (PPI) therapy, compared with patients not receiving PPI therapy. SEM standard error of mean

Risk of Hip Fracture

PPI



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



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”

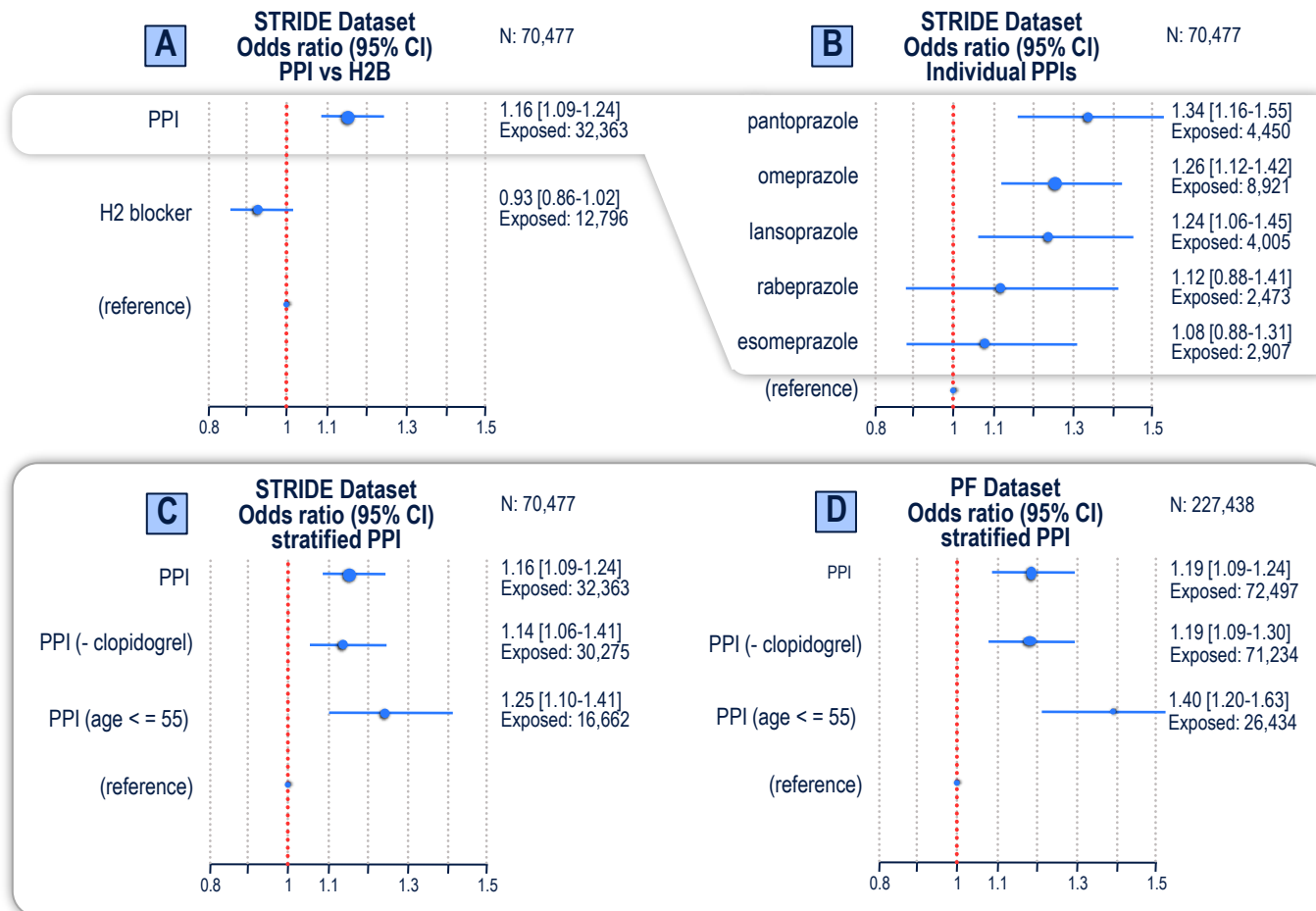
Table 2 Dose and total exposure relationship between proton pump inhibitors and fracture among subjects <18 years old

Proton pump inhibitors	Cases	Controls	Crude OR (95 % CI)	Adjusted OR ^a (95 % CI)
		Total:	1.16 (0.94 to 1.43)	1.13 (0.92 to 1.39)
Maximal dose				
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

^aAdjusted for prior use of histamine-2 receptor antagonists, anti-epileptic drugs, opiates, and oral glucocorticoids

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



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

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

Closing Thoughts

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PPI, to use, or not to useis 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 a role in NERD and hypersensitive esophagus
 - Not in functional heartburn
- There is very limited evidence for using PPI in extra-esophageal conditions (i.e. asthma, cough, ENT) associated with reflux disease
- PPIs are appropriate and indicated 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?