



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



Presenter and Disclosure Information


I have nothing to disclose



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 disorders²
 - Relatively safe medications³
- 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;5:41-7.
2. Tighe M et al. *Cochrane Database Syst Rev* 2014;24:11:CD008550.
3. Czinn S.J, 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

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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

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“Troublesome Symptoms”

- Recurrent vomiting
- Regurgitation
- Back arching
- Crying
- Irritability
- Food refusal

Davidson, et al J Pediatrics 2013

Pediatric GER Clinical Practice Guidelines (2001, 2009)

- Revised guidelines published in 2009: Dx of GERD was “being applied excessively to healthy infants with bothersome but harmless symptoms of GER.”
- Committee “confronted the ongoing problem that current reflux tests may identify variations from normal but cannot predict symptom severity, natural history, or response to therapy”

JPGN Vol 49, No.4 October 2009

Diagnosing GER(D)

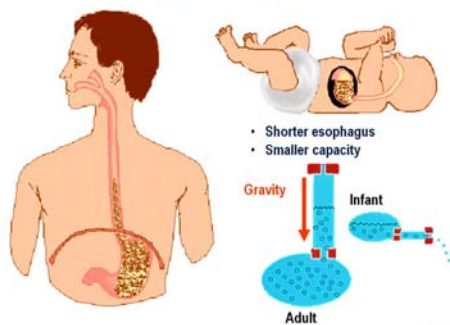
- Clinical history
- Endoscopy with biopsies
- pH impedance probe
- Upper GI xray should never be used to diagnose GER: only to document normal anatomy*

Diagnosing GER(D)

- Clinical Practice guidelines do not support routine diagnostic testing for GERD
- Most tests do not correlate well with symptoms

Chung E et al Hospital Pediatrics 2013

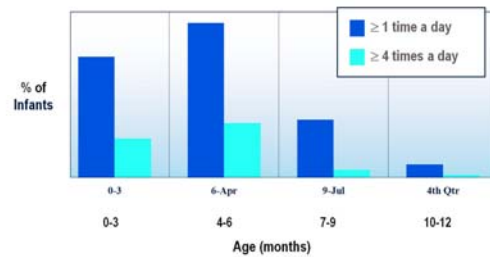
Esophageal Capacitance



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

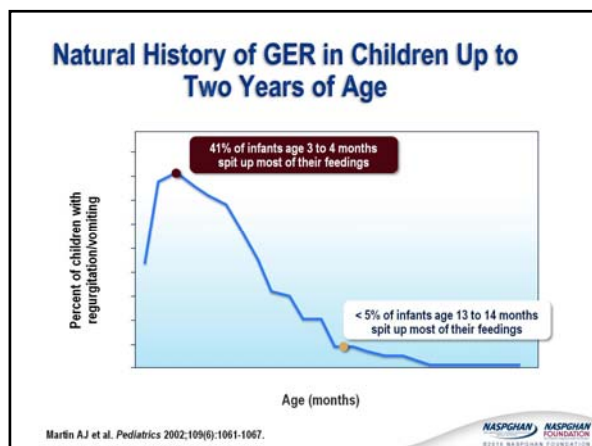
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Prevalence of Regurgitation in Infancy




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

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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.

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The Irritable Infant

- Irritability: caused by wide range of physiologic and/or pathologic conditions
- Healthy infants fuss or cry ~ 2 hours/day, up to 6 hours/day
- Crying peaks at ~ 6 weeks of age
- Concept of irritability and sleep disturbance being caused by GER: largely extrapolated from adult descriptions of GER

JPGN Vol 49, No.4 October 2009

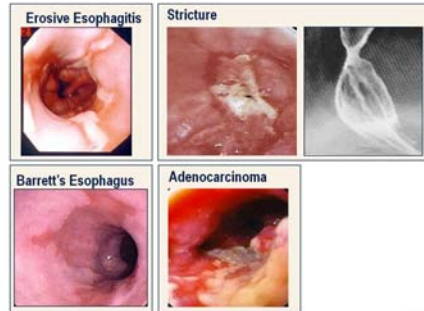
The Irritable Infant

- Available evidence does NOT support an empiric trial of acid suppression in infants with unexplained irritability or sleep disturbance
- GER is an uncommon cause of irritability or unexplained crying in otherwise healthy infants
- Consider other causes (CMPI, UTI, constipation, infection, neuro issue)

JPGN Vol 49, No.4 October 2009

Period of Purple Crying

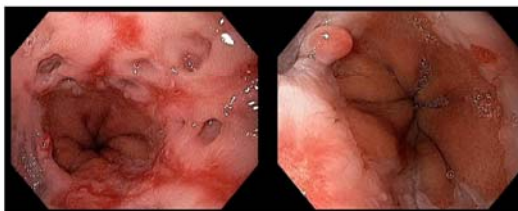
GERD-Related Complications



Endoscopic views courtesy of Benjamin D. Gold, MD.



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.



True GERD: alterations of protective mechanisms

- Insufficient clearance and buffering of refluxate
- Delayed gastric emptying
- Abnormalities in epithelial repair
- Decreased neural protective reflexes of the aerodigestive tract

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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.

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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.

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

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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 < .0017). The number of patients with adverse events was similar between treatment groups.

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

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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.

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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. Orensten, MD, SAC Hospital, FRCPC, FRCPC, Wanda Fajana-Duclos, MD, PhD, Stuart Anagnost, FRCPC, and Philip Swanson, MD

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 4- to 8-week course of esopharmacologic management.

Study design: This multicenter, double-blind, parallel-group study randomized infants with persistent 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 discontinuation data.

Results: Of the 216 infants screened, 162 met the inclusion/exclusion criteria and were randomized. Of these, 149 infants (74%) 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, 25% of lansoprazole-treated infants experienced 1 or more treatment-emergent AEs, versus 30% of placebo recipients ($P = .058$). Serious AEs (SAEs), particularly lower respiratory tract infections, occurred less frequently with lansoprazole than with placebo. (*J Pediatr* 2009;154:514-520)

See editorial, p 475

From the University of Pittsburgh School of Medicine, Pittsburgh, Pa (Orensten); Children 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.

Esomeprazole In Infants with GERD

Group	Baseline (n)	1 Week (n)
Esomeprazole 0.25 mg/kg	11.6 (26)	8.4 (23)
Esomeprazole 1 mg/kg	12.5 (23)	5.5 (22)

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

Omani 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

- 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

No warning signals or signs of complicated GER

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

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.

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ACTA PEDIATRICA
(MAY 1978 - PRESENT)

Acta Paediatrica ISSN 0803-5233

REGULAR ARTICLE

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

Y. Vandeplass (y.vandeplass@uzbrussel.be), E. De Greef, ALLAR study group¹
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, cough, wheezing)
 - Dermatological symptoms

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

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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

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

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Vomiting and Formula changes

- Studies support 2-4 week trial of hydrolyzed or a.a. based formula
- Withdrawal of cows milk and eggs from mom's diet
- no studies specifically evaluating soy protein
- no data on allergy to cereals/thickeners

JPGN Vol 49, No.4 October 2009

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

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 $\text{pHi} < 4$. 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.

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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%.

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Take Home Point: Reassurance is Key

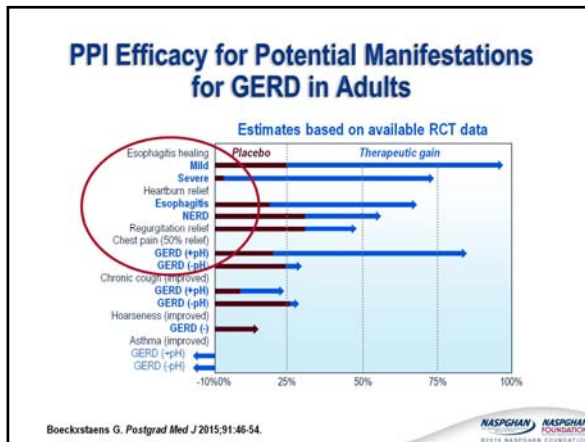
- Help parents redefine expectations of “normal”
- Emphasize the physics of GER; PPI therapy does nothing to alter this
- Emphasize improvement over time
- Consider our oath to “Do no harm”
- Emphasize the lack of true disease (no GERD) in vast majority of infants

Survey of Implementation of 2009 NASPGHAN/ESPGHAN guidelines

- Survey of ~600 general pediatricians in 11 European countries
- 1.8% of pediatricians managed children in full compliance with the guidelines
- 98.2% of pediatricians committed >1 violation of the guidelines in their clinical practice
- 36.2% treat uncomplicated recurrent regurgitation and vomiting in infants younger than 1 year with PPIs
- 38.9% prescribed PPIs to infants with unexplained crying and/or distressed behavior

JPGN Vol 58; No 4, April 2014

BEYOND INFANT GER

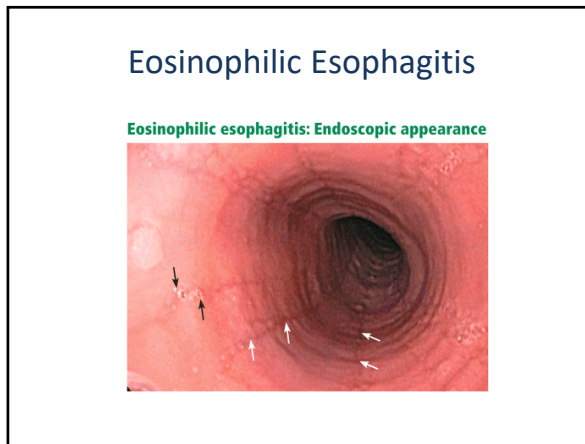


Eosinophilic Esophagitis or PPI-Responsive Esophageal Eosinophilia

- 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. *Allergen Pharmacol Ther* 2013;37:1157-64.

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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.

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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

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

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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. Collie I et al. Acta Gastroenterol Belg 2011;74:46-66.

4. Dellon ES et al. Am J Gastroenterol 2013;108:679-682.

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.

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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**



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← BEFORE PPI AFTER →

Therapeutic Challenge Therapeutic Challenge

Mucosal Healing
Managing ulcers, erosive esophagitis, recurrent strictures with antacids and H₂RAs antagonists






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← BEFORE PPI AFTER →



Therapeutic Challenge Therapeutic Challenge

Mucosal Healing
Managing ulcers, erosive esophagitis, recurrent strictures with antacids and H₂RAs antagonists





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



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Understanding the Risks of Treatment



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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

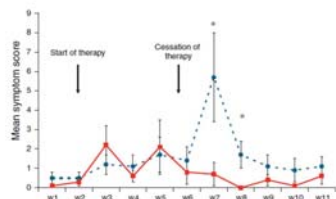
When to Stop Treatment

- In otherwise healthy pediatric patients, reflux esophagitis may not be a chronic problem or recur after treatment¹
 - 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	Outcomes Assessed
Guller et al ^a	Retrospective	Neonates	NICU	Penicillins, Vancomycin, Trimethoprim, Rifampin	NEC
Tamir et al ^a	Prospective	Neonates	NICU	Ranitidine	NEC, sepsis, pneumonia, UTI
Back-Sague et al ^b	Prospective	Neonates	NICU	H ₂ antagonists	Bloodstream infection
Rajes et al ^b	Prospective	Neonates	NICU	H ₂ antagonists	Nosocomial infection
Graham et al ^b	Retrospective	Neonates	NICU	H ₂ antagonists or PPI	Gram-negative bacteremia
Bianconi et al ^b	Retrospective	Neonates	NICU	Ranitidine	Late-onset sepsis
Eward et al ^b	Prospective	≤18 y	PICU	H ₂ antagonists	VAP
Yildizdas et al ^b	Prospective	Pediatric, age range not specified	PICU	Omeprazole, ranitidine, sucralfate	VAP
Lepore et al ^b	Retrospective	Pediatric, age range not specified	PICU	Ranitidine	VAP
Shams et al ^b	Prospective	1 mo-18 y	PICU	Ranitidine	VAP
Singh-Naz et al ^b	Prospective	Pediatrics, age range not specified	PICU	H ₂ antagonists	Nosocomial infection
Canani et al ^b	Prospective	4-36 mo	Pediatric GI centers	Omeprazole and ranitidine	Pneumonia, gastroenteritis
Orendsen et al ^b	Prospective	28 d-12 mo	Primary care centers	Lansoprazole	Lower respiratory tract infection
Tamir et al ^b	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

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; 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.



Minerals and Vitamins



Association Between Proton Pump Inhibitor Use and Anemia A Retrospective Cohort Study

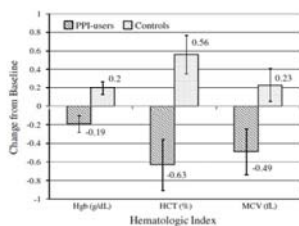


Fig. 2 Change in hematology indices (± SEM) in patients before and after initiating proton pump inhibitor (PPI) therapy, compared with patients not receiving PPI therapy. SEM standard error of mean

Sarzynski E et al. *Dig Dis Sci* 2011;56:2348-53.



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* (95 % CI)
Maximal dose				
None	86,578	422,162	Reference	Reference
Daily or less	424	1651	1.25 (1.12-1.40)	1.22 (1.08-1.36)
>Daily	69	253	1.33 (1.06-1.74)	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)
180-729 doses	41	278	1.07 (0.74-1.42)	1.03 (0.78-1.37)
>729 doses	53	199	1.30 (0.94-1.77)	1.29 (0.95-1.74)

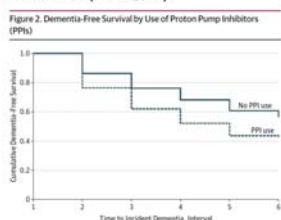
OR odds ratio, CI confidence interval, IQR interquartile range
 *Adjusted for prior use of histamine-2 receptor antagonists, anti-seizure drugs, opiates, and oral glucocorticoids

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



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)



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

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Dementia and PPI

- Unclear mechanism:
 - 1) Modulation of brain enzymes by PPIs?
 - 2) Enhancement of β -amyloid ($A\beta$) 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.

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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

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Choosing Wisely Campaign

- Established in 2011 by the American Board of Internal Medicine
- “Encourages physicians, patients, and other healthcare stakeholders to think and talk about medical tests and procedures that may be unnecessary”
- AAP section of Perinatal Pediatrics developed Top 5 list in newborn medicine

Choosing Wisely Campaign

- #1/5...“Avoid Routine use of Antireflux medications for treatment of symptomatic GERD or treatment of apnea and desaturation in preterm infants”

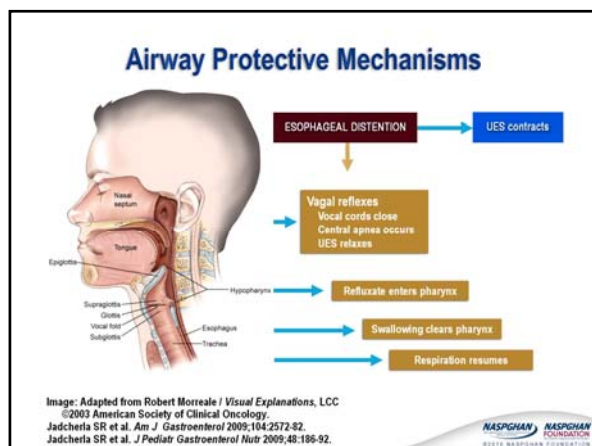
Aerodigestive Conditions and Associations with Reflux

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



Respiratory Disease and Reflux

Have they met the burden of proof for causality?

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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.

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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 Gastroenterol Nutr* 2009;49:498-547.
Field SK. *Chest* 1999;115:848-56.

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Asthma and GER



The NEW ENGLAND JOURNAL of MEDICINE

Efficacy of Esomeprazole for Treatment of Poorly Controlled Asthma

The American Lung Association Asthma Clinical Research Center*

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, NCT00098213)

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 ACOQ 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 (EOL, 95% CI, -0.1 to 0.1 L), asthma-related quality of life (AQL, 1.9% 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 outcomes. 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.

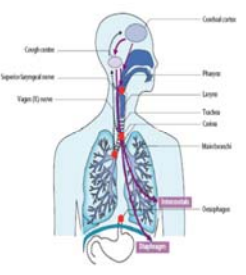
Mastomarde JG et al. *N Engl J Med* 2009;160:1487-99.
Holbrook JT et al. *JAMA* 2012;307:373-80.

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.
Pisogowicz I et al. *Adv Exp Med Biol* 2013;738:161-6.
Slake 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

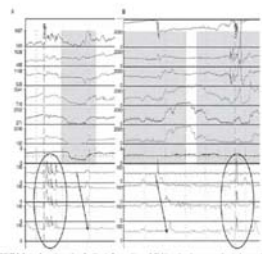


FIGURE 1. Traces of a cough-generating reflux (blue) with associated cough (E). Intraesophageal pressure recording usually, even in high amplitude, simultaneous pressure spikes, are seen in the table. Below spikes are phrenic gas. The area highlights mental propagation of cough stimuli. In contrast to esophageal 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

US News & World Report HEALTH Health Ratings & News

The Washington Post


By Jamie Koufman December 8, 2014

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.


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

By Dan Wooten April 30, 2015 | 1:57 a.m. EDT



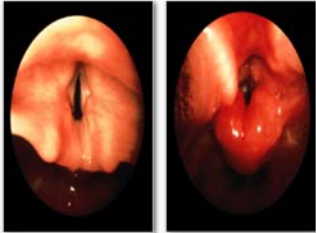
ENT Manifestations of GERD

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;60:965-78.



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.
 Liem HC et al. *Value Health* 2015;18:396-403.
 Vandeplass Y et al. *J Pediatr Gastroenterol Nutr* 2009;49:490-547.
 Sherman P et al. *Am J Gastroenterol* 2009;104:1278-95.
 Kahillis P et al. *Gastroenterology* 2008;135:1392-1413.
 Patel D et al. *Curr Gastroenterol Rep* 2016;18:12-26.



Laryngeal-pharyngeal Pathology and Reflux

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



Sleep Review
 Not Lighters Sleep by the Computer Side (October 2015)
 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.
 Vandeplass Y et al. *J Pediatr Gastroenterol Nutr* 2009;49:498-547.
 Sherman P et al. *Am J Gastroenterol* 2009;104:1273-95.
 Kahllis P et al. *Gastroenterology* 2008;135:1392-1413.
 Patel, D et al. *Curr Gastroenterol Rep* 2016;16:12-20.

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ENT Manifestations of GERD

Biological plausibility	<input checked="" type="checkbox"/> YES
Causality	<input checked="" type="checkbox"/> Not at present, more research needed
Is there a role for PPIs?	<input checked="" type="checkbox"/> Maybe

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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



Levenque D et al. *Dis Esophagus* 2013;26:392-87.
 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>

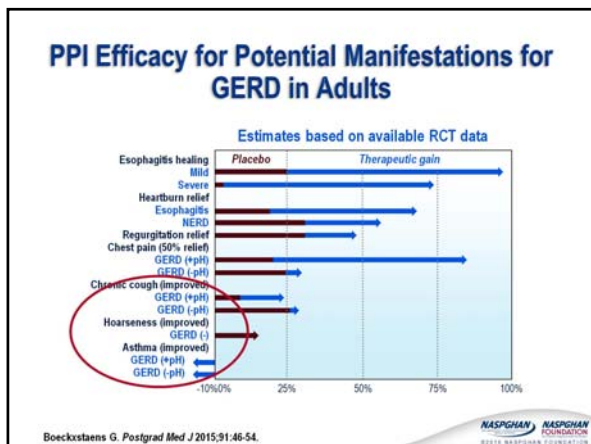
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Esophageal Atresia/ Tracheal-Esophageal Fistulae and GERD

Biological plausibility	<input checked="" type="checkbox"/> YES
Causality	<input checked="" type="checkbox"/> YES
Is there a role for PPIs?	<input checked="" type="checkbox"/> YES

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

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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.

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Beyond Erosive-reflux Disease (ERD) to NERD

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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

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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

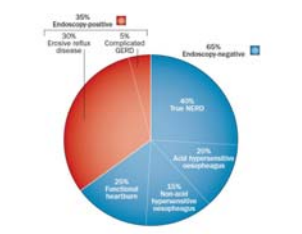


Differentiating Between Various Reflux Related Disorders

	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



- 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

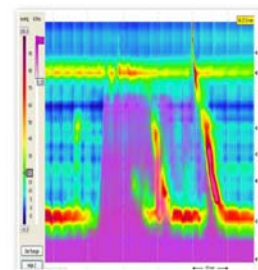
Reprinted by permission from Macmillan Publishers Ltd. ¹

1. Savarino E et al. *Nat Rev Gastroenterol* 2013;10:371-80.
2. Cheng FK et al. *Clinical Gastroenterol Hepatol* 2015;13:967-73.



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 ERD ²
- Visceral hypersensitivity is similar in patients with NERD and ERD ³

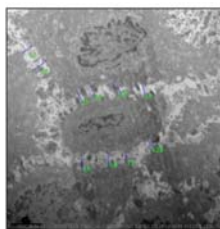


1. Ribolsi M et al. *Clin Gastroenterol Hepatol* 2014;12:52-7.
2. Wejtenberg PW et al. *Am J Physiol Gastrointest Liver Physiol* 2014;307:G323-9.
3. Thoma MM et al. *Aliment Pharmacol Ther* 2008;27:396-403.



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 trial⁴
- The microscopic presentation of ERD and NERD is similar; both with microscopic inflammation and dilated intracellular spaces^{5,6}



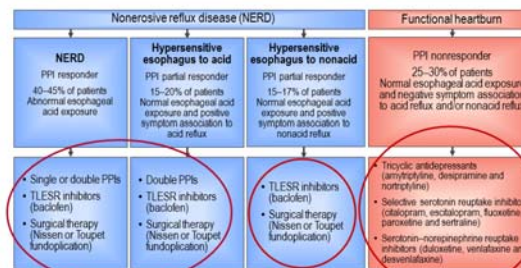
Microscopic view of dilated intracellular spaces
Reprinted by permission from Wolters Kluwer Health, Inc.
J Ped Gastroenterol Nutr. Ataf MA et al. 2014

- Kandulski A et al. *Alliment Pharmacol Ther* 2013;38:643-51.
- Savarino E et al. *Gut* 2009;58:1185-91.
- Nelson SP et al. *Arch Pediatr Adolesc Med* 2000;154:150-4.
- Dylzen P et al. *Clin Gastroenterol Hepatol* 2012;10:1360-6.
- Kandulski A et al. *Alliment Pharmacol Ther* 2013;38:643-51.
- Borrelli O et al. *Neurogastroenterol Motil* 2012;24:e28-e394.

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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.

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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

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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

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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 Impedance 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?