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

Introduction

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


Presenter and Disclosure Information

I have nothing to disclose

Introduction

- PPIs are extremely effective at acid suppression.
  - Preferred treatment for a number of acid related disorders.
  - Relatively safe medications.
- 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.

Introduction
• Aim of this talk is to discuss evidence-based 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 PPIs
- 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**

**“Troublesome Symptoms”**

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


- 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”
Diagnosing GER(D)

- Clinical history
- Endoscopy with biopsies
- pH impedance probe
- Upper GI x-ray 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

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*Chung E et al. Hospital Pediatrics 2013
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

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

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)
Period of Purple Crying

**GERD-Related Complications**

- Erosive Esophagitis
- Stricture
- Barrett’s Esophagus
- Adenocarcinoma

Endoscopic views courtesy of Benjamin D. Gold, MD.

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**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
Correlation of Symptoms and Injury

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

(Images are courtesy of Benjamin S. Gold, MD.)

FDA-Approved Pediatric Age Ranges and Indications for PPIs

<table>
<thead>
<tr>
<th>Age Range (Years)</th>
<th>Esomeprazole</th>
<th>Lansoprazole</th>
<th>Pantoprazole</th>
<th>Rabeprazole</th>
<th>Omeprazole</th>
</tr>
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<tbody>
<tr>
<td>0-1</td>
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<td>2-3</td>
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<td>14-15</td>
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<td>16-17</td>
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</tbody>
</table>

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

Comment as of October 2015. From: [www.accessdata.fda.gov/drugsatfda_docs/label/2015/022155s014s017lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022155s014s017lbl.pdf)

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** This randomized, double-blind, placebo-controlled multicenter study, neonates (premature to 1 month corrected age = 32 weeks); our primary endpoint was symptom improvement assessed by the Pediatric Reflux Scoring System and heartburn, chest pain, and vomiting.

**Results**: There were no significant differences between the esomeprazole and placebo groups in the percentage change from baseline in the mean total number of GERD episodes or symptoms (1.4% vs. 1.7%, respectively). The mean change from baseline in the total number of reflux episodes was not significantly different between esomeprazole and placebo (1.4% vs. 0.2%, respectively). However, the percentage of time that was not reflux was significantly decreased with esomeprazole (p = 0.003) compared to placebo (p = 0.003). The number of patients with adverse events was similar between treatment groups.


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.

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

Esameprazole In Infants with GERD

Managing Infants With Recurrent Vomiting

- History & physical exam generally sufficient
- Parental education
  - Biological signs
  - 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
**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.

**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.

**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.
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
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

Eosinophilic Esophagitis

Eosinophilic esophagitis: Endoscopic appearance
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.

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

Treatment

PPIs Should Be Used for...

<table>
<thead>
<tr>
<th>Indication</th>
<th>PPI Treatment Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI-REE</td>
<td>High dose (q.d. or b.i.d.) for 8 weeks followed by endoscopy and biopsy³¹</td>
</tr>
<tr>
<td>Erosive Erosions</td>
<td>Standard dose q.d. for 3 months followed by trials of tapering the dose towards final withdrawal of therapy</td>
</tr>
<tr>
<td>NSAID</td>
<td>Standard dose q.d. prophylaxis concurrent with NSAID therapy²</td>
</tr>
<tr>
<td>Bleeding</td>
<td>IV 1 mg/kg q.d. or 0.5 mg/kg b.i.d.¹</td>
</tr>
<tr>
<td>H. pylori</td>
<td>Standard dose b.i.d. (as part of a quadruple or triple regimen) for 10 to 14 days²</td>
</tr>
</tbody>
</table>

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
**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

**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
  
  - 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

How to Stop?

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Dyspeptic Symptom Development After Discontinuation of a Proton Pump Inhibitor

A Double-Blind Placebo-Controlled Trial

Weekly dyspeptic scores (mean and 95% CI) in the placebo group (dotted blue line) and in the placebo group (dotted line). Weeks: 0 = before treatment, weeks 3-4 = 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
- Neurologic enterocolitis and candidiasis
- Effects on vitamins and mineral absorption:
  - Iron
  - Calcium
  - Magnesium
  - Vitamin B12
- Gastric fundic gland polyps
- Interstitial nephritis (renal, idiosyncratic reaction)
- Myocardial infarction and Dementia

Risks of Acid Suppression in Children

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 H2RAs 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.\(^4\)

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**Minerals and Vitamins**

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**Association Between Proton Pump Inhibitor Use and Anemia**

**A Retrospective Cohort Study**

**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**

<table>
<thead>
<tr>
<th>PPI use</th>
<th>Cases</th>
<th>Controls</th>
<th>Odd Ratio (95% CI)</th>
<th>Adjusted Odd Ratio (95% CI)</th>
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<td>123</td>
<td>1.45 (1.17-1.78)</td>
<td>1.45 (1.17-1.78)</td>
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</tbody>
</table>

Footnotes:
*Italicized references are of Bunsen, Coates, and Cottrell. *Statistical analysis using logistic regression and chi-square tests; p-values for significant difference.
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

• 6½ 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

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

Asthma and GER; Association or Causation?
• Proposed mechanisms by which reflux aggravates asthma are:
  – Direct production of airway inflammation
  – Airway hyper-responsiveness
  – Visegly-mediated bronchial or laryngeal spasm
  – Neuronal-mediated inflammation
• Few studies have evaluated the impact of asthma on GERD
  – Chronic hypertalation may reduce resting LES pressure
  – Lung hyposensitization and airflow obstruction may increase negative intra-thoracic pressure
Asthma and GER

Lansoprazole for Children With Poorly Controlled Asthma: A Randomized Controlled Trial

Results: The mean decrease in PEF was 7% in the lansoprazole group and 1% in the placebo group. A post-hoc analysis showed a significant difference in PEF between the two groups (p=0.026). The mean decrease in FEV1 was 3% in the lansoprazole group and 1% in the placebo group. A post-hoc analysis showed a significant difference in FEV1 between the two groups (p=0.041).

Conclusion: The use of lansoprazole in children with poorly controlled asthma is associated with a significant improvement in lung function compared to placebo. Further research is needed to determine the long-term effects of lansoprazole on asthma control.

GER and Asthma...the Saga Continues

- Biological plausibility: Yes
- Causality: ? Not definitively characterized
- 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.

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
Cough and Reflux... a Possibility

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

ENT Manifestations of GERD

Have they met the burden of proof for causality?

Laryngeal: Normal vs. Erythema

Not all red in the airways = reflux!

References:

Laryngeal-pharyngeal Pathology and Reflux

- The sensitivity of laryngoscopic findings to identify laryngeal-pharyngeal disease related to reflux (LPR) is poor.
- New 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 of acid-suppression treatment and/or lifestyle changes suggests an association with GER.
- There is insufficient evidence to recommend OR against the use of acid suppression therapy.

References:
Laryngeal-pharyngeal Pathology and Reflux

ENT Manifestations of GERD

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

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

- Symptoms can include coughing with feeding, recurrent pneumonia, and episodic cyanosis concerning for ALTE
- L-Tube 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

Esophageal Atresia/Tracheo-Esophageal Fistulae and GERD

Biological plausibility: YES
Causality: YES
Is there a role for PPIs?: YES
PPI Efficacy for Potential Manifestations for GERD in Adults

Estimates based on available RCT data

Beyond Erosive-reflux Disease (ERD) to NERD

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

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-based for treating ERD and NERD versus not for treating functional heartburn or hypersensitive esophagus with PPI

Differentiating Between Various Reflux Related Disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>Typical Symptoms</th>
<th>Esopus by Endoscopy</th>
<th>Abnormal Acid-Reflux pH-MII testing</th>
<th>Symptom association with acid or non-acid reflex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopy</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
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<td>NERD</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
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<tr>
<td>Hypersensitive</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Esophagus</td>
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<tr>
<td>Heartburn</td>
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</table>

Incidence of Reflux Disease Subtypes in Adults

- In 221 adult patients, 54% did not have a diagnosis that would respond to PPI therapy 1
- There are no pediatric studies that systematically address this

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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

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

Why do we Care About the Names?

Treatments may be Different, at least in Adults

NERD
- PPI responders do not require therapy for GERD
- GERD patients respond (50-70% of patients)
- NERD patients respond (40-60% of patients)
- GERD patients typically respond to high doses of a single agent
- NERD patients may require combination therapy

Hypereosinophilic Esophagus
- PPI responders do not require therapy for GERD
- GERD patients respond (50-70% of patients)
- NERD patients respond (40-60% of patients)
- GERD patients typically respond to high doses of a single agent
- NERD patients may require combination therapy

Case

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Case Work-Up and Outcome

- Impedance results off therapy:
  - 45 total reflux episodes, 27 acid, 18 nonacid
  - pH<4 for 4.8% of the time (normal is 10%)
  - 6/8 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 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?