Proton Pump Inhibitors (PPIs):
Friend or Foe?
Appropriate PPI Use in Children

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Speaker Disclosures

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Introduction

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

Introduction

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

2. Thorne C et al. Curr Opin Gastroenterol 2015;31:1
3. O'Morain C et al. Gut 2015;64:1

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Page: 2
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

Section Objectives

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

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

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**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

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**Prevalence of Regurgitation in Infancy**

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>0-2</th>
<th>4-6</th>
<th>7-8</th>
<th>10-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Infants</td>
<td><img src="image" alt="Graph" /></td>
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</table>

> Adapted from [source](source)
Natural History of GER in Children Up to Two Years of Age

41% of infants age 3 or 4 months spit up most of their feedings

< 5% of infants age 13 to 14 months spit up most of their feedings

Age (months)

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

Absence of histologic changes does not rule out GERD

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.

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.

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

- Improvements in healing over time with Lansoprazole treatment.
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

Similar PPI Healing Rates in Adults and Children

- Hassall, 2000 (omeprazole)
- Tolia, 2002 (lansoprazole)
- Huang & Hunt, 1999 (meta-analysis)

FDA-Approved Pediatric Age Ranges and Indications for PPIs

- Treatment may begin as early as 1 month of age for this indication.
Insufficient Evidence to Associate GERD with a Number of Other Conditions

- Pathological apnea
- Acute life threatening events (ALTE)

Vomiting

Allergic Gastroenteropathy in Preterm Infants

- N=25, mean GA 20 weeks and PNA 78 days, all had bx,
- Presentation:
  1. GER (5)
  2. Feeding intolerance (8)
  3. Lower GI bleed (12)

15 responded to hydrolysate formula
10 responded to amino acid based formula
**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

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**Eosinophils**

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**Esophageal Eosinophilia Does Not Equal Eosinophilic Esophagitis**

Photo courtesy of Jane W. Green, MD.
**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

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**Diagnosis and Management of Eosinophilia and EoE**

- Assess for all cases of eosinophilic esophagitis
- Bi-annual esophagogastroduodenoscopy
- PPI trial followed by repeat endoscopy and biopsy
- GERD and eosinophilic esophagitis
- EoE without eosinophilic esophagitis

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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.
**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.

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**Treatment**

**PPIs Should Be Used for...**

<table>
<thead>
<tr>
<th>Indication</th>
<th>PPI Treatment Regimen</th>
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<tbody>
<tr>
<td>PPI-REE</td>
<td>High dose q.d. or b.i.d. for 8 weeks followed by endoscopy and biopsy.¹²</td>
</tr>
<tr>
<td>Erosive</td>
<td>Standard dose q.d. for 3 months followed by trials of tapering the dose towards final withdrawal of therapy.¹</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>Standard dose prophylaxis concurrent with NSAID therapy.²</td>
</tr>
<tr>
<td>Bleeding</td>
<td>IV 1 mg/kg q.d. or 0.5 mg/kg b.i.d.³</td>
</tr>
<tr>
<td><em>H. pylori</em></td>
<td>Standard dose b.i.d. (as part of a quad or triple regimen) for 10 to 14 days.⁴</td>
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What to do When PPIs Don’t Work?

• Assess for treatment compliance
  – Lack of efficacy of PPIs in gastric acid secretion is extremely rare
• Make sure the patient is taking the PPI on an empty stomach and at least 30 to 60 minutes before a meal
• Trial of b.i.d. dosing
• Add an H$_2$RA at night (tachyphylaxis)
• Make sure the diagnosis is correct

Summary: Indications for PPIs

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

Understanding the Risks of Treatment
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

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.
- The risk is further increased by concomitant use of antibiotics with a PPI. H2RAs may be less harmful.
- 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 2.2 times.
- FDA safety information: C. difficile associated diarrhea can be associated with gastric acid reducing drugs.

References:

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**Respiratory Infections**

- In patients with asthma the addition of lansoprazole compared with placebo:
  - 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.
  - However this may be explained by a maternal underlying condition.

References:

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

*Fig. 2: Change in hematologic indices (i.e., BMD) in patients before and after initiating proton pump inhibitor (PPI) therapy, compared with patients not receiving PPI therapy. Error bars represent the standard error of mean.*

**Risk of Hip Fracture**

*Fig. 3: Description of the study design and outcomes.*

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>
<thead>
<tr>
<th>Table 1</th>
<th>PPI use not associated with fracture in young adults age 19 years old</th>
</tr>
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<tbody>
<tr>
<td>PPI use</td>
<td>Case</td>
</tr>
<tr>
<td></td>
<td>Number</td>
</tr>
<tr>
<td></td>
<td>Daily use</td>
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<td></td>
<td>Weekly use</td>
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<td></td>
<td>Monthly use</td>
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*OR, odds ratio; CI, confidence interval.

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
Dementia

• 7,367 participants >75 y/o and free of dementia at baseline.
• Patients receiving regular PPI medication (n = 2,050) were found to have a significantly increased risk of incident dementia compared with the patients not receiving PPI medication (n = 70,729).

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

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

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

Dyspeptic Symptom Development After Discontinuation of a Proton Pump Inhibitor
A Double-Blind Placebo-Controlled Trial

Aerodigestive Conditions and Associations with Reflux
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?

Asthma and GER
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 infra-thoracic pressure

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)?
  - Yes: 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
- Yes, in select individuals

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
ENT Manifestations of GERD

Have they met the burden of proof for causality?

Laryngeal: Normal vs. Erythema

Not all red in the airways = reflux!

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

**ENT Manifestations of GERD**

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

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

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

[References:](http://www.srs-evar.org)

**Esophageal Atresia/Tracheal-Esophageal Fistulae and GERD**

- 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
  - Studies to validate adult-based patient-reported outcome tool in children
- Clearly a role for the PPI in infants and children with EA/TEF

Beyond Erosive-reflux Disease (ERD) to NERD

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></th>
<th>Typical Symptoms</th>
<th>Esophagus by Endoscopy</th>
<th>Abnormal acidic reflux on pH xMT testing</th>
<th>Symptom association with acidic or non-acidic reflux</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERD</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>NERD</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Hypersensitive Esophagus</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Functional Heartburn</td>
<td>+</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.
- There are no pediatric studies that systematically address this.

The Mechanisms

- The mechanism of reflux in NERD patients is transient lower esophageal sphincter relaxations (TLSRs).
- Patients with NERD have similar symptom severity to those with ERD.
- Visceral hypersensitivity is similar in patients with NERD and ERD.

References:
Diagnosing NERD

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

References:

Why do we Care About the Names?
Treatments may be different, at least in adults

<table>
<thead>
<tr>
<th>Nonerosive reflux disease (NERD)</th>
<th>Functional heartburn</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NERD</strong>&lt;br&gt; PM receptor&lt;br&gt; 2-5% of patients&lt;br&gt; Sensitized to acid and&lt;br&gt; pepsin secretion</td>
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</tr>
<tr>
<td><strong>ERD</strong>&lt;br&gt; PM receptor&lt;br&gt; 60-70% of patients&lt;br&gt; Sensitized to acid and&lt;br&gt; pepsin secretion</td>
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</tr>
<tr>
<td><strong>Esophageal hypersensitivity</strong>&lt;br&gt; Heartburn&lt;br&gt; Reflux&lt;br&gt; Normal biopsies&lt;br&gt; Response to PPI’s and&lt;br&gt; lifestyle modifications</td>
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<td><strong>Esophageal hypertrophy</strong>&lt;br&gt; Heartburn&lt;br&gt; Reflux&lt;br&gt; Normal biopsies&lt;br&gt; Response to lifestyle&lt;br&gt; modifications</td>
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<td><strong>Esophageal mini-barrett’s</strong>&lt;br&gt; Heartburn&lt;br&gt; Reflux&lt;br&gt; Normal biopsies&lt;br&gt; Response to lifestyle&lt;br&gt; modifications</td>
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</tr>
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</table>


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
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
  - Citralopram 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 Intraesophageal Impedence testing (pH-MII) may be to differentiate NERD from functional heartburn
  - Should be performed off-therapy
- Acid suppression has a role in NERD and hypersensitive esophagus but not in functional heartburn

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

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

Take Home Messages

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

Questions?

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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 2 oz --- 27 kcal/oz
  - 1 tbsp rice cereal per oz --- 33 kcal/oz (1.1 kcal/ml)

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

Body Positioning and Medical Therapy for Infantile Gastroesophageal Reflux Symptoms

| Eligibility | 8.5 study | Randomisation | T2 wk
|-------------|-----------|---------------|--------
| Gr | wk | Gr | Med | Pos |
| 1 | PP | LL | P |
| 2 | PP | HE | P |
| 3 | AA | LL | P |
| 4 | AA | HE | P |


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

- 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

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

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
- Acid suppression resulted in gastric bacterial overgrowth, in particular with organisms that cause pharyngeal and laryngeal disease
  - Could acid suppression for GERD result in, exacerbate, or worsen the very same extra-oesophageal disease it was used to treat?

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

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

Dementia and PPI

- Unclear mechanism:
  1. Modulation of brain enzymes by PPIs?
  2. Enhancement of β-amyloid (Aβ) levels in the brain (PPI inhibit degradation enzymes)?
  3. Decreased level of V4 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