2:15 – 3 pm

Burning Issues in GERD

SPEAKER
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Presenter Disclosure Information

The following relationships exist related to this presentation:

- Neil Gupta, MD: Independent contractor for Cook Medical and CDx Diagnostics. Consultant for Cosmo Pharmaceuticals.

Off-Label/Investigational Discussion

- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Learning Objectives

- Discuss the pathophysiology and changing epidemiology of GERD
- List the various treatment options for patients with GERD
- Evaluate the complications and extra esophageal manifestations of GERD

Case Presentation 1

47-year-old male with worsening heartburn

- Reports almost daily post-prandial symptoms in spite of daily omeprazole 20 mg
- Nocturnal heartburn can awaken him from sleep
- Denies weight loss, anorexia, nausea or vomiting, difficulty swallowing or painful swallowing
- Has gained 20 pounds over the past year but otherwise his health is unchanged

Case Presentation 1 (cont.)

Lab work 4 months ago:
- Normal CBC and CMP

Physical exam:
- White male
- Normal vital signs
- BMI 31.2 kg/m^2

Reason for appointment:
- He heard that heartburn can lead to cancer
- He also wants to know if there are any more effective treatments

CBC=complete blood count; CMP=complete metabolic panel; BMI=body mass index

GERD: Definitions

"symptoms or complications resulting from the reflux of gastric contents into the esophagus, oral cavity (including larynx) or lung"

"a condition that develops when the reflux of gastric content causes troublesome symptoms or complications"

ESOPHAGEAL SYNDROMES

Symptomatic Syndromes
- Typical reflux syndrome
- Reflux chest pain syndrome

Syndromes with injury
- Esophagitis
- Stricture
- Barrett's esophagus
- Adenocarcinoma

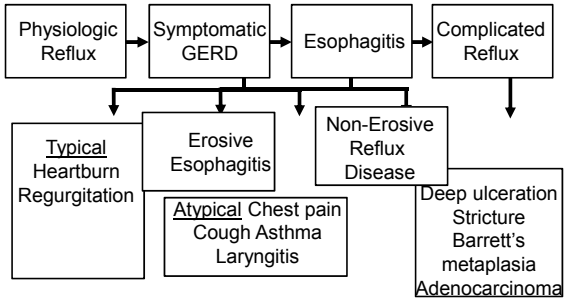
EXTRA-ESOPHAGEAL SYNDROMES

Established associations
- Cough
- Laryngitis
- Asthma
- Dental erosions

Proposed associations
- Pharyngitis
- Sinusitis
- Idiopathic pulmonary fibrosis
- Recurrent otitis media

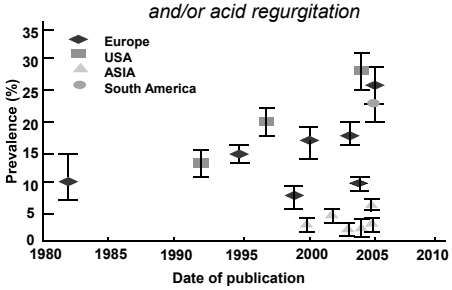
Katz et al. Am J Gastroenterol 2013;108:308–328
Vakil et al, Am J Gastroenterol 2006;101:1900

GERD: Clinical Spectrum



Time Trends of GERD Symptoms: Review of Cross-Sectional Population-Based Studies

Prevalence of at least weekly heartburn and/or acid regurgitation



EL-Serag HB. Clin Gastroenterol Hepatol. 2007;5:17-26

Factors Responsible for the Changing Epidemiology of GERD

- Aging population[1]
- Increasing prevalence of obesity[2]
- Use of drugs that affect LES pressure and gastric emptying[3]
- Self-treatment / access to OTC medications?
- Dietary habits, other lifestyle factors?

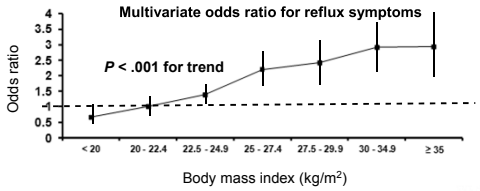
LES=lower esophageal sphincter

1. Lee et al. *Clin Gastroenterol Hepatol*. 2007;5:1392-1398.
2. Watanabe et al. *J Gastroenterol*. 2007;42:267-274.
3. Bonatti et al. *J Gastrointest Surg*. 2007. Jul;11(7):923-8.

Higher BMI Increases Risk of GERD Symptoms

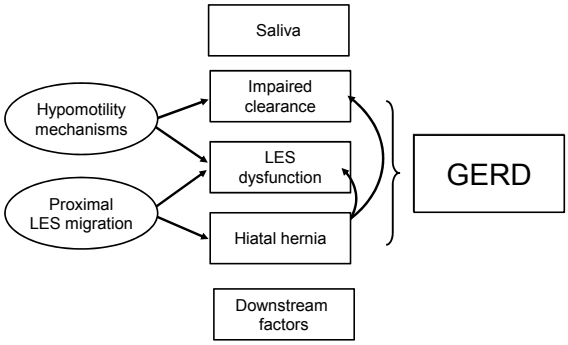
- Even moderate weight gain among persons of normal weight can cause or worsen reflux symptoms
- Weight loss is associated with a decreased risk of symptoms

Study of 2306 women with at least weekly GERD symptoms and 3904 with no symptoms



Jacobson BC, et al. *N Engl J Med*. 2006;354:2340-2348.

Events Leading to GERD



GERD "Typical" symptoms

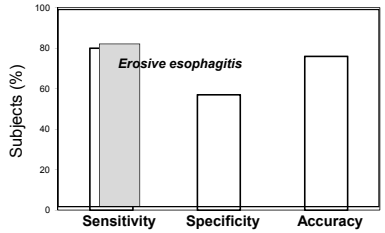
- Heartburn
- Burning feeling from stomach to neck
- Regurgitation
- Belching

If heartburn is the only or chief symptom the likelihood of GERD is 60-75%

A presumptive diagnosis of GERD can be established in the setting of typical symptoms of heartburn and regurgitation. Empiric medical therapy with a proton pump inhibitor (PPI) is recommended in this setting.

Dent J et al. Gut 2002;50(s4)17-20
Katz et al. Am J Gastroenterol 2013;108:308-28

Accuracy of Short-Term High-Dose PPI Trial* in Diagnosing Pathological Reflux



*The "omeprazole test" – 40 mg PO QAM and 20 mg PO QPM for 1 week

Fass R et al. Arch Intern Med 1999

Upper Endoscopy in GERD: Advice from the American College of Physicians

- Alarm Features
  - Dysphagia, bleeding, anemia, weight loss, vomiting
- Persistent symptoms despite PPI BID for 4-8 weeks
- Severe erosive esophagitis after 8 weeks of PPI (to assess healing & rule out Barrett's esophagus)
- History of esophageal stricture with recurrent dysphagia

Other indications:

- Men >50 years with >5 years of GERD symptoms & other risk factors, including:
  - nocturnal GERD, hiatal hernia, obesity, smoking, intra-abdominal fat
- Surveillance of Barrett's esophagus

PPI= proton pump inhibitor

Shaheen N, et al. *Ann Int Med*. 2012:157:808-16.

Diagnostic Testing for GERD cont'd

- **pH monitoring**
  - Useful for refractory GERD symptoms and chest pain
- **Multichannel intraluminal impedance**
  - Helpful for diagnosis in non-acidic reflux
- **Esophageal manometry**
  - Useful in evaluation of dysphagia and chest pain in selected patients

Rosen R, et al. *Am J Gastroenterol*. 2004;99:2452-2458
Stavroulaki P. *Int J Pediatr Otorhinolaryngol*. 2006;70:579-590
Rudolph CD, et al. *J Pediatr Gastroenterol Nutr.* 2001;32(suppl 2):S1-S31
Katz P, et al. *Am J Gastroenterol* 2013;108:308–328

Diagnostic Testing for GERD

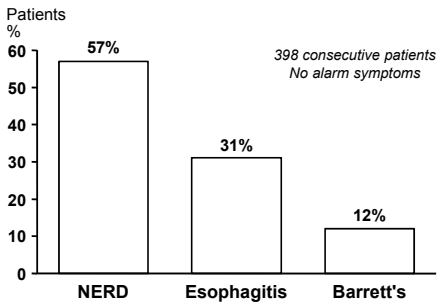
Barium swallow
Upper gastrointestinal series

- Useful to detect anatomic abnormalities (e.g. hiatal hernia, achalasia, stricture)
- Does NOT play a role in **GERD** diagnosis

Accuracy:
Severe esophagitis: 80%
Mild esophagitis: 25%
Barrett's: 26%

Reflux of barium during the study:
Seen in 25-75% of GERD pts
Falsely seen in 20% normals

What is Non-Erosive Reflux Disease?



Sharma et al, Gastroenterology 2002

Endoscopy Negative Disease

A heterogenous group of disorders presenting as typical GERD symptoms in the absence of visible esophageal injury at endoscopy

Non-Erosive Reflux Disease (NERD)

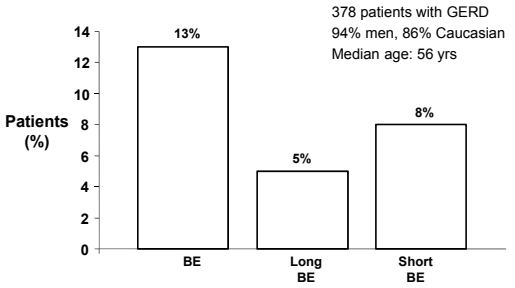
"The presence of typical GERD symptoms due to intraesophageal acid exposure in the absence of visible esophageal injury at endoscopy".

Functional Heartburn (Rome III)

- Burning retrosternal pain or discomfort
- Absence of evidence that GERD is the cause of symptoms
- Absence of histopathology-based esophageal motility disorders

➢ All that is endoscopy negative is not NERD

Prevalence of Barrett's Esophagus in GERD Patients



Westhoff B et al. Gastrointest Endosc 2005

Some Facts About Extra-Esophageal GERD

When to suspect GERD in asthma

- **Adult onset asthma**
- **Poor response to asthma therapy**
- **Nocturnal cough**
- **Worsening asthma:**
  - **big meal, alcohol, supine position**

Gaude GS. Ann Thorac Med. 2009 Jul;4(3):115-23

Comparison of typical and atypical GERD

	Typical	Atypical
Symptoms	**Heartburn/ regurgitation**	**Pulmonary/laryngeal**
Pathophysiology	**Transient relaxation of LES**	**Multi-factorial**
Endoscopy findings	**Common**	**Uncommon**
pH findings	**High sensitivity High specificity**	**Lower sensitivity**
Treatment response	**Excellent**	**Less predictable**

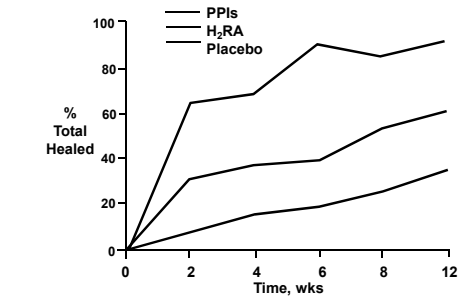
Management of GERD in 2015

Management of GERD

- Weight loss is recommended for GERD patients who are overweight or have had recent weight gain.
- Head of bed elevation and avoidance of meals 2 – 3 h before bedtime should be recommended for patients with nocturnal GERD.

Katz et al. Am J Gastroenterol 2013;108:308-28

PPIs vs H2RAs vs Placebo for Erosive Esophagitis (EE)

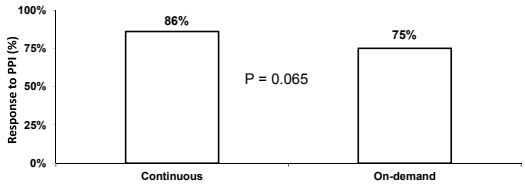


PPI=proton pump inhibitor; H2RA = h2 receptor antagonist

Chiba et al. *Gastroenterology*. 1997;112:1798-1810.
Khan et al. *Cochrane Database Syst Rev*. 2007;(2):CD003244.

On-Demand vs. Continuous PPI Therapy for GERD

176 patients with NERD or Grade I/II esophagitis and frequent relapses treated with rabeprazole 10 mg



Bour et al. Aliment Pharm Ther 2005;21:805

Management of GERD

- An 8-week course of PPIs is the therapy of choice for symptom relief and healing of erosive esophagitis.
- Non-responders to PPI should be referred for evaluation.
- In patients with partial response to PPI therapy, increasing the dose to twice daily therapy or switching to a different PPI may provide additional symptom relief.

Katz et al. Am J Gastroenterol 2013;108:308-28

Extraesophageal presentations of GERD: Asthma, Chronic cough and Laryngitis

- A PPI trial is recommended to treat extraesophageal symptoms in patients who also have typical symptoms of GERD.

Katz et al. Am J Gastroenterol 2013;108:308-28

Extraesophageal presentations of GERD: Asthma, Chronic cough and Laryngitis

- GERD can be considered as a potential co-factor in patients with asthma, chronic cough, or laryngitis. Careful evaluation for non-GERD causes should be undertaken in all of these patients.
- A diagnosis of reflux laryngitis should not be made based solely upon laryngoscopy findings.

Katz et al. Am J Gastroenterol 2013;108:308-28

PPI therapy: When is more better?

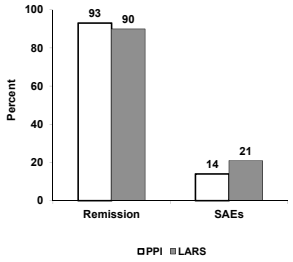
- Recent studies suggest that twice daily PPI controls intraesophageal acid exposure no better than once daily PPI in patients with GERD
- Daily PPI therapy controls intraesophageal acid exposure better than every other day PPI
- Sustained symptom response with daily PPI therapy is inversely related to BMI
- In ***obese*** patients with erosive esophagitis, twice daily PPI may provide better symptom relief than once daily PPI

Gawron AJ, et al. Clin Gastroenterol Hepatol 2012;10:620-5.
Bour et al. Aliment Pharm Ther 2005;21:805

LARS vs. Esomeprazole for Chronic GERD: 3 Year Analysis from the LOTUS Trial

- Open, parallel group study in 11 European sites
- 412 patients with chronic GERD (EE & response to PPI) randomized to LARS or esomeprazole 20 mg/day
- PPI dose escalation allowed
- Primary outcome: % of patients remaining in remission at 3 years
- 23% required increased PPI dose over time
- No between-group differences in improvement of microscopic esophagitis

LARS = laparoscopic antireflux surgery



Lundell, et al. Gut. 2008;57:1207
Fiocca, et al. Am J Gastroenterol 2010;105:1015

Surgical options for GERD

- Surgical therapy is a treatment option for long-term therapy in GERD patients.
- Surgical therapy is generally not recommended in patients who do not respond to PPI therapy.

Katz et al. Am J Gastroenterol 2013;108:308-28

Potential Safety Risks of PPIs

Safety Issue	Clinical Significance
Cytochrome P450 interaction	Negligible
Clopidogrel interaction	Avoid use with omeprazole
Clostridium difficile infection	Probable
Other enteric infections	Probable
Other enteric infections	Probable
Rebound hypersecretion	Negligible
Fractures	Unclear
Idiosyncratic reactions (AIN, hepatitis)	Rare
Anaphylaxis	Rare
Pregnancy	Likely negligible
Hypomagnesemia	Rare (seen with > 1 year treatment)

Adapted from Parikh NY, Howden CW. GI Clin NA. 2010;39:529

Warnings Added to PPI Labels in 2012

Safety Issue	Clinical Significance
Interaction with clopidogrel	Concomitant use of clopidogrel with 40 mg esomeprazole reduces pharmacologic activity of clopidogrel. Avoid concomitant use with clopidogrel.
Clostridium difficile associated diarrhea	Should be considered for diarrhea that does not improve.
Concomitant use with methotrexate (primarily at high dose)	PPI use may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. Temporary withdrawal of PPI may be considered.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020973s029lbl.pdf
http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020406s078-021428s025lbl.pdf

Potential risks with PPI use

- Patients with known osteoporosis can remain on PPI therapy. Concern for hip fractures and osteoporosis should not affect the decision to use PPI long-term except in patients with other risk factors for hip fracture.
- PPI therapy can be a risk factor for Clostridium difficile infection and should be used with care in patients at risk.

Katz et al. Am J Gastroenterol 2013;108:308-28

Heartburn: More Than One Disease

- Pathological acid reflux
- Non-acid reflux
- Disturbed motility
- Visceral hypersensitivity / brain-gut interactions
  - Chemical, osmolar, mechanical
- Psychological abnormalities
  - Somatoform disorder

Katz et al. Am J Gastroenterol 2013;108:308-28

Emerging Therapeutic Agents for GERD

- Acid inhibitors
  - Longer-acting PPIs
    - eg. ilaprazole, tenatoprazole, AGN-201904–2
  - P-CABs (potassium-competitive acid blocker)
- Reflux inhibitors
  - GABA-B agonists, mGlyR5 modulators
- Pain modulators
  - Antidepressants, melatonin, TPRV1 antagonists
- Prokinetics

None of these drugs are currently FDA approved for GERD

Management of GERD: Summary

- Prevalence of GERD and its complications are increasing
- PPIs are the most effective medical therapy
  - Minimum effective dosing should be utilized
  - BID dosing is common but offers little incremental benefit over QD dosing
- Surgery in expert hands provides another highly effective treatment option for GERD
  - Novel procedures and devices deserve further study
- A variety of emerging therapies are in development for patients with GERD symptoms