GERD: Gastroesophageal Reflux Disease

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**Learning Objectives**

1. Describe pathophysiologic mechanisms, clinical presentation, and diagnostic testing as they relate to gastrointestinal reflux disease
2. Differentiate between typical, atypical, and alarm GERD symptoms
3. Give a brief description of Barrett’s esophagus and the risk involved with the condition
4. Given a patient case, determine if a patient is a candidate for patient-directed therapy for GERD and recommend appropriate OTC therapy
5. Recommend appropriate GERD treatment for patients not eligible for patient-directed therapy
6. Provide patient counseling on lifestyle modifications to minimize GERD symptoms
7. Given a patient case identify drugs that may aggravate GERD symptoms
8. Provide patient counseling on the appropriate administration of GERD therapy for optimal efficacy
9. Provide recommendations for maintenance GERD therapy when indicated
10. Discuss the place in therapy of prokinetics for the treatment of GERD
11. Given a patient case recognize adverse reactions and drug interactions with the medications used to treat GERD
12. Adjust the dose of an H2-receptor antagonist for renal function when necessary
13. Discuss the long-term safety concerns of PPIs with other health care providers or patients

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| **Required textbook reading :**  **Pharmacotherapy: A Pathophysiologic Approach (eds. DiPiro et.al. 8th Edition, 2011), chapter 39**  (Chapter 38 is optional)  **Most recent treatment guideline:**  Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2013; 108:308-328. |

**Practice Case**

Mrs. B. comes with her husband to the pharmacy counter. She wants a recommendation since he doesn’t want to take the Tums she bought for him last month. “Go on dear, tell the pharmacist about it.”

Mr. B. says, “I have horrible heartburn every day. I hate the minty taste of the Tums my wife bought and they don’t help much anyway. It really burns in my throat a lot. It’s really bad when I bend over at work and when I’m lying in bed at night. It hurts to swallow sometimes. What can I take?”

**Definitions**

GERD

Gastroesophageal Reflux Disease

Symptoms or mucosal damage that results from abnormal reflux of the stomach contents into the esophagus

NERD

Non-erosive reflux disease

Typical GERD symptoms without visible esophageal mucosal damage

ERD

Erosive reflux disease

GERD symptoms with erosions present

Other definitions:

Esophagitis- inflammation of esophagus

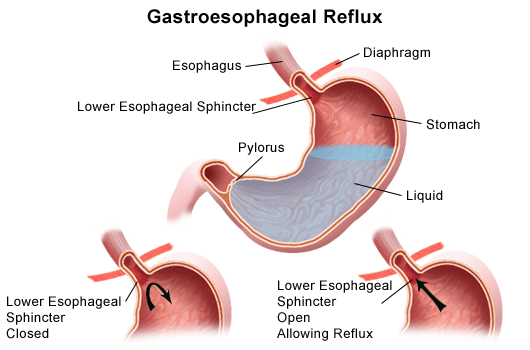
# Epidemiology

* Most common in people over \_\_\_ years old
* Mortality rare but high morbidity
* Prevalence difficult to assess
  + 10-20% of people in Western countries
  + Not much difference between men and women

**Pathophysiology**

* Gastric acid contents
  + Acid- low pH (around 1-2); saliva keeps pH of esophagus around 7
    - Principle stimulants of acid secretion- histamine, gastrin, and acetylcholine
  + Pepcin- proteolytic enzyme
  + Bile acids- solubilizes fat
  + Pancreatic enzymes- digest fats, proteins, and starches
* Abnormal reflux of gastric contents
  + Defective lower esophageal sphincter
    - LES is usually in a tonic contracted state preventing reflux
    - Relaxes during swallowing to allow food to pass into stomach
    - Three types of LES defects may be present

1. LES relaxation independent of swallowing
2. Increase in intra-abdominal pressure can overcome weak LES
3. Atonic LES permits free reflux



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| --- | --- | --- | --- |
| Risk factors/ Mechanism | **Decreased LES pressure** | **Direct irritants to esophageal mucosa** | **Other** |
| **Foods** | Fatty foods, garlic, onions, peppermint/spearmint, chili peppers, chocolate, coffee, tea, cola | Spicy foods, tomato juice, orange juice, coffee |  |
| **Medications** | Anticholinergics, nitrates, DHP CCBs, caffeine, theophylline, barbiturates, progesterone, estrogen | Bisphosphonates, iron, aspirin, NSAIDS, potassium chloride, quinidine |  |
| **Lifestyle** | Alcohol |  | Overweight, bad posture, tight clothes, cigarette smoking |

**Symptoms/Clinical Features**- symptoms do not predict severity of esophagitis nor do they predict complications

**Typical Symptoms**

Often worsen with bending over, recumbent position, or high-fat meal; relieved by antacids:

**Atypical Symptoms**

Sometimes may be the only symptoms, makes GERD difficult to recognize as the cause:

**Alarm symptoms** suggest complications of GERD (**Barrett’s esophagus, esophageal stricture, esophageal CA**):

**Complications**

* Barrett’s esophagus- columnar metaplasia of the lower esophagus
  + Orange, gastric- type epithelium that extends upward from the stomach in a tongue-like or circumferential fashion
  + Results from chronic reflux-induced injury to the esophageal epithelium
  + More prevalent in white adult men
  + Increased risk of esophageal adenocarcinoma (40- fold increased risk)

# GERD Diagnosis

* Based on clinical presentation
  + Type of symptoms, when they occur, what improves or worsens them
  + **It is appropriate to offer empiric treatment to those experiencing typical symptoms of GERD and reasonable to assume a diagnosis in patients who respond to treatment**
* Diagnostic Tests
  + Endoscopy
    - Upper endoscopy also known as esophagogastroduodenoscopy (EGD) with an endoscope: instrument with light and camera (and sometimes biopsy snares) goes in the nose or mouth and down the esophagus
    - Not routine unless the patient:
      * Does not respond to initial treatment
      * Has alarm symptoms at presentation
      * Is at high risk for complications
  + Ambulatory reflux monitoring: small probe in the esophagus measures pH over 24 hours
    - Used in refractory cases prior to surgery/interventional therapies
  + Manometry: small tube through the nose into the esophagus and stomach measures pressures and function of the esophagus
    - Only uses in pre-operative evaluation; no role in GERD diagnosis

# Treatment Goal

* Reduce frequency and severity of symptoms, reduce recurrence, promote healing of mucosa, and prevent complications.

# Treatment Concepts

* **Reduce acid so whatever get into the esophagus causes less damage\***
* Change what goes in
* Reduce what goes in
* Move what goes through the GI tract faster

## Pharmacologic Therapy

**Acid Suppression**- mainstay of GERD treatment

* Antacids- neutralize gastric acid (increases LES pressure)
  + Maalox, Mylanta (aluminum hydroxide, magnesium hydroxide and simethicone, calcium carbonate and magnesium hydroxide), Gaviscon (aluminum hydroxide and magnesium carbonate or trisilate), Tums (calcium carbonate)
  + Provide immediate symptom relief
  + Short half-life
  + **Adverse effects**: diarrhea, or constipation, absorption alterations, acid-base disturbances
  + **DDIs**: Decreased absorption/effect of: ferrous sulfate, quinolones, isoniazid, tetracycline, raltegravir
  + Monitoring: GERD symptoms
* H2 (histamine-2) receptor antagonists (H2RAs)- inhibit histamine at H2 receptors of the gastric parietal cells, which inhibits gastric acid secretion
  + Famotidine, ranitidine, nizatidine, cimetidine
  + Effective in treating mild to moderate GERD
  + Slower onset than antacids but longer duration
  + Chronic use may lead to tachyphlaxis
  + **Adverse effects** (rare): headache, somnolence, dizziness, fatigue, constipation or diarrhea
  + **DDIs**: H2RAs can increase levels of delayed-released risedronate and decreased the concentration of Rilpivirine
  + \_\_\_\_\_\_\_\_\_\_\_\_\_- may inhibit metabolism of warfarin, phenytoin, nifedipine, propranolol, theophylline, and others
  + Monitoring parameters: GERD symptoms, renal function if impaired or unstable
* Proton pump inhibitors- suppress gastric acid secretion by inhibiting the parietal cell H+/K+ ATP pump.
  + Omeprazole and omeprazole/sodium bicarbonate, esomeprazole, lansoprazole, pantoprazole, rabeprazole, dexlansoprazole
  + Agents are generally considered interchangeable
  + Superior in treating patients with moderate to severe GERD
  + Eliminate symptoms and heal esophagitis more frequently and more rapidly than other treatments
  + Best taken on empty stomach (30-60mins before a meal). Exception: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_. If BID, 2nd dose before evening meal.
  + Takes a few days for maximum acid suppression
  + Esomeprazole (S-isomer of omeprazole)
    - Slower metabolism than omeprazole
  + Dexlansoprazole (R-isomer of lansoprazole)
    - Dual delayed release (peaks at 1-2 hrs after administration then again at 4-5 hrs after administration)
    - Unknown comparative efficacy
  + Omeprazole/sodium bicarbonate
    - Immediate–release
    - More effective control of nocturnal pH vs other PPIs
    - 20 mg and 40 mg packets contain the same amount of sodium bicarbonate
  + Dose reduction recommended for \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_. No change in the elderly or renal failure.
  + **Adverse effects**: headache, somnolence, dizziness, nausea, constipation or diarrhea. Vitamin B12 deficiency with long-term use in elderly and high-risk patients. More below!
  + **DDIs**: All PPIs can reduce absorption of drugs which require an acidic environment to be absorbed such as itraconazole, rilpivirine, and atazanavir
  + Metabolized by cytochrome P450 system; 2C19 and 3A4
  + **Omeprazole is a strong inhibitor of 2C19**- DDI with clopidogrel(needs 2C19 to convert to active form)
  + Other DDIs are minor
    - Omeprazole- decreases clearance of diazepam, phenytoin, and warfarin (no significant interaction with esomeprazole)
    - Omeprazole interactions may be of more concern in “slow metabolizers,” more common in Asian population, 3% of Caucasians
    - Lansoprazole- small decreased in theophylline concentration
    - Pantoprazole, rabeprazole- no major CYP interactions
  + Monitoring parameters: GERD symptoms. Baseline and periodic Mg level with long-term use.

**Practice Case Revisited**

Mr. B. says, “I have horrible heartburn every day. I hate the minty taste of the Tums my wife bought and they don’t help much anyway. It really burns in my throat a lot. It’s really bad when I bend over at work and when I’m lying in bed at night. It hurts to swallow sometimes. What can I take?”

# Long-term Safety Concerns with PPI therapy

New data available recently

* Hypomagnesemia
  + Proposed mechanism(s): In some patients PPIs interfere with the transport of magnesium across the intestinal wall or cause excessive loss of magnesium in the intestine
  + *Bottom line:* 3/11 FDA update: PPI’s can cause low magnesium levels leading to serious adverse events in prolonged use (> 1 year)
* Community and hospital-acquired pneumonia
  + Proposed mechanism(s): Increased gastric pH allows more bacteria to grow
  + *Bottom line:*
* *Clostridium difficile*
  + Proposed mechanism(s): reduced gastric acidity changes the normal GI flora
  + *Bottom line*:
* Osteoporosis and fractures:
  + Proposed mechanism(s): H+/K+ ATPase pump indirectly inhibits bone resorption, increased pH reduces Ca+ absorption
  + *Bottom line:*

# GERD Treatment: determined by disease severity

### **Mild to moderate symptoms**

* **Antacids** 
  + Maalox or Mylanta 30mL PO prn or after meals and HS
  + Gaviscon 2 tabs PO after meals and HS
  + Calcium carbonate 500mg, 2-4 tablets PO prn

#### *AND/OR*

* **OTC H2-antagonists** 
  + Famotidine 10mg PO daily up to BID (or maximum strength 20mg)
  + Ranitidine 75mg PO daily up to BID (or maximum strength 150 mg)
  + Nizatidine 75mg PO daily up to BID
  + Cimetidine 200mg PO daily up to BID

#### *OR*

* **OTC PPI** (if using OTC PPI **continuously for two weeks**, f/u with physician if still having symptoms to r/o complications and evaluate for further workup)
  + Omeprazole 20mg PO daily
  + Lansoprazole 15mg PO daily

### **Frequent or severe symptoms**

* **Rx PPI once daily dosing (*Treatment of choice*)**
  + Omeprazole 20mg PO daily
  + Rabeprazole 20mg PO daily
  + Lansoprazole 30mg PO daily
  + Pantoprazole 40mg PO daily
  + Esomeprazole 20mg PO daily
  + Dexlansoprazole 30mg PO daily

#### *OR*

### **Rx H2-antagonist**

### Famotidine 20mg PO BID

### Ranitidine 150mg PO BID

### Nizatidine 150mg PO BID

### Cimetidine 400mg PO BID

### **Healing of erosive esophagitis**

* **Rx PPI once daily** (8 weeks)
  + Omeprazole 20mg PO daily
  + Rabeprazole 20mg PO daily
  + Lansoprazole 30mg PO daily
  + Pantoprazole 40mg PO daily
  + Esomeprazole **20-40mg** PO daily
  + Dexlansoprazole **60mg** PO daily

**Patient Directed Therapy**

* Patient can seek therapy on his/her own in the absence of alarm or atypical symptoms

# Renal Dosing for H2RA

* All H2RA require dose reduction with CrCl < 50 mL/min

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| **H2RA** | **Typical Dose** | **Renal Dose**  **(CrCl < 50mL/min)** |
| Famotidine | 20 mg BID | 10 mg BID or  20 mg daily |
| Ranitidine | 150 mg BID | 150 mg daily |
| Nizatidine | 150 mg BID | 150 mg daily |
| Cimetidine | 400 mg BID | 200 mg BID or  400 mg daily |

# Maintenance Therapy, Refractory Cases, and Clinical Pearls

* Patients with mild reflux disease can use most therapies
* PPIs are superior for acute healing and preventing relapse
* A PPI is the treatment of choice for maintenance in moderate and severe GERD
  + Use the lowest effective dose
* Suboptimal response or refractory GERD
  + Optimize PPI therapy: compliance, appropriate dosing, consider PPI switch, consider twice-daily dosing
  + Add an evening dose of H2RA
  + Further work-up by physician

**Discontinuing GERD Therapy**

* Many patients will relapse if acid suppression therapy is withdrawn. Continue therapy if:
  + Patient has symptoms after therapy is discontinued
  + Patient has GERD complications
* Consider tapering when discontinuing a PPI that has been used for > 2-3 months
* Consider on demand or intermittent dosing of PPI

**Adjunctive Therapies for GERD**

**Prokinetics**- considered in refractory patients or in patients with known motility defect

* Metoclopramide (Reglan, Metozolv ODT), typical dose: 10-15 mg po up to four times daily, 30mins before meals or food and at bedtime
  + Dopamine antagonist
  + Increases LES pressure
  + **Adverse effects**: bradycardia, CHF, fluid retention, hyper/hypo-tension, drowsiness/fatigue, restlessness, acute dystonic reactions, headache, insomnia, seizure, drug-induced Parkinson’s disease, EPS including tardive dyskinesia, agranulocytosis, neutropenia, diarrhea, nausea
    - Black box warning: tardive dyskinesia
  + **Contraindications/precautions**: GI obstruction, perforation or hemorrhage, history of seizures, Parkinson’s disease, pheochromocytoma, or concomitant use of other dopamine antagonists or anticholinergics

**Skeletal Muscle Relaxant**- considered an alternative in refractory patients

* Baclofen (Lioresal), typical dose 5-20 mg three times daily
  + GABA(b) agonist
  + Reduces transient LES relaxations and reflux episodes
  + Adverse effects: dizziness, somnolence, constipation
  + Efficacy shown in two short-term RCTs; not FDA approved for GERD

# Non-pharmacologic treatment/Lifestyle modifications: Recommend patient specific lifestyle modifications in addition to drug treatment; they are not curative on their own.

* Elevate the head of the bed (6-8 inch blocks under head of bed or foam wedge) if + nocturnal symptoms\*
* Weight reduction if overweight or obese\*
* Avoid alcohol
* Avoid tight clothes
* Discontinue drugs that may worsen GERD (if possible)
* Take irritating drugs with plenty of liquid if they cannot be avoided
* Food changes
  + Consider selective avoidance of foods that may worsen GERD
  + Eat smaller meals
  + Avoid recumbency or sleeping for 2-3 hours postprandially
  + Eat a protein-rich diet

# Other therapies

# Surgery: Laproscopic fundoplication or bariatric surgery if obese

* + Not generally recommended in patients who don’t respond to PPI therapy
  + As effective as drug therapy in carefully selected patients
  + Considered in patients who fail pharmacologic therapy, have complications of GERD, or those who have atypical symptoms
  + Reestablishes the antireflux barrier
  + Long-term efficacy is uncertain

# Endoscopic therapies

* + Less invasive than traditional surgery
  + Long-term efficacy is uncertain

**Special Situations**

* Barrett’s esophagus
  + Long-term PPI treatment
* Nocturnal acid breakthrough
  + Drop of pH below 4 for at least 1 hour between 10pm-6am. Occurs in about 70% of PPI-treated patients, even those on BID therapy. Implications unknown

# GERD in pregnancy

* Heartburn/GERD in pregnancy- symptoms affect 40-85% of pregnant women

# Antacids: First-line therapy

* + H2RAs: 2009 Meta-analysis suggest H2RAs are safe to use in pregnancy. All are pregnancy category B.
  + PPIs: 2009 Meta-analysis suggest PPIs are safe to use in pregnancy. All are pregnancy category B except omeprazole which is category C.

# Pharmacists Role

* Assess patient’s symptoms
  + Determine if patient-directed therapy is appropriate or if patient should be evaluated by a physician
    - Obtain thorough drug history including OTCs and herbals
  + Help patient monitor effectiveness of therapy
    - Frequency and severity of symptoms
* Provide education
  + Lifestyle modifications
  + How to take medications
  + Encourage compliance for best results
  + Adverse effects and drug-drug interactions
  + Alarm signs
* Help patients find the most cost-effective treatment options

**Case 1:**

MS, a 53 year-old F comes to the ambulatory clinic for a BP follow-up.

Current meds:

Lisinopril /HCTZ 20/25mg po daily for HTN

Amlodipine 10mg po daily for HTN

Sertraline 25mg po daily for depression

Ranitidine 150mg po BID for GERD (started 6 months ago)

As you are reviewing her meds with her she tells you she recently saw a commercial for Nexium. “It sounds like a better drug than the one I’m taking, doesn’t it?” she asks. When asked about her GERD symptoms she says she hasn’t had any heartburn or belching in over 5 months.

What do you tell MS?

##### Case 2:

DE, a 63 year-old man has just been diagnosed with erosive esophagitis by his GI specialist. He describes his GERD symptoms as burning in his chest and throat particularly at bedtime. He also complains of choking attacks and frequent belching. Which of his medications may be contributing to his symptoms?

Which lifestyle modification(s) would you recommend to DE?

**Case 3:**

JJ comes to the pharmacy during your shift on Wednesday morning. She purchased omeprazole for her GERD symptoms on Tuesday night. “I don’t think this medication I got works. I started it last night and I still have a burning feeling?”

What counseling and/or recommendations can you provide to JJ?

GERD

Typical Symptoms

Atypical or Alarm Symptoms

Refer for Evaluation

Mild and/or Infrequent

Moderate to Severe and/or Frequent

Antacids

Maalox or Mylanta

Gaviscon

Calcium carbonate

OTC H2RA

Famotidine 10mg PO daily up to BID

Ranitidine 75mg PO daily up to BID

Nizatidine 75mg PO daily up to BID

Cimetidine 200mg PO daily up to BID

OTC PPI

Omeprazole 20mg PO daily

Lansoprazole 15mg PO daily

PPI (Preferred)

Omeprazole 20mg PO daily

Rabeprazole 20mg PO daily

Lansoprazole 30mg PO daily

Pantoprazole 40mg PO daily

Esomeprazole 20mg PO daily

Dexlansoprazole 30mg PO daily

H2RA

### Famotidine 20mg PO BID

### Ranitidine 150mg PO BID

### Nizatidine 150mg PO BID

### Cimetidine 400mg PO BID

Adapted from Applied Therapeutics, 2011.