Gastroesophageal Reflux Disease

Thad Wilkins, MD, MBA, FAAFP

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Dr. Wilkins is a practicing family physician who has been teaching residents and medical students since 1998. He earned his medical degree from the Medical University of South Carolina, Charleston, and completed a family medicine residency at Eglin Air Force Base, Valparaiso, Florida. Subsequently, he completed a faculty development fellowship at the University of North Carolina at Chapel Hill, and earned a Master of Business Administration (MBA) degree from Columbus State University in Georgia. He has contributed numerous articles to American Family Physician on gastrointestinal (GI) topics including colorectal cancer screening, diverticulosis, diverticulitis, irritable bowel syndrome, and hepatitis B and C. As a primary care endoscopist, Dr. Wilkins frequently performs esophagogastroduodenoscopies (EGDs) and colonoscopies for his practice. His research interests include family medicine resident training in flexible sigmoidoscopy, colonoscopy, and EGD. He has also published on his experiences performing office based unsedated ultrathin EGD and esophagoscopy.

Learning Objectives

1. Distinguish between gastroesophageal reflux, dyspepsia, or GERD in patients who present with typical and atypical symptoms.
2. Select appropriate imaging studies to confirm the diagnosis of GERD from dyspepsia and appropriately interpret test results for patients.
3. Screen patients with asthma for symptoms of GERD.
4. Develop collaborative treatment plans for patients with GERD or dyspepsia to include lifestyle modifications and effective medication use, and ensure patient compliance with treatment.
5. Educate parents of infants and children with GERD or dyspepsia on effective feeding strategies and safe medication use.

Audience Engagement System

Step 1

Step 2

Step 3

1. Identify common symptoms of GERD and dyspepsia in patients.
2. Explain the importance of accurate diagnosis in managing GERD and dyspepsia.
3. Discuss the role of lifestyle modifications and medication in the treatment of GERD and dyspepsia.
4. Highlight the importance of patient education in managing GERD and dyspepsia.
Definitions

- Gastroesophageal reflux – some reflux is physiologic (postprandially, short, and asymptomatic)
- Dyspepsia (Rome IV) - one or more of the following: postprandial fullness, early satiation, epigastric pain or burning, and no evidence of structural disease to explain the symptoms
- GERD – symptoms suggestive of reflux or its complications, e.g. dysphagia or odynophagia
- Reflux esophagitis – symptoms of reflux AND endoscopic or histologic evidence of esophageal inflammation

Symptoms

- **Typical Symptoms:** heartburn, acid regurgitation
- **Atypical Symptoms:** wheezing, hoarseness, atypical chest pain
- Diagnosis usually based on history and physical, and trial of empiric therapy

Incidence and Prevalence

- Peak prevalence at ages 30-60 years, more common in women
- Prevalence 10-20% in the Western world (lower prevalence in Asia)
- Most common GI-related diagnosis in the U.S.
- 14% of U.S. population has frequent GERD symptoms

AES POLL QUESTION

What diagnostic test is the best first-line test in a patient with “classical” GERD symptoms determined to be low risk for complications?

A. PPI trial
B. Barium swallow
C. Upper endoscopy
D. Esophageal manometry
E. 24-hour pH monitoring

Diagnostic testing

- Barium radiographs NOT recommended to diagnose GERD (SORT A)
- Upper endoscopy NOT required in patients with typical heartburn and regurgitation symptoms
- Obtain upper endoscopy in patients with alarm symptoms or those at high risk for complications (SORT B)

Diagnostic testing

- Esophageal manometry is recommended in the pre-operative evaluation, e.g. Nissen fundoplication (SORT C)
- Esophageal manometry is NOT recommended in the diagnosis of GERD
- 24-hour pH monitoring is recommended in patients refractory to PPI therapy or when the diagnosis is in question (SORT C)
- 24-hour pH monitoring is NOT recommended in the routine diagnosis of GERD and is NOT required in the presence of Barrett’s esophagus (SORT B)
### Summary of diagnostic testing for GERD

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Indication</th>
<th>Highest level of evidence</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI trial</td>
<td>Classic symptoms and no red flags</td>
<td>Meta-analysis</td>
<td>Negative trial does not rule out GERD</td>
</tr>
<tr>
<td>Barium swallow</td>
<td>Not for GERD, use for dysphagia</td>
<td>Case-control</td>
<td>Not recommended for culprit diagnosis</td>
</tr>
<tr>
<td>Upper endoscopy</td>
<td>Alarm symptoms or screening of high-risk patients</td>
<td>RCT</td>
<td>Not recommended for Barrett's esophagus, non-cardiac CP, unresponsive to PPI</td>
</tr>
<tr>
<td>Esophageal manometry</td>
<td>Pre-operative evaluation</td>
<td>Observational</td>
<td>Not recommended for GERD diagnosis</td>
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</tbody>
</table>

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**Barrett esophagus**

- Systematic review of 26 studies evaluating association between GERD and Barrett esophagus (BE)
- GERD symptoms associated with increased risk of BE (odds ratio 4.9)
- Risk of BE is <1% in patients with chronic GERD symptoms

Am J Gastroenterol. 2010 Aug;105(8):1729
Am J Gastroenterol. 2016 Jan;111(1):30-50

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**Barrett’s Esophagus**

- The risk of developing esophageal adenocarcinoma (EAC) in patients with nondysplastic BE is estimated to be 0.1 to 0.4 percent per year (30-fold higher than the general population)
- All patients with BE should receive treatment with PPIs rather than reserving treatment only for patients who are symptomatic

Am J Gastroenterol. 2016 Jan;111(1):30-50

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**Proton Pump Inhibitors Do Not Reduce the Risk of EAC in Patients with BE**

- Systematic Review and Meta-Analysis. 9 observational studies including 5712 patients with BE
- PPIs found to have no association with the risk of EAC or HGD in patients with BE
- Analysis for duration response relationship revealed no significant trend toward protection against EAC or HGD with PPIs usage for >2-3 years when compared usage for shorter time periods
- No dysplasia- or cancer-protective effects of PPIs usage in patients with BE were identified


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**Esophageal Adenocarcinoma**

- Risk factors: BE, obesity, smoking, and possibly GERD
- 50 to 60% of patients with esophageal cancer present with incurable locally advanced or metastatic disease
- Tumor location and staging determine therapeutic options
- Locoregional disease is treated with curative intent with multimodality therapy (radiation, chemotherapy, with or without surgery)
- Many patients present with metastatic disease, where the goal of therapy is to provide palliation of symptoms

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**Barrett’s Esophagus**

- Screening for BE may be considered in men with chronic (>5 years) and/or frequent symptoms of gastroesophageal reflux and two or more risk factors for BE or EAC
- Risk factors include: age >50 years, Caucasian race, presence of central obesity, current or past history of smoking, and a confirmed family history of BE or EAC (in a first-degree relative)
- Given the substantially lower risk of EAC in females with chronic GER symptoms (when compared with males), screening for BE in females is NOT RECOMMENDED
- If initial endoscopic evaluation is negative for BE, repeating endoscopic evaluation for the presence of BE is NOT RECOMMENDED

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**Testing for *H pylori* Infection is NOT Recommended in GERD Patients**

- Negative association between the prevalence of HP infection and the prevalence and severity of GERD
- BE is more common among individuals who are not infected with HP
- The risk of EAC among patients with BE is lower among those with HP infection
- Testing for *H. pylori* infection is NOT recommended in patients with typical symptoms of GERD who do not have a history of PUD
- However, for those who are tested and found to be infected, treatment should be offered, acknowledging that effects on GERD symptoms are unpredictable

**Screen for GERD in Patients with Poorly Controlled Asthma**

- Reflux during sleep can contribute to nocturnal asthma
- Treatment with PPIs reduce nocturnal symptoms, reduce asthma exacerbations, and improve quality of life related to asthma
- Surgical treatment has been reported to reduce the symptoms of asthma and the requirement for medication
- For patients who have poorly controlled asthma, particularly with a nocturnal component, investigation for GERD may be warranted even in the absence of suggestive symptoms

**Medical management of GERD**

- Avoiding heavy meals, fried food, caffeine, and alcohol
- Avoiding food and drink within 3 hours of going to bed
- Elevating the head of the bed on 6- to 8-inch blocks
- Using appropriate pharmacologic therapy


**Treatment – lifestyle changes**

- Limited evidence regarding lifestyle measures for GERD
- Weight loss if overweight or obese (SORT C)
- Elevate head of bed if regurgitation or heartburn when lying down (SORT C)
Pharmacotherapy

• Acute symptoms
  – Initial Presentation
  • 1st line – Standard-dose PPIs PLUS lifestyle changes
• Chronic symptoms
  – PPI responsive
  • 1st line – continue PPIs
  – Incomplete response to PPIs
  • 1st line - High-dose PPIs PLUS additional testing
  • Adjunct – Add H2 antagonist at bedtime

AES POLL QUESTION

A 52-year-old male with a history of severe esophageal reflux and dysphagia undergoes upper GI endoscopy that reveals a mid-esophageal stricture and severe erosive esophagitis. The stricture is dilated by the gastroenterologist and he recommends long-term proton pump inhibitor therapy.

While long-term proton pump inhibitor therapy should alleviate symptoms of reflux, it may be associated with an increased risk of which one of the following?

A) Helicobacter pylori infection
B) Clostridium difficile infection
C) Type 2 diabetes mellitus
D) Iron deficiency anemia
E) Hypothyroidism

Risks of PPIs

• Increase risk for Clostridium difficile and other enteric infections
• Elderly patients and those with significant comorbid conditions may already be at increased risk
• Studies have not shown an increased risk for iron deficiency, hypothyroidism, Helicobacter pylori infection, or type 2 diabetes mellitus

Treatment - PPIs

• PPIs are more effective for relieving heartburn than H2RA or prokinetic agents (SORT A)
• Different PPIs have similar efficacy at standard doses (SORT A)

PPIs

• Standard-dose
  – omeprazole : 20 mg orally once daily
  – lansoprazole : 30 mg orally once daily
  – pantoprazole : 40 mg orally once daily
  – rabeprazole : 20 mg orally once daily
  – dexlansoprazole : 60 mg orally once daily

• High-dose
  – omeprazole : 20 mg orally twice daily
  – esomeprazole : 40 mg orally twice daily
  – rabeprazole : 20 mg orally twice daily
  – pantoprazole : 40 mg orally twice daily
  – lansoprazole : 30 mg orally twice daily
  – dexlansoprazole : 60 mg orally once daily

On-demand maintenance therapy versus continuous PPI therapy for GERD

• Cochrane review, 6 trials including 1758 participants
• All were from outpatient settings and had non-erosive reflux disease or mild esophagitis on EGD
• There was a 71% increase risk of lack of symptom control with on-demand versus continuous PPI therapy (5 trials, n=1653)
• There was a clinically significant reduction in PPI pill use per week with on-demand therapy

Gastroenterology 2008 Oct;135(4):1383
AES POLL QUESTION

A 68-year-old female with diabetes mellitus, coronary artery disease, fibromyalgia, and dyspepsia presents for follow-up. She has been taking omeprazole (Prilosec) for 10 years. It was started during a hospitalization, and her symptoms have returned with previous trials of discontinuation.

Which one of the following adverse events is this patient at risk for as a result of her omeprazole use?
A) Hypermagnesemia
B) Urinary tract infections
C) Nephrolithiasis
D) Hip fractures

Potential risks associated with PPIs

- Patients with known osteoporosis can remain on PPI therapy (SORT C)
- Increased fractures of the hip, wrist, and spine (SORT B)
- Community-acquired pneumonia (SORT B)
- Clostridium difficile and other enteric infections (SORT C)
- Hypomagnesemia (SORT B)
- PPIs may also affect the absorption of vitamins and minerals, including iron, vitamin B12, and folate (SORT C)

Concomitant users of PPIs and clopidogrel therapy

- PPI therapy does not need to be altered in concomitant clopidogrel (Plavix) users
- FDA issued warning in 2009 regarding potential for increased adverse cardiovascular risk in concomitant users of PPIs and clopidogrel
- Antiplatelet activity of clopidogrel requires activation by CYP 2C19, the same pathway required for metabolism of some PPIs (omeprazole, lansoprazole, and esomeprazole)
- Subsequent studies (2 RCTs and meta-analysis) failed to show evidence that PPIs increase the risk of adverse events in patients receiving clopidogrel

Treatment – H2RA

- Less effective than PPIs (less expensive than PPIs)

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Adult dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>nizatidine</td>
<td>Axid</td>
<td>150 mg twice daily</td>
</tr>
<tr>
<td>ranitidine</td>
<td>Zantac</td>
<td>150 mg twice daily</td>
</tr>
</tbody>
</table>

Lack of Evidence for additional bedtime H2RA to daily PPI therapy

- Cochrane review involving 8 small RCTs
- The addition of bedtime H2RA (to daily PPI therapy) decreased the prevalence rate of nocturnal gastric acid breakthrough
- Authors did not recommend bedtime H2RA until large-scale RCTs with long-term followup to determine the effectiveness and safety

Medical versus surgical treatment

- Medical treatment as effective as surgery (SORT B)
- Surgery
  - Laparoscopic fundoplication increases quality of life in patients with GERD but many patients still require medication after surgery (SORT B)
- Endoscopic procedures
  - May reduce symptoms in patients with GERD
Medical versus surgical treatment
- Cochrane review of 4 trials involving 1232 randomized participants
- All 4 studies reported improved GERD-specific QOL after surgery compared to medical therapy
- Heartburn, reflux, and bloating improved after surgery compared to medical therapy
- Low risk of postoperative complications, e.g. dysphagia
- Costs are significantly higher with surgery compared to medical therapy (at least in the short-term)

Medical versus surgical treatment
- Cochrane review, 4 RCTs, 1160 participants
- Quality of evidence was low or very low
- None of the trials reported long-term health-related quality of life (HRQoL) or GERD-specific quality of life (QoL)
- Considerable uncertainty in the balance of benefits versus harms of surgery compared to long-term treatment with PPIs

Practice Recommendations
Adults
- Obtain upper endoscopy in patients with alarm symptoms or those at high risk for complications (SORT B)
- Strong evidence supports association of GERD and esophageal adenocarcinoma with Barrett esophagus as precursor lesion (SORT A)
- PPIs are more effective for relieving heartburn in short-term than H2RA or prokinetic agents (SORT A)

Practice Recommendations
Adults
- Different PPIs have similar efficacy at standard doses (SORT A)
- Patients with known osteoporosis can remain on PPI therapy (SORT C)
- Concomitant use of PPIs and clopidogrel appears safe (SORT B)

AES POLL QUESTION
3-month-old male with frequent “spitting-up” after feedings. Parents deny that he has increased irritability, poor feeding, blood in stool, or weight loss. Which of the following is not recommended?

A. Provide smaller feedings
B. Thicken feeds
C. Keep infant upright for 10-20 minutes after feeding
D. Start omeprazole

GERD
Infants and Children
Background - Infants
- Extremely common in healthy infants
- Regurgitation was most common around four months (61%), decreasing to 21% between six and seven months
- Frequent episodes of regurgitation during infancy may be associated with an increased likelihood of having GERD symptoms in later childhood
- GERD in children occasionally causes esophageal strictures or Barrett’s esophagus.
- Weakly associated with sinusitis, otitis media, laryngitis, and asthma

Clinical approach - Infants
- Determine if symptoms are caused by underlying pathological disease
- Assess for red flags: failure to thrive, weight loss, feeding refusal, irritability, or occult blood in the stool
- Reflux is uncomplicated (majority of infants)
- Uncomplicated GER: infant with good weight gain, feeds well, and is not unusually irritable and no red flags

Treatment - Infants
- Limit exposure to tobacco smoke
- Provide smaller feedings to reduce the frequency or quantity of reflux
- Remove cow’s milk from the diet for infants with problematic (GER)
- Continue breast feeding if practicable
- Modest benefit of thickened feeds
- Keep infant upright for 10-20 minutes after feeding

Pharmacotherapy - Infants
- Not indicated for infants with uncomplicated reflux (GER)
- PPI preferred over H2RA (Off label use, only approved for use in infants >1 yr of age)
- Possible safety concerns with use of PPIs (short-term acid rebound, and increased risks for pneumonia and diarrhea)
- Cimetidine approved for neonates, ranitidine approved for use in infants >1 month of age
- Prokinetic agents have a minimal role in infants

Pharmacotherapy - Children
- Omeprazole, esomeprazole, and lansoprazole extensively studied in children and approved by FDA
- Data on the long-term safety of PPIs is from studies in adults
- Try H2RA for children with mild or intermittent symptoms
- Increased risk of C. difficile and community-acquired pneumonia with H2RAs and PPIs
- Concern for vitamin B12, iron malabsorption, and hypomagnesemia with PPIs

Practice Recommendations
- PPIs and H2RAs are reasonably safe and effective for treatment of GERD (not GER) (SORT C)
- Prokinetic agents have limited efficacy and significant safety concerns and are NOT recommended for the routine treatment of children with GER or GERD (SORT B)
- In children with esophagitis, use pharmacotherapy and lifestyle changes, PPIs preferred over H2RAs (SORT C)
Questions

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