

Gastroesophageal Reflux Disease

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Gastroesophageal Reflux Disease

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Continuing Education Activity

Gastroesophageal reflux disease (GERD) is a condition that develops when there is a retrograde flow of stomach contents back into the esophagus. It can present as non-erosive reflux disease or erosive esophagitis. This activity illustrates the evaluation and treatment of GERD and highlights the role of the interprofessional team in improving care for patients with this condition.

Objectives:

- Explain the pathophysiology of gastroesophageal reflux disease.
- Describe the signs and symptoms of a patient with gastroesophageal reflux disease.
- Describe the tests used to diagnose gastroesophageal reflux disease.
- Describe the importance of improving coordination among interprofessional team members to enhance the delivery of care for patients with gastroesophageal reflux disease.

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Introduction

Gastroesophageal reflux disease (GERD) is a chronic gastrointestinal disorder characterized by the regurgitation of gastric contents into the esophagus. It is one of the most commonly diagnosed digestive disorders in the US with a prevalence of 20%, resulting in a significant economic burden in direct and indirect costs and adversely affects the quality of life[1][2]. GERD is caused by multiple different mechanisms that can be intrinsic, structural, or both, leading to the disruption of the esophagogastric junction barrier resulting in exposure of the esophagus to acidic gastric contents. Clinically, GERD typically manifests with symptoms of heartburn and regurgitation. It can also present in an atypical fashion with extra-esophageal symptoms such as chest pain, dental erosions, chronic cough, laryngitis, or asthma[3][4]. Based on endoscopic and histopathologic appearance, GERD is classified into three different phenotypes: non-erosive reflux disease (NERD), erosive esophagitis (EE), and Barrett esophagus (BE)[5]. NERD is the most prevalent phenotype seen in 60-70% of patients followed by erosive esophagitis and BE seen in 30% and 6-12% of patients with GERD, respectively. [1][5][6]. Over the years, the mainstay in the management of GERD has been lifestyle modifications, and proton pump inhibitors (PPIs). However, medically refractory GERD is becoming increasingly common, requiring a tailored approach in the management of GERD.

Etiology

Currently, there is no known cause to explain the development of GERD. Over the years, several risk factors have been identified and implicated in the pathogenesis of GERD. Motor abnormalities such as esophageal dysmotility causing impaired esophageal acid clearance, impairment in the tone of the lower esophageal sphincter (LES), transient LES relaxation, and delayed gastric emptying are included in the causation of GERD [7]. Anatomical factors like the presence of hiatal hernia or an increase in intra-abdominal pressure, as seen in obesity are associated with an increased risk of developing GERD [7]. A meta-analysis by Hampel H *et al.* concluded that obesity was associated with an increased risk of developing GERD symptoms, erosive esophagitis, and esophageal carcinoma [8]. The ProGERD study by Malfertheiner, *et al.* evaluated the predictive factors for erosive reflux disease in more than 6000 patients with GERD and noted that the odds ratio for the erosive disease increased with the body mass index (BMI) [9]. Several other risk factors have been independently associated with the development of GERD symptoms that include age ≥ 50 years, low socioeconomic status, tobacco use, consumption of excess alcohol, connective tissue disorders, pregnancy, postprandial supination, and different classes of drugs which include anticholinergic drugs, benzodiazepines, NSAID or aspirin use, nitroglycerin, albuterol, calcium channel blockers, antidepressants, and glucagon[10][11][12].

Epidemiology

GERD is one of the most common gastrointestinal disorders, with a prevalence of approximately 20% of adults in western culture. A systematic review by El-Serag *et al.* estimated the prevalence of GERD in the US between 18.1% to 27.8%. However, the true prevalence of this disorder could be higher because more individuals have access to over-the-counter acid, reducing medications[2][13][2]. The prevalence of GERD is slightly higher in men compared to women[14]. A large meta-analysis study by Eusebi *et al.* estimated the pooled prevalence of GERD symptoms to be marginally higher in women compared with men (16.7% (95% CI 14.9% to 18.6%) vs. 15.4% (95% CI 13.5% to 17.4%)[12]. Women presenting with GERD

symptoms are more likely to have NERD than men who are more likely to have erosive esophagitis[15]. However, men with longstanding symptoms of GERD have a higher incidence of Barrett's esophagus (23%) compared to women (14%)[16].

Pathophysiology

The pathophysiology of GERD is multifactorial and is best explained by various mechanisms involved, including the influence of the tone of the lower esophageal sphincter, the presence of a hiatal hernia, esophageal mucosal defense against the refluxate and esophageal motility.

Impaired Lower Esophageal Sphincter (LES) Function and Transient Lower Esophageal Sphincter Relaxations (TLESRs)

The LES is a 3-4 cm tonically contracted smooth muscle segment located at the esophagogastric junction (EGJ) and, along with the crural diaphragm forms the physiological EGJ barrier, which prevents the retrograde migration of acidic gastric contents into the esophagus[17]. In otherwise healthy individuals, LES maintains a high-pressure zone above intragastric pressures with transient relaxation of the LES that occurs physiologically in response to a meal facilitating the passage of food into the stomach. Patients with symptoms of GERD may have frequent transient LES relaxations (TLESRs) not triggered by swallowing, resulting in exceeding the intragastric pressure more than LES pressures permitting reflux of gastric contents into the esophagus[18]. The exact mechanism of increased transient relaxation is unknown, but TLESRs account for 48-73% of GERD symptoms[19]. The LES tone and TLESRs are influenced by factors such as alcohol use, smoking, caffeine, pregnancy, certain medications like nitrates, and calcium channel blockers [18].

Hiatal hernia

Hiatal hernia is frequently associated with GERD and can exist independently without causing any symptoms. Nonetheless, the presence of hiatal hernia plays a vital role in the pathogenesis of GERD as it hinders the LES function[20]. Patti et al. reported that patients with proven GERD with or without a small hiatal hernia had similar LES function abnormalities and acid clearance. However, patients with large hiatal hernias were noted to have shorter and weaker LES resulting in increased reflux episodes. It was also pointed out that the degree of esophagitis was worse in patients with large hiatal hernias[21]. A study evaluating the relationship between hiatal hernia and reflux esophagitis by Ott *et al.* demonstrated the presence of hiatal hernia in 94% of patients with reflux esophagitis [22].

Impaired esophageal mucosal defense against the gastric refluxate

The esophageal mucosa comprises various structural and functional constituents that function as a protective defense barrier against the luminal substances encountered with GERD [18]. This defensive barrier can be breached by prolonged exposure to the refluxate, which consists of both acidic gastric contents (hydrochloric acid and pepsin) and alkaline duodenal contents (bile salts and pancreatic enzymes) leading to mucosal damage. The influence of gastroparesis on GERD is unknown. It is believed that delayed gastric emptying contributes to GERD symptoms due to gastric distention and increased exposure to the gastric refluxate[18].

Defective esophageal peristalsis

Normally, the acidic gastric contents that reach the esophagus are cleared by frequent esophageal peristalsis and neutralized by salivary bicarbonate[23][18]. In a prospective study by Diener *et al.*, 21% of patients with GERD were noted to have impaired esophageal peristalsis leading to decreased clearance of gastric reflux resulting in severe reflux symptoms and mucosal damage[24].

Histopathology

The esophageal squamous epithelium serves to function as a protective defense barrier against the retrograde migration of refluxate. Disruption of this epithelial defense is a common phenomenon in GERD and NERD [25]. The histopathological features of GERD are not unique to this condition due to minimal biopsy criteria for diagnosis and varying sensitivity and specificity in the diagnosis[26]. In fact, the histopathologic diagnosis of GERD is made based on an array of microscopic findings that include features of inflammation, basal cell hyperplasia, papilla elongation, and dilatation of intercellular spaces[26].

History and Physical

The typical clinical presentation of GERD is heartburn and regurgitation. However, GERD can also present with various other symptoms that include dysphagia, odynophagia, belching, epigastric pain, and nausea [27]. Heartburn is defined as a retrosternal burning sensation or discomfort that may radiate into the neck and typically occurs after the ingestion of meals or when in a reclined position[28]. Regurgitation is a retrograde migration of acidic gastric contents into the mouth or hypopharynx[28]. GERD presentation is considered to be atypical when patients present with extraesophageal symptoms such as chest pain, chronic cough, asthma, laryngitis, dental erosions, dysphonia, and hoarseness, and globus sensation[3][4].

Evaluation

The diagnosis of GERD is imprecise as there is no gold standard test available. The diagnosis of GERD is made solely based on presenting symptoms or in combination with other factors such as responsiveness to antisecretory therapy, esophagogastroduodenoscopy, and ambulatory reflux monitoring.

Proton pump inhibitor (PPI) trial

GERD can be presumptively diagnosed in most patients presenting with typical symptoms of heartburn and regurgitation [29]. Unless there are no associated alarm symptoms that include dysphagia, odynophagia, anemia, weight loss, and hematemesis, most patients can be initiated on empiric medical therapy with proton pump inhibitors (PPIs) without further investigations with a response to treatment confirming the diagnosis of GERD [29]. However, a meta-analysis published literature by Numans et al. refuted the accuracy of this empiric PPI trial diagnostic strategy [30].

Esophagogastroduodenoscopy (EGD)

Patients presenting with typical GERD symptoms associated with any one of the alarm symptoms should be evaluated with an EGD to rule out complications of GERD. These include erosive esophagitis, Barrett's esophagus, esophageal stricture, and esophageal adenocarcinoma or rule out peptic ulcer disease. Distal esophageal biopsies are not routinely recommended to make a diagnosis of GERD as per the current American College of Gastroenterology (ACG) guidelines [29]. Patients with a high index of suspicion for coronary artery disease presenting with GERD symptoms should undergo evaluation for underlying cardiovascular disease. In contrast, patients presenting with noncardiac chest pain suspected due to GERD should have a diagnostic assessment with an EGD and pH monitoring before initiation of PPIs [31]. Current ACG guidelines recommend against screening for *Helicobacter pylori* infection in patients with GERD symptoms [29].

Radiographic studies

Radiographic studies like barium radiographs can detect moderate to severe esophagitis, esophageal strictures, hiatal hernia, and tumors. However, their role in the evaluation of GERD is limited and should not be performed to diagnose GERD [29].

Ambulatory esophageal reflux monitoring

Medically refractory GERD is increasingly common, and patients often have normal endoscopy evaluation as PPIs are incredibly effective in healing esophagitis caused by the refluxate. Ambulatory esophageal reflux monitoring can assess the correlation of symptoms with abnormal acid exposure. It is indicated in medically refractory GERD and in patients with extraesophageal symptoms suspicious for GERD. Ambulatory reflux (pH or in combination with impedance) monitoring employs the utility of a telemetry pH capsule or a transnasal catheter. It is the only available test that detects pathological acid exposure, frequency of reflux episodes, and correlation of symptoms with reflux episodes [29]. Current practice guidelines recommend mandatory preoperative ambulatory pH monitoring in patients without evidence of erosive esophagitis [29].

Treatment / Management

The goals of managing GERD are to address the resolution of symptoms and prevent complications such as esophagitis, BE, and esophageal adenocarcinoma. Treatment options include lifestyle modifications, medical management with antacids and antisecretory agents, surgical therapies, and endoluminal therapies.

Lifestyle Modifications

Lifestyle modifications are considered to be the cornerstone of any GERD therapy. Counseling should be provided about the importance of weight loss given that underlying obesity is a significant risk factor for the development of GERD, and studies have shown that weight gain in individuals with a normal BMI has been associated with the development of GERD symptoms [32]. Individuals should also be counseled about avoiding meals at least 3 hours before bedtime and maintaining good sleep hygiene as it has been shown that minimal disturbances in sleep are associated with suppression of TLESRs, resulting in decreased reflux episodes [27][33]. Studies have also shown improvement in GERD symptoms and pH monitoring studies with the elevation of the head end of the bed. Diet modification with the elimination of chocolate, caffeine, and spicy foods, citrus, and carbonated beverages in GERD is controversial and is not routinely recommended as per current ACG guidelines [29].

Medical Therapy

Medical therapy is indicated in patients who do not respond to lifestyle modifications. Medical therapy is comprised of antacids antisecretory agents like histamine (H₂) receptor antagonists (H₂RAs) or PPI therapy and prokinetic agents. Currently, there are two US Food and Drug Administration (FDA) approved H₂RAs (famotidine and cimetidine) available in the US and are available over-the-counter. The other commonly used H₂RA known as ranitidine has been recalled as a potential health hazard or safety risk due to an unexpected impurity in the active ingredient. The less commonly known prescription-only H₂RA nizatidine has also been recalled as well due to similar concerns. In the US, there are six PPIs that are currently

available, of which three (omeprazole, lansoprazole, and esomeprazole) are available over-the-counter, and the remaining three (pantoprazole, dexlansoprazole, and rabeprazole) are prescription-only medications. Of the available medical options, PPI therapy is considered to be the most effective for both erosive and non-erosive GERD based on multiple large-scale studies. These studies have also shown improved symptom control, healing of underlying esophagitis, and decreased relapse rates compared to H2RAs [34][35]. ACG guidelines recommend PPI therapy be initiated at once a day dosing before the first meal of the day[29]. Patients with incomplete responses to once-daily dosing can be treated with twice-daily dosing or adjustment of dose timing, specifically in patients with nighttime symptoms [29]. As needed, bedtime administration of H2RAs is recommended for individuals with nighttime symptoms not optimized with maximal PPI therapy[29]. The role of prokinetic agents such as metoclopramide and domperidone in GERD is limited due to lack of data and also due to their profound adverse effects on the central nervous system and cardiovascular system.

Surgical therapy

Patients who present with either medically refractory GERD, noncompliance, or experience side effects with medical therapy, underlying large hiatal hernia, or individuals who desire to discontinue long-term medical treatment can be considered for surgical management[36]. The available surgical options for GERD are laparoscopic Nissen fundoplication, Laparoscopic anterior 180° fundoplication (180° LAF), or bariatric surgery in obese patients[29]. Laparoscopic Nissen fundoplication has been the gold standard surgical treatment in the management of GERD patients. However, given the rapid prevalence of obesity in the United States, gastric bypass surgery is becoming the most common surgical treatment for GERD[29]. It should be considered in obese patients with symptoms of GERD who prefer surgical therapy[27][29][36][29][27]. Current ACG guidelines recommend performing preoperative ambulatory pH monitoring in patients without erosive esophagitis and esophageal manometry to rule out achalasia or undiagnosed scleroderma-like esophagus prior to surgical therapy [29]. Two large meta-analyses comparing medical therapy with surgical therapy reported contrary conclusions with one reporting improvement of symptoms of GERD after surgery compared with medical therapy and the other reporting considerable uncertainty in the benefits of surgical therapy compared to medical therapy [37][37][37]. However, patients undergoing fundoplication are at risk for developing postoperative adverse events that include bloating, which is seen in 15 to 20% of patients, dysphagia, and belching. The most common bariatric surgeries performed are Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric banded plication (LAGP), and sleeve gastrectomy[36]. Studies have shown that the resulting weight loss from surgical management of obesity has had positive effects on GERD. Of all the bariatric surgeries available, RYGB has proven to be the most effective bariatric surgery for reducing GERD symptoms[36]. It is recommended as the bariatric procedure of choice in patients with severe GERD preoperatively[36].

Endoluminal Therapy

In the era of minimally invasive surgery techniques, many different types of endoscopic therapies have been developed for GERD management. Most of them were discontinued after failing to demonstrate long-term efficacy. The current available endoluminal therapies include magnetic sphincter augmentation (MSA) and transoral incision-less fundoplication using the EsophyX (*EndoGastric Solutions, Redmond, WA, United States*)[29]. A recent meta-analysis by Gerson et al. that included data from 233 patients demonstrated that subjects who underwent TIF 2.0 procedure had improved esophageal pH, decreased need for PPIs, and significant improvement in the quality of life at three years after TIF 2.0 procedure [38]. Another prospective study by Testoni et al. demonstrated TIF with EsophyX as an effective long-term treatment option for patients with symptomatic GERD with associated hiatal hernia less than 2 cm. A meta-analysis comparing Nissen fundoplication and magnetic sphincter augmentation that included data from 688 patients with 415 who underwent MSA and the rest who were treated with Nissen fundoplication concluded that MSA was an effective therapeutic option for GERD as short-term outcomes with magnetic sphincter augmentation appeared to be comparable to Nissen fundoplication[39].

Differential Diagnosis

- Coronary artery disease
- Achalasia
- Eosinophilic esophagitis (EoE)
- Non-ulcer dyspepsia
- Rumination syndrome
- Esophageal diverticula
- Gastroparesis
- Esophageal and gastric neoplasm
- Peptic ulcer disease (PUD)

Complications

Erosive Esophagitis (EE)

EE is characterized by erosions or ulcers of the esophageal mucosa[28]. Patients may be asymptomatic or can present with worsening symptoms of GERD. The degree of esophagitis is endoscopically graded using the Los Angeles esophagitis classification system, which employs the A, B, C, D grading system based on variables that include length, location, and circumferential severity of mucosal breaks in the esophagus [40].

Esophageal Strictures

Chronic acid irritation of the distal esophagus can result in scarring of distal the esophagus leading to the formation of a peptic stricture. Patients can present with symptoms of esophageal dysphagia or food impaction. ACG guidelines recommend esophageal dilation and continue PPI therapy to prevent the need for repeated dilations [29].

Barrett Esophagus

This complication occurs as a result of chronic pathological acid exposure to the distal esophageal mucosa. It leads to a histopathological change of the distal esophageal mucosa, which is normally lined by stratified squamous epithelium to metaplastic columnar epithelium. Barrett's esophagus is more commonly seen in Caucasian males above 50 years, obesity, and history of smoking and predisposes to the development of esophageal adenocarcinoma[28]. Current guidelines recommend the performance of periodic surveillance endoscopy in patients with a diagnosis of Barrett's esophagus[41].

Enhancing Healthcare Team Outcomes

The majority of patients presenting with typical symptoms of GERD are usually recognized and managed by primary care providers. Patients with medically refractory GERD and alarm symptoms are generally referred to gastroenterologists. The management of GERD requires an interprofessional approach involving primary care providers, gastroenterologists, otolaryngologists, pulmonologists, bariatric surgeons, and pharmacists. Primary care physicians should obtain a good history to evaluate for any alarm symptoms or intrinsic cardiac causes and should promptly refer patients for further cardiac evaluation. Considering lifestyle modifications are the cornerstone of GERD management, patients should be counseled about weight loss, tobacco and alcohol cessation, and avoidance of late meals. Bariatric surgery should be discussed with morbidly obese patients presenting with GERD symptoms and should be promptly referred for bariatric surgery evaluation. Otolaryngologists and pulmonologists should consider GERD in their differentials when evaluating patients presenting with atypical symptoms that include chronic cough, laryngitis, asthma, and hoarseness. Cases of patients with medically refractory GERD should be discussed in a multidisciplinary approach with the surgeons, pharmacists, and endoscopy nurses. Complications of GERD should be promptly recognized, evaluated, and treated to prevent long-term morbidity. This interprofessional approach helps in the management of GERD, resulting in improved patients outcomes and increased quality of life.

Review Questions

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