Evaluation of the adult with chest pain of esophageal origin

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INTRODUCTION

Recurring substernal chest pain that is not due to cardiac disease is a common clinical problem [1-4]. Recurrent unexplained chest pain can significantly impact patient quality of life and represents a major economic burden because of continued utilization of clinical resources and emergency facilities [5,6].

This topic will review the pathophysiology, etiology, and evaluation of chest pain of presumed esophageal origin. The etiology and evaluation of patients with dysphagia/odynophagia and other common causes of chest pain in primary care practice and in the emergency department are discussed elsewhere. (See "Outpatient evaluation of the adult with chest pain" and "Evaluation of the adult with chest pain in the emergency department" and "Approach to the evaluation of dysphagia in adults", section on 'Symptom-based differential diagnosis'.)

EPIDEMIOLOGY

Among outpatients who present with chest pain, approximately 10 to 30 percent of patients have musculoskeletal chest pain, 10 to 50 percent have a gastrointestinal cause dominated by gastroesophageal reflux disease (GERD), 2 to 10 percent have ischemic heart disease, 5 percent have respiratory conditions, and 2 to 24 percent have psychiatric disorders [7-9]. A meta-analysis found the pooled prevalence of noncardiac chest pain in the community is 13 percent

and is similar in males and females [10]. Considerable heterogeneity in the prevalence exists based on the definition of chest pain and populations assessed.

GERD is the most likely cause for recurring unexplained chest pain of esophageal origin [11]. Approximately 50 percent of patients with recurrent noncardiac chest pain have abnormal esophageal acid exposure [12-14]. As GERD is common in the general population, the detection of increased esophageal acid exposure or reflux esophagitis on endoscopy does not definitively establish GERD as the cause of the chest pain. While an empiric diagnosis of "esophageal spasm" was previously applied to patients with unexplained noncardiac chest pain of esophageal origin, underlying esophageal motility disorders (eg, achalasia, distal esophageal spasm, jackhammer esophagus) are uncommon [12,15,16]. (See "Clinical manifestations and diagnosis of gastroesophageal reflux in adults" and "Distal esophageal spasm and hypercontractile esophagus" and "Achalasia: Pathogenesis, clinical manifestations, and diagnosis".)

ETIOLOGY

Gastroesophageal reflux — Chest pain due to gastroesophageal reflux disease (GERD) can mimic angina pectoris and may be described as squeezing or burning located substernally. It can last minutes to hours, and resolves spontaneously or with antacids. Bitter refluxate and regurgitation may be present. GERD may occur after meals, awaken patients from sleep, and be exacerbated by emotional stress. Tobacco use, obesity, and hiatus hernia are recognized risk factors. (See "Clinical manifestations and diagnosis of gastroesophageal reflux in adults", section on 'Clinical features'.)

Esophageal motility disorder — Patients with an esophageal motility disorder may have retrosternal chest pain that patients may often describe as squeezing retrosternal pain or spasm. Patients with an esophageal motility disorder usually also present with dysphagia for solids and liquids. Patients have esophageal dysphagia characterized by difficulty swallowing several seconds after initiating a swallow and a sensation of food getting stuck at the suprasternal notch or chest. In some cases, patients have symptoms of heartburn or regurgitation. (See "Distal esophageal spasm and hypercontractile esophagus" and "Distal esophageal spasm and hypercontractile esophagus", section on 'Clinical features'.)

Functional chest pain — Functional chest pain is defined as retrosternal chest pain or discomfort and **absence** of associated esophageal symptoms such as heartburn and dysphagia [17]. A cardiac etiology, gastroesophageal reflux, eosinophilic esophagitis (EoE), and major esophageal motor disorders (achalasia, esophagogastric junction outflow obstruction, distal

esophageal spasm, jackhammer esophagus, absent contractility) must be excluded [18]. These criteria must be fulfilled for the last three months, with symptom onset at least six months before diagnosis.

Potential mechanisms underlying functional chest pain include esophageal hypersensitivity and altered cerebral processing of esophageal pain, autonomic dysregulation, and abnormal mechanophysical properties of the esophagus [19,20]. Esophageal hypersensitivity has been defined as the perception of nonpainful esophageal stimuli as being painful, and painful esophageal stimuli as being more painful [21]. Studies using intraesophageal balloon distension have shown that many patients with esophageal hypersensitivity experience their pain at a lower volume of balloon inflation than that found in appropriate control subjects [22-24]. Studies using intraluminal ultrasonography suggest that muscle contractions producing thickening of the esophageal wall may be associated with unexplained chest pain [25]. Studies suggest that esophageal hyperalgesia represents altered central neural processing of the sensory information rather than abnormal receptors within the esophagus [26,27]. Possible mediators include serotonin, bradykinin, tachykinins, and neurotrophins [28].

Gastric volvulus — Paroxysmal chest pain can be a manifestation of a gastric volvulus secondary to a paraesophageal hernia. Acute chest pain from a gastric volvulus is a surgical emergency with associated risks that include ischemic injury of the stomach, bleeding, and perforation. (See "Gastric volvulus in adults".)

Iatrogenic esophageal injury — Esophagitis may be related to caustic injury, pill esophagitis, chemotherapy, endoscopic procedures, esophageal surgery, and radiation injury. Patients with pill-induced or acute radiation esophagitis may present with sudden onset retrosternal chest pain in addition to marked odynophagia. Esophageal variceal band ligation, endoscopic mucosal resection, and ablation therapies for Barrett esophagus often produce chest pain and odynophagia. Chest pain following surgical fundoplication can be due to recurrent GERD or dehiscence of the fundoplication. Chest pain and odynophagia are common following esophageal dilation of long esophageal strictures, such as seen with EoE, and are usually related to deep mucosal tears rather than overt esophageal perforation. (See "Pill esophagitis" and "Overview of gastrointestinal toxicity of radiation therapy", section on 'Esophagitis'.)

Eosinophilic esophagitis — EoE has emerged as one of the most common etiologies for esophageal symptoms, with a prevalence in the United States of approximately 1 per 1250 [29]. Although EoE may mimic GERD in its presentation, with complaints of heartburn or chest pain, most adolescents and adults have symptoms that are dominated by dysphagia and food impaction [17,30]. Isolated chest pain or heartburn are uncommon presentations for EoE. Some patients may identify self-limited food impactions as episodes of chest pain during meals. In

addition, a food-induced immediate response of the esophagus has been identified in a subset of patients with EoE triggered by specific food allergens in the absence of dysphagia events [31]. (See "Clinical manifestations and diagnosis of eosinophilic esophagitis (EoE)" and "Clinical manifestations and diagnosis of eosinophilic esophagitis (EoE)", section on 'Clinical manifestations'.)

Infectious esophagitis — Several viral infectious etiologies may present with primary esophageal involvement, including herpes simplex, HIV, and cytomegalovirus. Odynophagia is typically due to ulcerations that characterize infectious etiologies. (See "Epidemiology, clinical manifestations, and treatment of cytomegalovirus infection in immunocompetent adults", section on 'Gastrointestinal manifestations'.)

Other rare causes — Other causes include lichen planus and lymphocytic esophagitis, which may also cause chest pain, but their clinical presentation is usually with associated dysphagia.

DIAGNOSTIC EVALUATION

The approach to and extent of diagnostic evaluation of a patient with chest pain of esophageal origin is based on the presence or absence of alarm features.

History and physical examination — The initial assessment of patients with chest pain should focus on the exclusion of life-threatening conditions (eg, pulmonary embolism, aortic dissection, esophageal rupture, tension pneumothorax) and acute coronary syndrome [32]. Although the clinical presentation often does not provide adequate clues to distinguish cardiac from esophageal pain, some symptoms that are suggestive but not specific of an esophageal etiology include the presence of associated esophageal symptoms (heartburn, regurgitation, dysphagia, odynophagia) and relief with antacid or antisecretory agent (eg, histamine 2 receptor antagonist or proton pump inhibitor) ingestion [2,33]. The evaluation of chest pain is presented separately. (See "Outpatient evaluation of the adult with chest pain" and "Evaluation of the adult with chest pain in the emergency department" and "Initial evaluation and management of suspected acute coronary syndrome (myocardial infarction, unstable angina) in the emergency department".)

In patients with chest pain of suspected esophageal origin, a detailed history can narrow the differential diagnosis. As examples:

- Pill esophagitis should be suspected in patients with retrosternal pain or heartburn, odynophagia, or dysphagia and a history of ingestion of medications known to cause esophageal injury (eg, tetracycline, doxycycline, aspirin, nonsteroidal antiinflammatory

drugs, potassium chloride, quinidine preparations, iron compounds, bisphosphonates). (See "Pill esophagitis", section on 'Etiology'.)

- Infectious esophagitis typically occurs in immunocompromised patients with marked odynophagia in addition to chest pain. An exception is herpes simplex, which occurs in immunocompetent and immunocompromised hosts.

- Past history of esophageal surgery (eg, antireflux surgery, cancer resection) or recent endoscopic intervention (eg, esophageal dilation, mucosal resection, ablation therapy) identify patients at risk for pain due to iatrogenic esophageal injury.

- Eosinophilic esophagitis (EoE) should be considered in patients with dysphagia in the setting of allergic conditions such as food allergies, environmental allergies, asthma, and atopic dermatitis. (See "Clinical manifestations and diagnosis of eosinophilic esophagitis (EoE)", section on 'Associations with other disorders'.)

- A gastric volvulus is rare but should be suspected in patients with acute symptoms, including pain in the upper abdomen or lower chest associated with severe vomiting (which may become unproductive), particularly in patients with risk factors (diaphragmatic anatomic abnormalities, the most common of which is paraesophageal hernia in adults). The combination of pain, vomiting, and an inability to pass a nasogastric tube, known as Borchardt's triad, is present in as many as 70 percent of patients with acute gastric volvulus.

The physical examination in patients with chest pain of esophageal origin is usually normal. Examination of the abdomen is important to assess for referred pain, with attention to the right upper quadrant, epigastrium, and the abdominal aorta. (See "Evaluation of the adult with abdominal pain".)

Alarm signs and symptoms — Clinical features or alarm symptoms and signs that identify patients who may need early evaluation include:

- Dysphagia
- Odynophagia
- Gastrointestinal bleeding
- Iron deficiency anemia
- Weight loss
- Recurrent vomiting

Patients with alarm features

Imaging in patients with a suspected gastric volvulus — In patients with a suspected gastric volvulus based upon clinical features (acute pain in the upper abdomen or lower chest associated with severe vomiting), we suggest plain radiography as the initial diagnostic test. The classic finding of acute gastric volvulus on plain abdominal radiograph is a single large, spherical gas bubble located in the upper abdomen or chest with an air-fluid level. If the classic features are not present on plain radiography but acute gastric volvulus is suspected, we suggest computed tomography [CT] of the chest/abdomen. CT of the abdomen or chest typically demonstrates a dilated stomach, often abnormally positioned in the chest, and defines other anatomic abnormalities, such as diaphragmatic defects. (See "Gastric volvulus in adults", section on 'Diagnostic evaluation'.)

Early upper endoscopy — An early upper endoscopy (within two weeks) should be performed for the evaluation of chest pain of esophageal origin in patients with alarm features to determine the underlying etiology. Endoscopic findings are frequently related to gastroesophageal reflux disease (GERD) [34]. Endoscopic features (edema, rings, exudate, furrows, stricture) are common in patients with EoE but there is a low sensitivity of endoscopic findings for EoE and variable positive predictive value. Biopsies of the esophagus should be obtained to rule out EoE in patients with chest pain and dysphagia even in the absence of these endoscopic features. (See "Clinical manifestations and diagnosis of eosinophilic esophagitis (EoE)", section on 'Endoscopy'.)

If the upper endoscopy is normal and the symptoms persist, patients should receive an eight-week trial of acid suppression (eg, omeprazole 40 mg once daily or 20 mg twice daily or equivalent) similar to patients without alarm features. In the absence of a symptom response, patients should undergo additional evaluation to exclude other esophageal etiologies with esophageal function testing. (See 'Trial of acid suppression' below and 'Esophageal function testing' below.)

Patient without alarm features

Trial of acid suppression — Given the high prevalence of GERD in patients with recurring chest pain, we use a trial of proton pump inhibitor (PPI) therapy early in the course of evaluation [12,35,36]. We use high-dose PPIs for a period of up to eight weeks for treatment for acid reflux (eg, omeprazole 40 mg once daily or 20 mg twice daily or equivalent) [37]. In patients whose symptoms resolve, the PPI dose can subsequently be lowered to the lowest effective dose to control recurrent symptoms. (See "Medical management of gastroesophageal reflux disease in adults", section on 'Recurrent symptoms'.)

A response to a trial with PPIs is often used to implicate reflux as the cause of noncardiac chest pain. Importantly, symptom response to a PPI is not specific for GERD and occurs with functional heartburn and chest pain. Nevertheless, absence of a convincing symptom response to a PPI trial reduces the likelihood of GERD and an etiology for chest pain. Two meta-analyses have estimated the accuracy of this approach compared with esophageal pH testing or endoscopy as the reference standard, both concluding that a clinical response to a trial of a PPI performs fairly well as a diagnostic test for identifying pathologic reflux in patients with noncardiac chest pain [38,39]. However, a potential problem with these conclusions is the way in which endpoints were defined in the individual trials. A 50 percent decrease in pain is much less specific than complete pain relief; thus, the estimates of specificity may be optimistic. Furthermore, patients included in the primary studies were generally referred to tertiary care centers and had undergone a thorough evaluation for other causes of pain. Whether similar accuracy would be observed in a less selected group of patients with presumed noncardiac chest pain is unclear. An earlier meta-analysis found that a response to a PPI was not an accurate predictor of GERD when GERD was defined by endoscopy or pH studies, but primary studies of patients with noncardiac chest pain were excluded [40].

Additional evaluation in patients who fail PPI trial — In order to determine the underlying etiology in patients who fail to respond to a trial of PPIs, we perform upper endoscopy to rule out esophagitis as well as structural pathology (hiatal hernia). If the endoscopy is normal, we perform **esophageal function testing.** However, some experts perform an upper endoscopy only in patients without a diagnosis following esophageal function testing.

Patients with chest pain of presumed esophageal origin who fail to respond to a trial with PPIs may have continued symptoms due to persistent reflux or reflux hypersensitivity, underlying esophageal motility disorder, or esophagitis. Up to 20 percent of patients have continued acid secretion despite twice-daily dosing of PPIs [41,42]. This includes patients who have no improvement from the outset and those with an initial "false-positive" response representing a placebo effect. (See "Approach to refractory gastroesophageal reflux disease in adults", section on 'Residual acid reflux' and "Non-acid reflux: Clinical manifestations, diagnosis, and management", section on 'Clinical features'.)

Patients with continued symptoms of chest pain or discomfort that is not of burning quality for three months, with symptom onset at least six months before diagnosis, and no evidence of GERD, structural abnormalities of the esophagus, or a primary motility disorder such as achalasia to explain the symptoms, should be diagnosed and treated as functional chest pain. (See 'Etiology' above.)

Esophageal function testing consists of esophageal manometry and an assessment of esophageal pH with either wireless pH monitoring or 24-hour combined esophageal impedance and pH monitoring off or on PPI therapy.

An important caveat to the interpretation of testing is in the attribution of causality of chest pain to GERD. Demonstration of erosive esophagitis on endoscopy or abnormal esophageal acid exposure on pH testing is consistent with GERD but does not prove that GERD is responsible for an individual patient's symptoms. Thus, the clinical presentation and therapeutic response are important considerations in determining the underlying etiology.

Upper endoscopy — Upper endoscopy allows direct visualization of the esophageal mucosa for evidence of esophagitis and for biopsies to be taken for histology. However, upper endoscopy is a low-yield procedure in patients with noncardiac chest pain, with reports indicating that as few as 6 percent of patients have esophagitis [12,21]. The yield may be even lower after a trial of PPI therapy. Endoscopic abnormalities are present in the majority of patients with infectious esophagitis, eosinophilic esophagitis, or inflammatory esophagitis and obviate the need for physiologic testing.

Esophageal function testing

- **Ambulatory pH monitoring** — Ambulatory reflux monitoring should be performed off PPI (two to four days) for diagnosis of GERD. This can be performed with esophageal catheter-based 24-hour pH impedance monitoring to clarify whether persistent symptoms are due to acid or non-acid reflux [43].

  Alternatively, prolonged wireless pH monitoring using a wireless capsule attached to the distal esophagus can record acid reflux events over two to four days and is useful in adults with infrequent symptoms or day-to-day variation in esophageal symptoms. A wireless pH capsule can be attached immediately after a normal endoscopy to streamline the diagnosis evaluation. Acid reflux events can be statistically correlated with symptoms of chest pain. While wireless pH monitoring does not detect non-acid reflux events, such events are uncommon when monitoring is done in the absence of acid suppressant medications. (See "Esophageal multichannel intraluminal impedance testing" and "Non-acid reflux: Clinical manifestations, diagnosis, and management", section on 'Impedance pH testing' and "Approach to refractory gastroesophageal reflux disease in adults", section on 'Patients with impedance-pH results'.)

- **High-resolution esophageal manometry** — Esophageal manometry testing serves to determine if an underlying esophageal motility disorder is a cause of the patient's symptoms. However, a major limitation must be considered. Since diffuse esophageal

spasm is an intermittent motility disorder and since manometry is typically performed when the patient is not having chest pain, this diagnosis cannot be completely excluded with a normal manometry evaluation [44]. (See "Achalasia: Pathogenesis, clinical manifestations, and diagnosis", section on 'Diagnosis' and "Distal esophageal spasm and hypercontractile esophagus", section on 'Diagnostic criteria'.)

- **Other tests** — Impedance planimetry, a catheter-based technology that measures pressure-volume relationships in the esophagus, [45,46] is being increasing applied as a complementary diagnostic tool in the diagnosis and post-therapeutic monitoring of achalasia and other esophageal motility disorders. As the technique is performed during endoscopy, further validation of the analysis paradigms may streamline clinical assessment of esophageal diseases by obviating the subsequent need for esophageal manometry [47].

MANAGEMENT

The management of patients with chest pain of esophageal origin depends on the underlying etiology.

Treatment of underlying organic disorder — The management of gastroesophageal reflux disease (GERD), eosinophilic esophagitis (EoE), pill esophagitis, infectious esophagitis, and esophageal motility disorders is discussed separately. (See "Medical management of gastroesophageal reflux disease in adults", section on 'Initial management' and "Treatment of eosinophilic esophagitis (EoE)" and "Oropharyngeal candidiasis in adults" and "Pill esophagitis", section on 'Management' and "Distal esophageal spasm and hypercontractile esophagus", section on 'Management' and "Overview of the treatment of achalasia", section on 'Treatment approach'.)

Functional chest pain — In patients with functional chest pain of esophageal origin, we use low doses of tricyclic antidepressants as these may attenuate abnormal sensory processing of esophageal events and treat coexisting anxiety or depression. We usually begin with nortriptyline or imipramine starting at 10 to 25 mg at night and titrate up after four weeks in patients with no response and no major side effects to 50 mg [48-51]. It may take at least four weeks at the optimal dose for the drug to provide a major benefit. Duration of tricyclic antidepressant treatment is not well established but 6 to 12 months at the lowest effective dose is reasonable if patients are tolerating therapy. The tricyclic antidepressant should then be tapered over two to four weeks before discontinuation (drug holiday). Although data are limited, patients who respond to antidepressants appear to have a durable benefit [52]. Other

neuromodulators (eg, serotonin reuptake inhibitors and serotonin noradrenaline reuptake inhibitors) may also be effective [48,53-56].

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Chest pain (The Basics)")
- Beyond the Basics topics (see "Patient education: Chest pain (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Etiology** – Gastroesophageal reflux disease (GERD) is the most common cause for recurring unexplained chest pain of esophageal origin. Approximately 50 percent of patients with recurrent noncardiac chest pain have abnormal esophageal acid exposure. Other causes of chest pain of esophageal origin include an esophageal motility disorder, non-reflux esophagitis (eg, infectious or medication-induced), gastric volvulus, eosinophilic esophagitis, and functional chest pain of presumed esophageal origin. (See 'Epidemiology' above and 'Etiology' above.)
- **Initial assessment** – The initial assessment of patients with chest pain should focus on the exclusion of life-threatening conditions that include gastric volvulus, pulmonary embolism, and acute coronary syndrome. Symptoms that are suggestive but not specific of an esophageal etiology include the presence of associated esophageal symptoms (heartburn, regurgitation, dysphagia) and relief with antacid or antisecretory agent (eg,

histamine 2 receptor antagonist or proton pump inhibitor [PPI]) ingestion. (See 'Diagnostic evaluation' above and "Outpatient evaluation of the adult with chest pain".)

- **Alarm features** – Clinical features or alarm symptoms and signs that identify patients who may need early evaluation include (see 'Alarm signs and symptoms' above):
  - Dysphagia
  - Odynophagia
  - Gastrointestinal bleeding
  - Iron deficiency anemia
  - Weight loss
  - Recurrent vomiting
- **Diagnostic evaluation** – The approach to and extent of diagnostic evaluation in a patient with chest pain of esophageal origin is based on a history of prior esophageal surgical or endoscopic intervention and the presence or absence of alarm features:
  - **Patients with alarm features** – In patients with a suspected gastric volvulus (acute pain in the upper abdomen or lower chest associated with severe vomiting), we suggest plain radiography as the initial diagnostic test. We perform early upper endoscopy (within two weeks) in patients with alarm features. Biopsies of the esophagus should be obtained to rule out eosinophilic esophagitis in patients with chest pain and dysphagia even in the absence of these endoscopic features. Patients are managed based on the results of upper endoscopy. If the early upper endoscopy is negative, patients are managed similarly to those without alarm features. (See 'Patients with alarm features' above.)
  - **Patients without alarm features** – In the absence of alarm features, patients with chest pain of presumed esophageal origin should be treated with an empiric trial of PPIs for eight weeks. Patients with chest pain of presumed esophageal origin who fail to respond to a trial with PPIs may have continued symptoms due to persistent reflux or reflux hypersensitivity, underlying esophageal motility disorder, or esophagitis. Further evaluation with upper endoscopy, pH monitoring, and esophageal manometry can distinguish between these causes. (See 'Patient without alarm features' above.)
- **Diagnosis of functional chest pain** – Patients with continued symptoms of chest pain or discomfort that is not of burning quality for three months, with symptom onset at least six months before diagnosis, and no evidence of GERD, structural esophageal abnormalities, or a primary motility disorder to explain the symptoms, should be diagnosed and treated as functional chest pain. (See 'Additional evaluation in patients who fail PPI trial' above.)

- **Management** – The management of chest pain of esophageal origin is based on the underlying etiology. (See 'Etiology' above and 'Management' above.)

  In patients with functional chest pain of esophageal origin, we suggest treatment with a tricyclic antidepressant (**Grade 2C**). These may attenuate abnormal sensory processing of esophageal events and treat coexisting anxiety or depression. We usually begin with nortriptyline or imipramine starting at 10 to 25 mg at night and titrate up after four weeks in patients with no response and no major side effects to 50 mg. Other antidepressant medications are reasonable alternatives. (See 'Functional chest pain' above.)

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