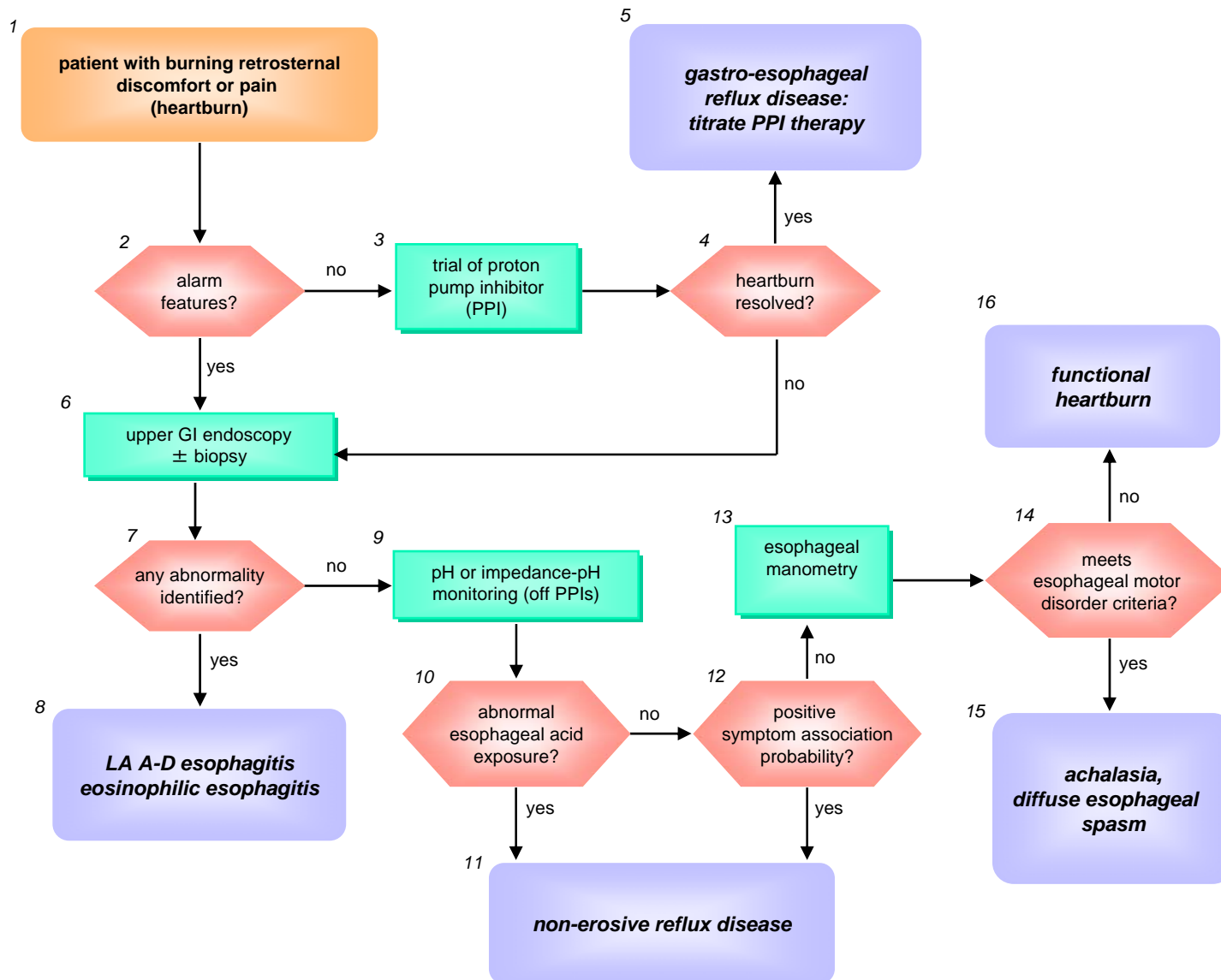


Figure 1: Recurrent heartburn



Recurrent heartburn

Case history

A 34-year old lawyer is referred to a gastroenterologist by her primary care physician because of “therapy-resistant” reflux symptoms. She has suffered for about 5 years with daily episodes of heartburn which has partially responded to treatment with a proton pump inhibitor (PPI), prescribed by her primary care physician. An upper gastrointestinal (GI) endoscopy, carried out 3 years before, had revealed no macroscopic signs of esophagitis and no hiatus hernia.

When the history is taken by the gastroenterologist it becomes clear that the episodes of burning retrosternal pain (Box 1, Fig 1) experienced by the patient last from 10 minutes to some hours, bear no clear temporal relationship to meals, and are not posture-dependent. She does not suffer from regurgitation, or other types of chest pain. There is no dysphagia, odynophagia or other alarm features (Box 2). The use of omeprazole 40 mg daily (Box 3) seems to ameliorate the symptoms somewhat, but the result is described as unsatisfactory, even at a 40mg twice daily dose (Box 4). The patient requests surgical treatment.

The gastroenterologist decides to repeat the upper GI endoscopy (Box 6), after a period of PPI avoidance of 2 weeks. At endoscopy no macroscopic abnormalities are seen (Box 7). No biopsies are taken. 24-hour esophageal pH and impedance monitoring is then undertaken (Box 9). This test is done after the patient discontinues omeprazole for 7 days. Esophageal acid exposure (Box 10) is found to be in the normal range (time with pH < 4: upright 3.2 %, supine 0 %, total 2.3%). During the 24-hour recording 6 symptom episodes are indicated by the patient. None of these are temporally associated with the onset of a reflux episode, neither acid, nor non-acid, leading to a Symptom Association Probability (SAP) of 0% (Box 12). Before placement of the pH/impedance catheter a manometric study was carried out, in order to measure the distance of the lower esophageal sphincter (LES) to the nose (Box 13). During this test, normal esophageal peristalsis and normal LES resting pressure and relaxation were observed (Box 14). A diagnosis of **functional heartburn** is made (Box 16).

Figure Legend

1. It should be noted that heartburn is described quite differently between different cultures and languages. Most descriptions of this symptom include discomfort or burning sensation behind the sternum that may radiate toward the neck. Heartburn is an intermittent symptom, most commonly experienced in the early postprandial periods, during exercise, and while lying recumbent. The discomfort is relieved with drinking water or antacid. The symptom can interfere with normal activities. Epigastric pain or discomfort that does not rise to the retrosternal region should not be called heartburn (1).
2. History and physical examination should look for alarm features suggestive of cancer. This would include evidence of persistent dysphagia, GI bleeding, unintentional weight loss, lymphadenopathy, an epigastric mass, and evidence of anemia.
3. There is no convention for the dosage, duration, or specific drug to be used in a PPI trial for heartburn, making it reasonable to treat with a standard once daily dose for two weeks (11).
4. If insufficient response is achieved with standard dose PPI, this should be increased to twice daily for at least 2 weeks before considering it a treatment failure.
5. Once a satisfactory response has been achieved, the PPI dosage should be reduced to the lowest amount that is still associated with a satisfactory treatment effect.
6. Biopsies should be obtained at the time of endoscopy if there are any visual abnormalities suggestive of metaplasia or eosinophilic esophagitis or if dysphagia is an additional presenting symptom. If eosinophilic esophagitis is suspected, 5 mucosal biopsies should be obtained (12-13). Although histological criteria for esophagitis may also be detected (basal cell hyperplasia, rete pegs extending toward surface) these findings lack specificity for gastro-esophageal reflux disease (GERD) (14).

7. Relevant abnormalities at upper GI endoscopy that would exclude a diagnosis of functional heartburn are reflux esophagitis or eosinophilic esophagitis.
8. The Los Angeles Classification of esophagitis is based on the occurrence and extent of visible mucosal breaks in the distal esophageal mucosa. Los Angeles A is the mildest with only short breaks (< 5 mm) confined to folds of the epithelium while Los Angeles D is the most severe with nearly circumferential breaks (15). Eosinophilic esophagitis is often attributable to allergy to ingested (food) or inhaled allergens and defined by finding ≥ 15 eosinophils per high power field in esophageal mucosal biopsies (16).
9. pH or Impedance-pH monitoring is performed after withholding PPI therapy for 7 days to obtain a meaningful assessment of esophageal acid exposure and to provide the greatest chance of finding a positive association between heartburn episodes and reflux events (17-18).
10. The cutoff for abnormal esophageal acid exposure is typically <5%, although this value varies slightly among centers (19).
11. The Rome III definition of non-erosive reflux disease is either abnormal acid exposure or a positive symptom-reflux association in the absence of macroscopic endoscopic signs of reflux esophagitis (20-21).
12. The Symptom Association Probability (SAP) is a statistical test to determine if the co-occurrence of symptoms and reflux events within 2-minute periods is happening by chance or because the two are likely related. An SAP > 95% equates to a $p < 0.05$ that they are related (22). Although some centers use the Symptom Index (SI) to gauge symptom-reflux association, the SI is not a validated method and has no statistical basis (23).
13. It would be preferable to obtain a high resolution manometry (esophageal pressure topography) study if available because of a greater sensitivity in the diagnosis of achalasia (24).

14. For the purposes of establishing a diagnosis of functional heartburn the only two exclusionary diagnoses are achalasia or diffuse esophageal spasm (DES). Other, less severe, peristaltic abnormalities are still consistent with a diagnosis of functional heartburn.

15. Achalasia is defined by absent peristalsis and impaired deglutitive LES relaxation; DES by $\geq 20\%$ of test swallows exhibiting simultaneous or spastic contractions in the distal esophagus (25).

16. **Rome III diagnostic criteria for functional heartburn are: 1) burning retrosternal discomfort or pain, and 2) absence of evidence that gastroesophageal reflux is the cause of the symptom, and 3) absence of histopathology-based esophageal motility disorders, and 4) criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis (26).**