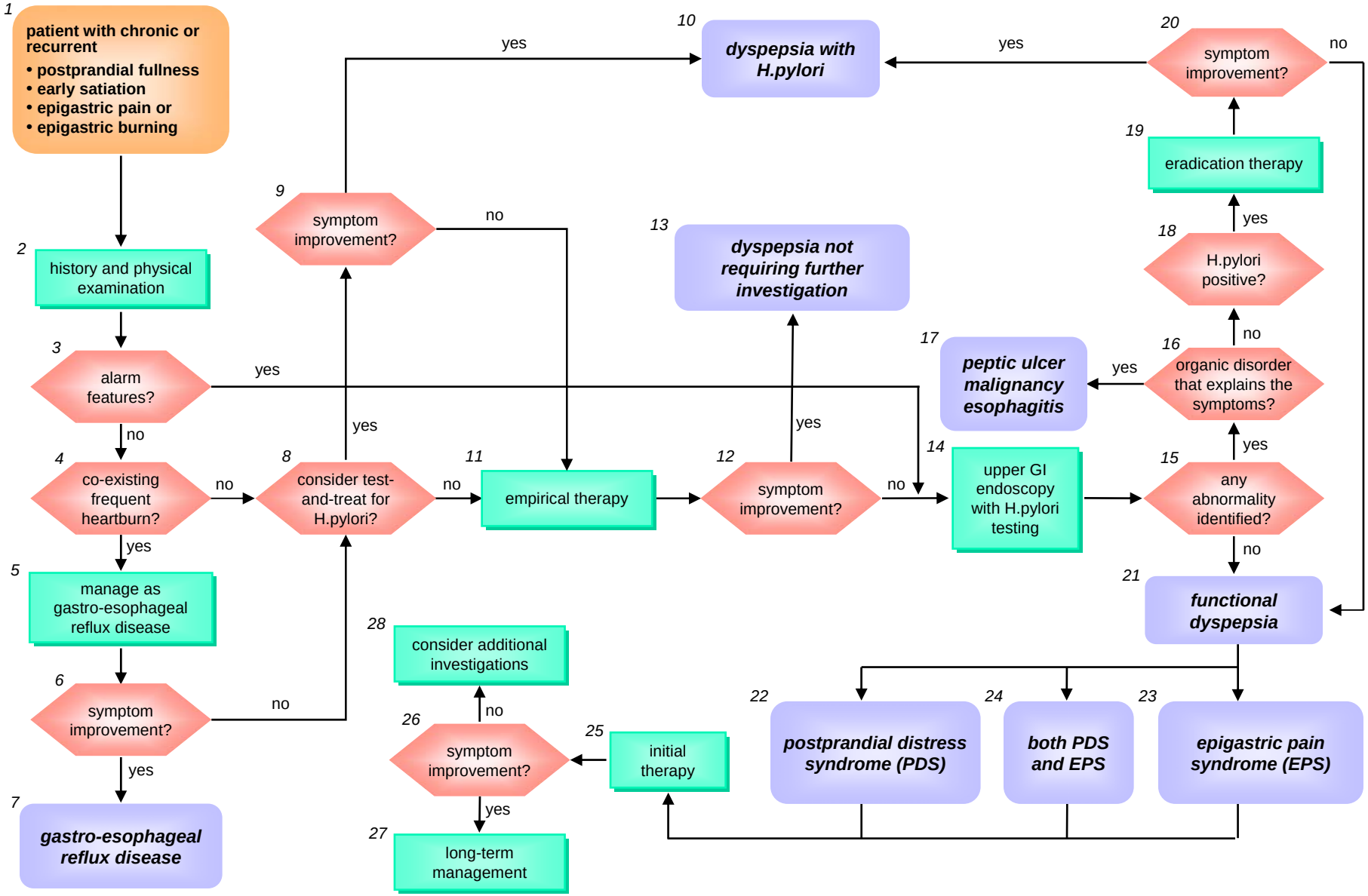
Figure 1: Recurrent dyspepsia



Recurrent dyspepsia

Case history 1

A 38 year old secretary is referred to a gastroenterologist by her primary care physician (PCP) because of epigastric pain which has been present during the last year (Box 1, Fig 1). The pain is located between the umbilicus and the lower end of the sternum. It is intermittent, though present on most days of the week, and lasts between 10 minutes and 2 hours. It is often moderately severe, and described as 'nagging' in character, with no colicky component, and associated with epigastric burning (Box 1). The pain does not radiate up the sternum, nor to the right subscapular region nor through to the back. It is not related to food ingestion, is not associated with nausea or vomiting, and is not relieved by defecation or passage of flatus. Her bowel habit is normal. Occasionally the pain may prevent her from falling asleep but it does not wake her at night (Box 2). She has no dysphagia, weight loss (Box 3), or typical heartburn (Box 4). There is occasional mild postprandial fullness, but this is infrequent and does not occur at the time of the epigastric pain, and there is no early satiation (Box 1), or excessive belching, and rarely does she have upper abdominal bloating.

A similar episode of pain occurred 3 years ago, which was not responsive to antacids. It only lasted for several weeks and then spontaneously disappeared. The patient does not take NSAIDS, is a non-smoker and uses alcohol only sporadically. There are no previous or current medical conditions to explain the pain (Box 2), and she reports no family history of gastrointestinal disease (Box 3). Physical examination is normal (Box 2). Her PCP had arranged blood tests, including a serum test for H. pylori (Box 8), which was negative. She was treated with an H2-blocker for 6 weeks (Box 11), but this did not provide relief (Box 12). The PCP recommended metoclopramide, but there is no clear benefit with this medication.

The gastroenterologist performs an upper gastrointestinal endoscopy (Box 14), which does not reveal any peptic or other lesions, and biopsies from the antrum are negative for H. pylori (Boxes 15-18). A diagnosis of

functional dyspepsia – epigastric pain syndrome (EPS) is made (Boxes 21, 23). Full-dose PPI therapy is prescribed for the next 8 weeks (Box 25).

At the end of this period, the patient reports no improvement in the pain (Box 26), and she feels unable to function properly. She is concerned that the symptoms are continuing despite PPI treatment, and that no abnormality has been found. The condition – functional dyspepsia, epigastric pain syndrome – is explained and the concept of visceral hypersensitivity is discussed as a potential underlying mechanism. The option of starting a low-dose tricyclic agent is proposed, and the disadvantages of other possible strategies such as an increase in the PPI dose (no evidence that this would provide better symptom control), a formal trial with a prokinetic agent (more likely to be effective in PDS), or undertaking additional investigations (unlikely to yield another diagnosis) are discussed (Box 28). The patient agrees to start a tricyclic agent after explanation of the concept of visceral hypersensitivity and the possible beneficial effects of this class of agents.

Case history 2

A 24 year old student is referred to a gastroenterologist because of increasing difficulty tolerating food. She was well until 7 months earlier, when she noticed progressively increasing symptoms of bothersome fullness, early satiation and upper abdominal bloating after meals (Box 1, Fig 1). This was accompanied by an inability to finish a meal of normal size and composition. The fullness and bloating is reported in the region between the umbilicus and the lower end of the sternum, and the experience is clearly different from pain (Box 2). There was no gastroenteritis-like episode prior to the onset of the symptoms. The symptoms improved to some degree when the patient eliminated fatty and spicy foods, and switched to multiple small meals, and this allowed her to maintain a stable body weight. Currently, the symptoms are triggered by, and continue after, every normal-sized meal, and may persist for up to 4 hours. There is no relief with belching, defecation or passage of flatus. Nausea occurs when the symptoms are most intense, but without vomiting (Box 2). She has no dysphagia or weight loss, and there is no heartburn (Box 3, 4). Her bowel habit is normal and unchanged. The patient is a non-smoker and takes alcohol only occasionally. She does not take any regular medications,

including NSAIDs. She has no previous or current medical conditions which may explain the pain (Box 2), and there is no family history of gastrointestinal disease (Box 3).

Physical examination does not reveal any specific abnormalities (Box 2). The patient has tried over-the-counter antacids without any improvement. Her primary care physician arranged blood tests which were reportedly normal. She was treated with a single dose PPI for 8 weeks (Box 11), but this failed to provide any relief (Box 12). The primary care physician referred her to the gastroenterologist.

The gastroenterologist performs an upper gastrointestinal endoscopy (Box 14), which does not reveal any peptic disease or other lesions, and biopsies from the antrum do not reveal H. pylori (Boxes 15-18). A diagnosis of ***functional dyspepsia – postprandial distress syndrome (PDS)*** is made (Boxes 21, 22). A low dose of metoclopramide is prescribed for the next 8 weeks (Box 25).

At the follow-up visit, she reports no benefit from the metoclopramide (Box 26). The gastroenterologist explains that she has functional dyspepsia, postprandial distress syndrome, and discusses the concept of abnormal motility (delayed emptying, impaired accommodation) as a potential underlying mechanism. A therapeutic trial with a prokinetic agent (different specific agents are available in different parts of the world: e.g. domperidone, erythromycin, cleboprid) or a fundus-relaxing agent (e.g. buspirone) is proposed, and the limitations of other possible strategies such as an increase in the PPI dose (no evidence that this would provide better symptom control), a trial with a low-dose tricyclic agent (more likely to be effective in EPS), or undertaking additional investigations such as abdominal ultrasound or gastric motility testing (unlikely to yield another diagnosis or to change management) are discussed (Box 28). The patient agrees to start a prokinetic drug before meals.

Figure legend

1. A patient with one or more of these symptoms is referred to as a patient with dyspepsia. In this context, it is assumed there are no known systemic or organic disorders such as diabetes mellitus or connective tissue disease. When no additional investigations are performed, this condition is referred to as uninvestigated dyspepsia. After additional investigations, in approximately 70% of these patients, no organic cause is identified, and these patients are referred to as patients with functional dyspepsia (see below) (1).

2. A detailed history and clinical examination at the initial visit are essential to both detect the presence of alarm features and to accurately identify the particular dyspeptic symptom or symptoms present (1,2).

3. Alarm features include age, unintentional weight loss, symptoms that awaken the patient at night, dysphagia, lymphadenopathy, abdominal mass and signs of anemia. If any of these is present, prompt endoscopy is indicated, although the yield may be relatively low (3,4).

4. Frequent heartburn is defined as heartburn several times per week. A brief description of heartburn in a few sentences may help the patient to recognize heartburn (1,2).

5. Dyspeptic symptoms may accompany gastro-esophageal disease (GERD) and may often respond to appropriate GERD management, which will generally consist of PPI therapy (5). Also see 'recurrent heartburn' algorithm.

6,7. PPI therapy is expected to relieve heartburn, but may also relieve co-existing dyspeptic symptoms. If this is the case, the patient is considered to have GERD with associated dyspeptic symptoms (1,5,6).

8. The use of test-and-treat strategies for *H. pylori* eradication in uninvestigated dyspepsia is considered standard of care (5,6). Detection of H. pylori by a urease breath or stool antigen test (or less optimally serology) is most likely to be cost effective in the situation where there is high prevalence of H. pylori infection

in the population. The yield of this approach decreases as the population prevalence of *H. pylori* infection decreases, especially when it falls below 20% (5,6).

9,10. If the patient responds symptomatically to eradication therapy, this does not firmly establish H. pylori as the cause of the symptoms. Confounding factors are placebo effect, effects of the PPI included in the eradication regimen, or spontaneous improvement (2,5-7).

11. Empirical therapy choice will be driven by drugs available locally and the restrictions to their use. Antacids, antisecretory drugs or prokinetics can be considered here (5-9).

12,13. Response to empirical therapy does not confirm a diagnosis of functional dyspepsia. Organic causes of dyspepsia, for instance a peptic ulcer, may respond to empirical antisecretory therapy. However, resolution of symptoms abolishes the need for further investigation in most cases. Additional investigation may be considered if the patient is above 50 years of age, or when there are specific risk factors present such as the use of NSAIDs or risks for Barrett's esophagus. Expectant management, without performing endoscopy, in a young patient with no alarm features, can still be considered at this point, even when symptoms have not resolved (10).

14. According to the Rome guidelines(1), an upper GI endoscopy not showing pathology that may explain the symptoms, is the key study for helping to establish a diagnosis of FD. However, this investigation is not indicated in all cases of dyspepsia, as indicated above. Moreover, the impact of recent antisecretory therapy on endoscopic findings and the optimal time window of interrupting failed antisecretory therapy have not been defined.

15. Abnormal findings include either the presence of a relevant organic lesion, or a positive H. pylori test.

16,17. Relevant organic diseases that may present with dyspeptic symptoms include peptic ulcer disease, erosive esophagitis and upper gastrointestinal malignancy. These diseases require specific therapy.

18,19. The role of *H. pylori* infection and the yield of *H. pylori* eradication in case of negative endoscopy are areas of controversy. Meta-analyses indicate a small but statistically significant gain after eradication in those who are *H. pylori* positive, with an estimated number to treat around 15. However, the symptom response is often delayed (9).

20,10. If the patient responds to eradication therapy, this does not establish *H. pylori* as the cause of the symptoms. Confounding factors are placebo effect, effects of the PPI added to the eradication regimen, or spontaneous improvement.

21. Functional dyspepsia is defined as the presence of one or more dyspepsia symptoms that are considered to arise from the gastroduodenal region, in the absence of any organic, systemic, or metabolic disease that is likely to explain the symptoms.

Rome III diagnostic criteria for functional dyspepsia (FD) are: 1) one or more of bothersome postprandial fullness, early satiation, epigastric pain and epigastric burning; 2) no evidence of structural disease likely to explain the symptoms; and 3) criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis (1).

22. Postprandial distress syndrome (PDS) is a subgroup of FD characterized by postprandial fullness and early satiation.

Rome III diagnostic criteria for PDS are: 1) one or both of (i) bothersome postprandial fullness, occurring after ordinary-sized meals, at least several times per week (ii) early satiation that prevents finishing a

regular meal, at least several times per week; and 2) criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis (1).

The presence of upper abdominal bloating or postprandial nausea or excessive belching are supportive of PDS.

23. Epigastric pain syndrome (EPS) is a subgroup of FD characterized by epigastric pain or epigastric burning.

Rome III diagnostic criteria for EPS are: 1) pain or burning localized to the epigastrium of at least moderate severity, at least once per week, 2) the pain is intermittent, 3) not generalized or localized to other abdominal or chest regions , 4) not relieved by defecation or passage of flatus, 5) not fulfilling criteria for gallbladder or sphincter of Oddi disorders; and 6) criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis (1).

Supportive criteria are that the pain is of a burning quality, but without a retrosternal component, and that the pain is induced or relieved by ingestion of a meal, although it may occur during fasting.

24. Many patients have overlap of both EPS and PDS symptoms. The prevalence of overlap of both conditions has been explored in population studies as well as in patient samples, and may comprise up to 50% of the dyspepsia population.

25, 26. Initial therapy choice may depend on the FD subgroup but is all off-label. There is evidence for limited efficacy of PPIs in FD. Based on studies using the Rome II classification, it seems reasonable to suggest that response to PPIs is highest in the EPS subgroup, where this class of medication is the first choice of therapy (1,2,7,8). Evidence for the efficacy of prokinetic drugs is not conclusive, although they seem to be active in subgroups of patients. Based on studies using the Rome II classification, it seems reasonable to suggest that response to prokinetics is highest in the PDS subgroup (1,2,8). As there is no evidence of exclusive actions of PPIs or prokinetic in one of the FD subgroups, switching to the other class of agent or adding it can also be

considered. The optimal approach for overlapping PDS and EPS has not been studied in depth, but a start with a PPI seems reasonable. It is often suggested that a low-dose tricyclic antidepressant can be prescribed for EPS symptoms that do not respond to PPI therapy. In case a prokinetic does not relieve PDS symptoms, a fundus-relaxing drug like for instance buspirone could be considered (2,11).

27. The optimal long-term strategy for FD that responds to initial therapy (maintenance therapy/on demand/interruption) has not been studied (10).

28. Additional investigations can be considered if there is a lack of symptomatic response:

Abdominal ultrasound may help exclude biliary, pancreatic or vascular disease. However, there is no evidence of diagnostic gain with ultrasound, in the absence of symptoms suggestive of biliary tract pathology, like colicky abdominal pain.

Routine blood tests such as full blood count, liver function tests, amylase and lipase, and kidney function tests can also be considered at this stage, if not already performed. There is no clear evidence of the usefulness of such testing in this setting, but many clinicians would consider this at this time. The same applies to thyroid function testing. Especially in high prevalence areas, celiac disease screening can be considered.

Esophageal pH monitoring (patient off PPI) can reveal abnormal findings in a subset of FD patients, mainly those with epigastric pain and burning. However, the role of esophageal pH monitoring in clinical management, and its impact on subsequent management, have not been defined.

Abdominal CT scan enables visualization of the pancreatico-biliary system and to screen for vascular disorders which may mimic FD. It is mainly indicated in case of refractory pain associated with weight loss. Repeated CT scans should be avoided.

The yield of gastric emptying in FD as a group has not been established. However, it may be considered useful in refractory patients, especially if vomiting or weight loss are also present.

Psychosocial problems such as anxiety or depression may also present with dyspeptic symptoms. It is important to consider these early on in the course of investigations, and to obtain expert opinion in case of refractoriness. A useful tool is the *Rome III psychosocial alarm questionnaire* (see Appendix A). Therapeutic trials using antidepressants can be considered with the endpoint of benefit being symptom improvement or improved daily functioning even in the presence of the symptoms. Augmentation therapy combining two psychotropic agents, or a psychotropic agent with psychologic treatment, may be considered in difficult cases who have failed all other therapies, have impaired quality of life and where abdominal pain is a significant component.