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# CLINICAL REVIEW

## Investigating dyspepsia

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Dyspepsia is a complex condition comprising chronic and recurrent symptoms related to the upper gastrointestinal tract. The cardinal symptoms are epigastric pain and discomfort, including postprandial fullness and early satiety, which may overlap with heartburn and regurgitation. Box 1 shows the various definitions of dyspepsia. Around 25-40% of adults in the general population have dyspepsia,<sup>1,2</sup> and dyspepsia accounts for 2-5% of all consultations in primary care.<sup>3</sup> Although several guidelines have been published,<sup>1,2,4-7</sup> the management of patients with uninvestigated dyspepsia is still controversial. One outstanding dilemma is the choice of the most appropriate empirical strategy<sup>8</sup>; the benefit of early endoscopy in older patients without alarm symptoms is also widely debated.<sup>9</sup> Dyspepsia has a substantial economic impact, and appropriate management is essential to reduce costs.<sup>2</sup>

This review examines strategies for managing patients with uninvestigated dyspepsia in primary care. We provide an overview of current guidelines and recommendations and report recent evidence from systematic reviews and clinical trials.

### What is the differential diagnosis in patients with dyspeptic symptoms?

Dyspeptic symptoms can have several organic causes (box 2), but in many patients no obvious cause is identified (functional dyspepsia). Extragastric causes, such as hepatobiliary and pancreatic diseases, are infrequent but important and should always be considered. However, most cases of dyspepsia can be ascribed to one of four causes—gastro-oesophageal reflux disease with or without oesophagitis, peptic ulcer disease, malignancy, and functional dyspepsia. Functional dyspepsia remains essentially a diagnosis of exclusion,<sup>1</sup> and its causes are uncertain. Symptoms are often associated with gastroduodenal motor and sensitivity disorders, but the root causes of these disturbances are unknown.<sup>10</sup> Functional dyspepsia is the most common cause of dyspeptic symptoms, accounting for about 50% of cases. Of the remaining patients, around 20% have endoscopy negative reflux disease, 20% have oesophagitis, 10% have peptic ulcer disease, 2% have Barrett's oesophagus, and 1% have malignancy.<sup>11</sup> Therefore, around two thirds of patients with dyspeptic symptoms have no structural lesions.

### Can dyspeptic symptoms predict the underlying cause of dyspepsia?

Individual dyspeptic symptoms or subgroups of symptoms, such as predominant epigastric pain (ulcer-like) or discomfort (dysmotility-like), poorly predict the presence of underlying organic lesions. A systematic review found that neither primary care doctors nor gastroenterologists could distinguish patients with organic lesions from those with functional dyspepsia on the basis of symptom evaluation.<sup>11</sup>

However, the presence of predominant heartburn and regurgitation may help predict underlying gastro-oesophageal reflux disease. A well conducted clinical study, where 371 patients underwent 24 hour oesophageal pH monitoring, showed that predominant heartburn or regurgitation were good predictors of pathological gastro-oesophageal reflux.<sup>12</sup> International guidelines support the view that uninvestigated patients with dyspeptic symptoms and predominant

#### Box 1 Definitions of dyspepsia

##### Symptoms relating to the upper gastrointestinal tract

Epigastric pain, postprandial fullness, early satiety, heartburn, and regurgitation

##### UK (National Institute for Health and Clinical Excellence)

Dyspepsia—any chronic and recurrent symptoms referable to the upper gastrointestinal tract

##### US (American Gastroenterological Association, American College of Gastroenterology)

Dyspepsia—chronic and recurrent pain or discomfort centred in the upper abdomen (epigastrium). Discomfort is a subjective feeling that is not painful and includes early satiety and postprandial fullness

Patients presenting with concomitant predominant or frequent (more than once a week) heartburn and regurgitation should be considered to have gastro-oesophageal reflux disease until proved otherwise

##### Canada (Canadian Dyspepsia Working Group)

Dyspepsia—chronic and recurrent pain or discomfort centred in the upper abdomen (epigastrium) regardless of whether heartburn and regurgitation are predominant

Patients with heartburn and regurgitation only should be considered to have gastro-oesophageal reflux disease

#### SOURCES AND SELECTION CRITERIA

This review is based on search results of PubMed and the *Cochrane Database of Systematic Reviews*, using the keywords “dyspepsia”, “uninvestigated dyspepsia”, and “upper gastrointestinal diseases” (cut-off date April 2008). We also searched published international guidelines. We identified supplementary studies from our personal reference database and from our knowledge of the current literature

**Sensitivity and specificity of non-invasive *H pylori* tests<sup>26-28</sup>**

Test	Sensitivity (%)	Specificity (%)
<sup>13</sup> C-urea breath test	95	95
Stool antigen test	91	93
Serology	85	79

heartburn or regurgitation can be considered to have gastro-oesophageal reflux disease<sup>1 4-7</sup>; conversely, patients with predominant epigastric pain or discomfort are more likely to have peptic ulcer or functional dyspepsia. However, these criteria have been criticised and have not been accepted by guidelines in the United Kingdom.<sup>2</sup> For instance, a Canadian study of 1040 primary care patients with uninvestigated dyspepsia reported that those with predominant heartburn were as likely as those with predominant epigastric pain or discomfort to have underlying peptic ulcer disease.<sup>13</sup> However, in investigated patients without structural lesions, predominant heartburn or regurgitation can reliably identify those with endoscopy negative reflux disease, whereas those with predominant epigastric pain or discomfort should be considered as having functional dyspepsia.<sup>1 2 4</sup>

**How should I investigate the patient with dyspepsia?**

**Clinical history and physical examination**

A careful clinical history and physical examination will help to exclude non-gastrointestinal causes of dyspeptic symptoms such as the use of drugs (box 2). Lifestyle and dietary factors may also be identified. Obesity, smoking, alcohol, and fatty foods may be associated with gastro-oesophageal reflux disease and may exacerbate dyspeptic symptoms.<sup>2</sup>

**Box 2 Common organic causes of dyspeptic symptoms**

**Upper gastrointestinal tract**

- Gastro-oesophageal reflux disease with or without oesophagitis
- Peptic ulcer disease (gastric or duodenal ulcer)
- Malignancy of the oesophagus and stomach (cancer, mucosa associated lymphoid tissue lymphoma)

**Other origins**

- Cholelithiasis, cholecystitis
- Pancreatitis and pancreatic cancer
- Hepatobiliary disorders and malignancy
- Ischaemic heart disease
- Drugs (non-steroidal anti-inflammatory drugs, aspirin, steroids, antibiotics, calcium antagonists, theophyllines, and bisphosphonates)

**Blood test**

A full blood count allows anaemia to be detected, and liver tests and serum lipase may be useful if hepatobiliary or pancreatic disease is suspected. In the last case ultrasonography is also recommended.<sup>1</sup>

**Oesophagogastroduodenoscopy**

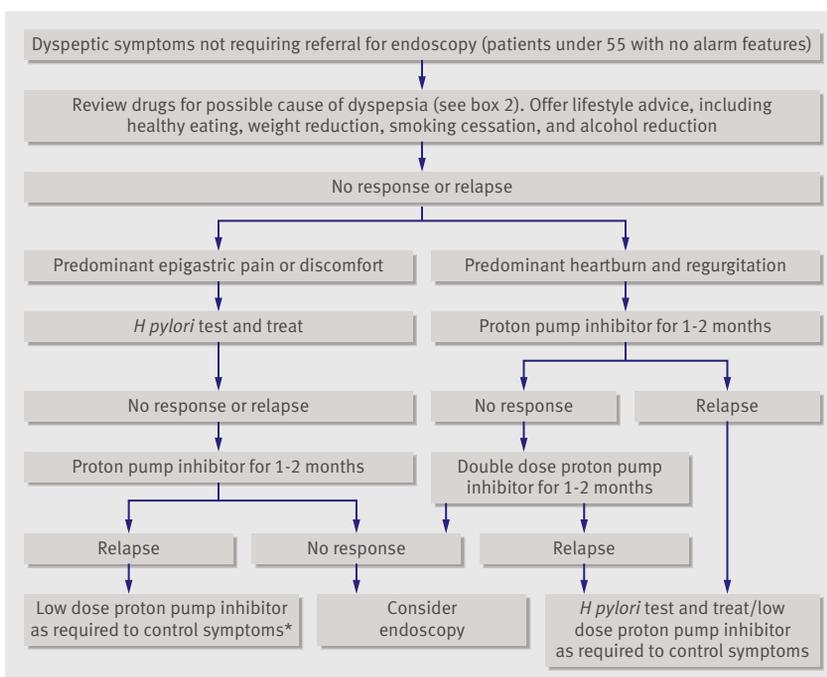
Endoscopy is the “gold standard” for the investigation of the upper gastrointestinal tract. Its accuracy in detecting organic lesions is higher than 95%, and biopsies can be taken to diagnose *Helicobacter pylori* infection, precancerous conditions, and malignancy.<sup>14</sup> Antisecretory drugs should be stopped at least two weeks before endoscopy because this treatment may heal early malignant ulcers and promote overgrowth of normal mucosa in sites of malignant tissue, thus masking early gastric cancer.<sup>15</sup> However, endoscopy cannot be used to investigate all patients with dyspepsia because it is invasive, expensive, and has limited availability. Barium meal radiography may be more readily available than endoscopy, but it is less sensitive and specific and may miss early malignancy.<sup>14</sup>

**Non-invasive *H pylori* tests**

A non-invasive test for *H pylori*, such as the <sup>13</sup>C-urea breath test, can be used as an indirect “peptic ulcer test.” Several observational studies have found that a positive *H pylori* test is a good predictor of peptic ulcer in patients with uninvestigated dyspepsia.<sup>16</sup>

**Who should be investigated and who should be treated empirically?**

International guidelines recommend prompt endoscopy for patients with dyspepsia and alarm features (box 3), and all older patients with new onset dyspepsia.<sup>1 4-7</sup> Patients with alarm features, such as gastrointestinal bleeding, dysphagia, or weight loss, should be promptly investigated to exclude ulcer complications and malignancy, although only a minority of these patients will have structural lesions.<sup>17</sup> Older patients have an increased risk of



**Management algorithm for patients with uninvestigated dyspepsia. Discuss the use of on demand treatment. Review long term patient care to discuss drugs and symptoms**

**Box 3 Alarm features in dyspepsia****Alarm symptoms or signs**

Gastrointestinal bleeding  
 Iron deficiency anaemia  
 Progressive unintentional weight loss  
 Progressive dysphagia  
 Odynophagia  
 Persistent vomiting  
 Epigastric mass on palpation

**High risk factors for cancer**

Family history of upper gastrointestinal malignancy  
 Previous gastric ulcer  
 Previous gastric surgery  
 Known Barrett's oesophagus  
 Known intestinal metaplasia or atrophic gastritis

malignancy, and early endoscopy is recommended even in the absence of alarm features. The age at which endoscopy should be performed routinely ranges from 45 in Asia<sup>8</sup> to 55 in the United States.<sup>15</sup> The advantage of investigating all older patients with uncomplicated dyspepsia in Western countries is now unclear because the prevalence of gastric cancer in these countries has fallen.<sup>9</sup> A recent prospective study in the UK reported that only 0.3% of patients over 55 with uncomplicated dyspepsia had malignancy,<sup>17</sup> and a Scottish cohort study showed that a policy of routine endoscopy for older people with new onset dyspepsia may have minimal effect on mortality for cancer of the upper gastrointestinal tract.<sup>18</sup>

For this reason, UK guidelines suggest that patients over 55 with uncomplicated dyspepsia should receive empirical treatment first and endoscopy is recommended only if symptoms persist after one to two months.<sup>2</sup> This may be a reasonable approach in Western countries because it reduces the endoscopic workload, but the doctor's clinical judgment is required.

Patients with dyspepsia who are under 55 and have no alarm features can be managed empirically. Upper gastrointestinal malignancy is rare in these patients and, when found, is often incurable. In the UK, a

retrospective study found that, of the 3293 patients with dyspepsia diagnosed with malignancy over two years in Scotland, 21 (0.6%) were under 55 and without alarm features, and only two (0.1%) had curative surgery.<sup>19</sup> Studies from the US have found similar results.<sup>1</sup>

**What empirical treatments are useful?**

Two strategies are available—a non-invasive test for *H pylori* and treatment of positive patients with eradication therapy (test and treat), and empirical anti-secretory therapy. A Cochrane review showed that proton pump inhibitors are the most effective anti-secretory drug for treating uninvestigated dyspepsia.<sup>20</sup>

International guidelines recommend test and treat for patients with predominant epigastric pain or discomfort and proton pump inhibitors for those with predominant heartburn or regurgitation.<sup>14-7</sup> Proton pump inhibitors are recommended as a second line strategy in patients with persistent symptoms after *H pylori* eradication and in those who are *H pylori* negative.

The main benefit of test and treat over proton pump inhibitors is that it definitively cures most patients with underlying peptic ulcer and a small group of those with functional dyspepsia. However, the prevalence of *H pylori* and peptic ulcer has decreased in the past decade,<sup>1</sup> and it is not clear whether test and treat is still the best first line strategy.<sup>29</sup>

Two recent studies compared the efficacy and cost effectiveness of these two strategies in Denmark and the UK, where the prevalence of *H pylori* is about 20-30%. The Danish cluster randomised trial showed that test and treat and proton pump inhibitors were similarly effective in terms of patients being free of symptoms after one year, but that test and treat resulted in fewer endoscopies and was more cost effective.<sup>21,22</sup> The UK randomised controlled trial reported similar results but found no difference in cost between the two strategies.<sup>23</sup> These results suggest that, even in areas with a relatively low prevalence of *H pylori*, test and treat has a persistent, albeit modest, benefit over treatment with proton pump inhibitors. Taking into account the potential long term benefits of *H pylori* eradication in reducing the risk of gastric cancer and preventing future peptic ulcer,<sup>24</sup> test and treat remains a valuable first line strategy.

Test and treat is not recommended for patients with heartburn predominant dyspepsia, because these patients are thought to be most likely to have underlying gastro-oesophageal reflux disease.<sup>14-7</sup> However, evidence now suggests that this strategy may also be beneficial for these patients. The Danish and UK trials found that the test and treat strategy also reduces symptoms in patients with heartburn predominant dyspepsia.<sup>21,23</sup> This suggests that a subgroup of these patients has an underlying peptic ulcer, as recently reported by a Canadian study.<sup>13</sup> Furthermore, a recent randomised controlled trial reported that a sequential strategy that uses proton pump inhibitors followed by test and treat if symptoms recur was more cost effective than early endoscopy in the management of these

**TIPS FOR NON-SPECIALISTS**

As is standard practice, patients who present with progressive unintentional weight loss or dysphagia should be referred for prompt endoscopy

Patients younger than 55 without alarm features should be managed empirically with both *H pylori* test and treat and proton pump inhibitors before endoscopy is considered

Young patients without alarm signals can be reassured that their symptoms are probably benign and that any organic disease is likely to respond to *H pylori* eradication or acid suppression therapy

*H pylori* test and treat should be used first in patients with mainly epigastric pain and discomfort; proton pump inhibitors should be used first in patients with mainly heartburn and regurgitation

**SUMMARY POINTS**

Around 25-40% of adults have chronic and recurrent dyspeptic symptoms  
 Most patients have no structural lesions and malignancy is rare, especially in Western populations  
 Two empirical strategies show results—a non-invasive test for *H pylori* and treatment of *H pylori* positive patients with eradication therapy (test and treat), and empirical treatment with proton pump inhibitors  
 The <sup>13</sup>C-urea breath test and stool antigen test are the recommended non-invasive tests for *H pylori* infection. Patients should stop proton pump inhibitors two weeks before and antibiotics four weeks before performing either of these tests

patients.<sup>25</sup> Undoubtedly, a subgroup of patients with heartburn predominant dyspepsia would benefit from *H pylori* eradication, and test and treat may be useful as a second line strategy in those whose symptoms relapse after treatment with proton pump inhibitors. An endoscopy should be considered in patients whose symptoms do not improve after either empirical strategy (figure).

**How do I test for *H pylori* infection?**

The <sup>13</sup>C-urea breath test is the most accurate non-invasive test and is the preferred test for the initial diagnosis of *H pylori* (table).<sup>6,26-28</sup> The stool antigen test may be a valid alternative because it has a similarly high sensitivity and specificity.<sup>6</sup> However, proton pump inhibitors should be stopped at least two weeks before and antibiotics at least four weeks before performing either of these tests because these drugs can lead to false negative results.<sup>6</sup> Serology is widely available and inexpensive, but its sensitivity and specificity are too poor for it to be recommended in patients with uninvestigated dyspepsia.

**How do I treat patients after investigation?**

When a patient is referred for endoscopy, biopsy specimens should be taken from the antrum and the body of the stomach for the diagnosis of *H pylori* infection. Endoscopy may show oesophagitis or peptic ulcer, which should be treated with proton pump inhibitors or *H pylori* eradication. However, most patients will have no structural lesions. Patients with endoscopy negative reflux disease should be treated with proton pump inhibitors.<sup>2</sup> Eradication of *Helicobacter pylori* does not usually provide symptom relief in these patients,<sup>6</sup> but it may be considered because it does not worsen symptoms,<sup>29</sup> and it may have other long term benefits.<sup>24</sup> Eradication of *H pylori* should, however, be the first line treatment in patients with functional dyspepsia.<sup>10</sup> A Cochrane review reported that 10% of patients with functional dyspepsia benefit from *H pylori* eradication when compared with placebo.<sup>30</sup> Although this benefit is small, eradication is the most cost effective approach for these patients because it is given once only to have long term benefit. Proton pump inhibitors should be given to *H pylori* negative patients and those who fail to respond to eradication therapy.<sup>10</sup> However, reassurance and explanation of the benign nature of symptoms may be the best treatment for functional dyspepsia and may be sufficient for many patients. Prokinetics, antidepressants, and spasmolytics should be reserved for patients with refractory disease.<sup>10</sup>

**Conclusion**

A combination of *H pylori* test and treat proton pump inhibitor therapy is still a valuable strategy for the empirical management of most patients. In Western countries, an initial empirical treatment may also be considered in older patients with uncomplicated dyspepsia.

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**ADDITIONAL EDUCATION RESOURCES**

**Resources for healthcare professionals**

The National Institute for Health and Clinical Excellence (NICE) has produced comprehensive evidence based guidance for managing dyspepsia in adults in primary care ([www.nice.org.uk/Guidance/CG17](http://www.nice.org.uk/Guidance/CG17))

The Cochrane Library provides evidence based reviews on various aspects of treating dyspepsia ([www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD001961/frame.html](http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD001961/frame.html); [www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD001960/frame.html](http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD001960/frame.html); [www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD002096/frame.html](http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD002096/frame.html))

Clinical Evidence provides authoritative medical resources for informing management decisions on dyspepsia ([www.clinicalevidence.bmj.com/ceweb/conditions/dsd/0406/0406.jsp](http://www.clinicalevidence.bmj.com/ceweb/conditions/dsd/0406/0406.jsp))

**Resources for patients**

Patient UK ([www.patient.co.uk/showdoc/40001656/](http://www.patient.co.uk/showdoc/40001656/))—Patient oriented advice about dyspepsia from a UK based site partially funded by advertisements

Dyspepsia ([www.dyspepsia.com](http://www.dyspepsia.com))—Patient oriented advice about dyspepsia from an American based site

MD Consult Preview ([www.mdconsult.com/das/patient/body/103326033-2/0/10062/15201.html](http://www.mdconsult.com/das/patient/body/103326033-2/0/10062/15201.html))—Advice about dyspepsia provided by the American Academy of Family Physicians

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