

## DYSPEPSIA MANAGEMENT

# Management of uninvestigated dyspepsia: review and commentary

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Up to 40% of individuals complain of dyspepsia but only 25% of these present to their general practitioner. If symptoms have been present for a relatively short period the majority can be managed by reassurance and symptomatic treatment. Those with a longer history require empirical treatment with more powerful medication, endoscopy, testing for *Helicobacter pylori*, or a combination of these approaches. There is some debate about whether the treatment of *Helicobacter pylori* infection is an appropriate strategy for patients with dyspepsia. It is the general practitioner who determines how the uninvestigated patient with dyspepsia will be managed because those referred to hospital usually undergo endoscopy at an early stage.

### SUMMARY

Patients with dyspepsia present to their general practitioner for a variety of reasons. They are usually anxious about serious disease, they want an explanation for their symptoms, to be treated, and to avoid unpleasant medical tests. If symptoms have been present for a relatively short period and no alarm symptoms exist, the majority can be managed by reassurance and symptomatic treatment, with review. Those with a longer history require empirical treatment with more powerful medication, endoscopy, testing for *Helicobacter pylori*, or a combination of these approaches. Patients over 45 years of age or those who have alarm symptoms should undergo endoscopy because of the risk of gastric cancer. Data suggest that empirical treatment of dyspepsia with a proton pump inhibitor leads to acceptable symptom relief in 54–65% of patients compared with 33–53% with placebo. Another strategy is to test for *H pylori* and treat if positive. This provides reassurance for both the patient and doctor that peptic ulcer has been properly managed, it utilises the high patient placebo response, gives an explanation for symptoms, protects against future gastroduodenal disease, and may avoid endoscopy. A number of objections have been raised to this policy as some physicians believe that *H pylori* should not be treated unless a peptic ulcer is present. Data from this symposium suggest that functional dyspepsia does not respond to *H pylori* eradication; however, the evidence shows that this therapy does not induce or worsen gastro-oesophageal reflux disease.

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### INTRODUCTION

Few clinical syndromes can compete with dyspepsia for the number of management protocols and algorithms produced by consensus groups over recent years. Local, national, and international groups have produced such a variety of recommendations that practising clinicians are able to treat patients much as they would wish to in the knowledge that most management plans are likely to be supported by one consensus group or another! The enthusiasm for producing management protocols has been stimulated by a variety of circumstances. Firstly, increased numbers of patients continue to present with this common condition. Secondly, there is some debate about whether the treatment of *H pylori* infection is an appropriate strategy for patients with dyspepsia. Thirdly, the development of drugs that control gastric acid secretion and provide effective therapy for acid related diseases are widely used. These drugs are expensive and health providers are anxious to ensure they are prescribed for appropriate indications. Finally, it is fashionable in healthcare circles to base management on “evidence based medicine”. It is difficult to assess the impact of these management protocols on general practitioners. It is however the general practitioner who determines how the uninvestigated patient with dyspepsia will be managed because those referred to hospital usually undergo endoscopy at an early stage.

### WHY DO PATIENTS PRESENT WITH DYSPEPSIA?

In Western countries, up to 40% of individuals complain of dyspepsia.<sup>1</sup> However, only 25% of these present to their general practitioner. Some attend because their symptoms are severe and others because they are worried that they may have cancer or another serious disease. There is little objective difference in the severity of symptoms between those who consult and the remainder who do not, although the ones who do consult have a greater perception of their symptoms and are most worried about their implication.<sup>2</sup> Most patients therefore seek advice in order to gain reassurance that nothing is seriously wrong with them, and to obtain an explanation as to why their symptoms are present. If sufficiently severe, they expect to receive treatment for their problem. In earlier times, individuals were often prepared to accept that gastrointestinal upsets were the result of over indulgence in alcohol or food, or the result of advancing age. The only treatments that were available for dyspeptic symptoms were lifestyle changes and/or antacids that could be obtained over the counter. Before

double contrast barium meal and endoscopy were introduced in the late 1960s and early 1970s, techniques for the diagnosis of dyspepsia were rudimentary.

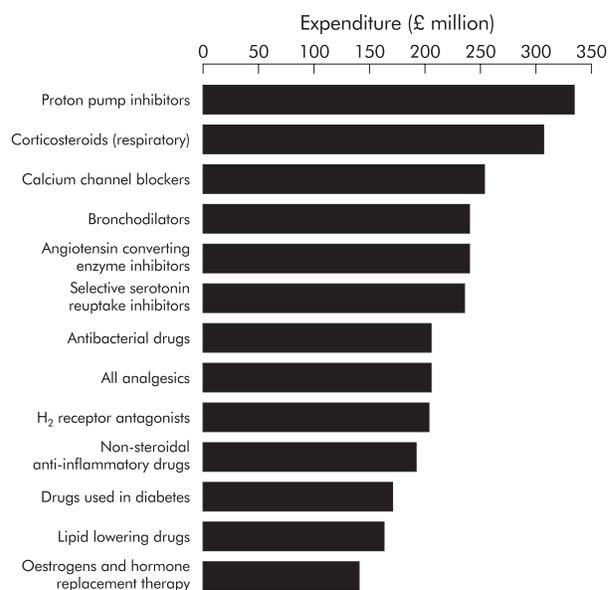
The revolution in the management of dyspepsia occurred in the mid-1970s when accurate diagnosis by upper digestive endoscopy became available and, at the same time, H<sub>2</sub> receptor antagonists came onto the market. For the first time, peptic ulcer could be accurately diagnosed and an effective treatment was available. These innovations, widely reported in the media, raised the profile of dyspepsia in the mind of the general public while the discovery of *H pylori* and the introduction of the proton pump inhibitors in the mid-1980s provided further publicity. The decline in peptic ulcer disease coinciding with the rise in gastro-oesophageal reflux disease in recent years has been associated with an overall increase in the incidence of patients complaining of dyspeptic symptoms.<sup>3</sup> Patients today are inclined to consult their doctors more readily for unexplained symptoms, so conditions as widespread as dyspepsia and gastro-oesophageal reflux disease have meant that disproportionately large numbers of patients now seek advice.

### DOCTORS AND DYSPESIA

The attitude of doctors towards dyspepsia has also changed. An earlier generation of general practitioners had no direct access to sophisticated investigations and were aware that hospital referral was unlikely to be of great benefit, except for those patients with sufficiently severe symptoms to warrant surgery for peptic ulcer. The tendency therefore was for them to manage dyspepsia themselves. A modern generation recognises that an accurate diagnosis is essential to avoid missing serious disease such as peptic ulcer and malignancy. Open access endoscopy is readily available. Eradication of *H pylori* cures peptic ulcer and powerful acid suppressing treatment eliminates symptoms arising from gastro-oesophageal reflux disease. General practitioners appreciate that patients expect a definitive diagnosis and to be provided with effective medication. The symptoms of gastro-oesophageal reflux disease tend to be continuous and recurrent but can be virtually eliminated in most patients by proton pump inhibitors. Once started, it is difficult to avoid long term therapy. The combination of patient demand, easy access to diagnostic modalities, and the availability of effective treatment has led to an escalating cost in the management of dyspeptic disease. A greater proportion of the British drug budget is spent on proton pump inhibitors alone than any other group of drugs<sup>4</sup> (fig 1). It is not surprising therefore that health providers are anxious to introduce some measure of control.

### GUIDELINES

The use of management algorithms is an apparently logical way of restricting the prescription of drugs to those who really benefit from them. With the discovery of *H pylori*, there was a widespread belief that eradication of this organism would substantially reduce dyspepsia in the community, thereby controlling the costs of prescribing. This view was widely held by doctors as well as providers, in spite of the fact that it was already well recognised that the prescription of proton pump inhibitors for peptic ulcer disease was very small in comparison with the amount used for gastro-oesophageal reflux disease (for which *H pylori* was not responsible). Endoscopy is believed to represent a significant cost in managing dyspepsia. Few randomised controlled trials exist that have compared immediate investigation with empiric therapy for patients with dyspepsia.<sup>5</sup> The cost of an endoscopy under the British National Health Service is approximately £200—roughly equivalent to the cost of prescribing a proton pump inhibitor for six months. An early endoscopy that finds a cause of the symptoms will facilitate appropriate treatment. However, up to 60% of patients presenting with dyspepsia have no apparent



**Figure 1** Current annual UK National Health Service expenditure. Source: Department of Health Prescribing Costs Analysis, England 1997 (values adjusted for UK); NHS Executive; Specialty in Impotence, Obesity Management; UK Transplant and Support Service.<sup>4</sup> Published with permission.

endoscopic abnormalities.<sup>6</sup> A negative endoscopy in these patients may provide reassurance and enable long term therapy to be avoided although treatment may still be required for continuing symptoms.<sup>7</sup> Furthermore, it is important to remember that the outcome of all management guidelines depends on the assumptions included, and these may not reflect true clinical practice.

### EVIDENCE BASED MEDICINE

The final factor that has driven the development of management algorithms is the current vogue for practising “evidence based medicine”. This approach is based on the proposition that the management of patients visiting their doctor should be guided by proven scientific principles; it implies that a drug should not be used unless there is a sufficient body of evidence to support its effectiveness. Today, this almost invariably means that the form of treatment used should have been tested in a randomised clinical trial, preferably of double blind design. The trial should have been properly monitored and should conform to the best clinical standards (as defined by the US Food and Drug Administration). These trials are extremely expensive to undertake and are a necessary prerequisite before the drug can be registered. In practice, most of these studies are performed with industrial sponsorship.

### Drawbacks of the randomised trial

A serious problem with the controlled clinical trial is the effect that the trial itself has on “outcome”. One of the difficulties in science is that an attempt to measure an outcome itself influences the result. Patients with dyspepsia who are to be randomised have to give informed consent. The patient who is told that he or she fulfils the criteria for inclusion in a trial is likely to believe that there is indeed something wrong with him/her. A careful assessment of the symptoms using a questionnaire will reinforce this belief, as will the knowledge that a special, new, and expensive drug is to be used for treatment. The patient with functional dyspepsia entering a trial is unlikely to feel fully reassured by the experimenter that nothing is wrong with him or her and that he/she does not really need medication. On the contrary, at regular intervals until the

end of the trial, the patient will be questioned for minute symptoms and adverse events. It is not surprising that total relief of symptoms in dyspeptic patients recruited to the trials presented during this symposium has been generally disappointing. A double blind clinical trial is an excellent tool to identify the most effective method of curing *H pylori* infection where the end point is objective; however, it is not as good an instrument for determining the most effective treatment for a patient who is concerned about a minor discomfort in the upper abdomen. The end points chosen for these trials are not without flaws. If 40% of the population is troubled with dyspepsia, is it realistic to choose "total relief of symptoms" as an endpoint?

### Publication bias

A further criticism of evidence based medicine concerns publication bias. Medical journals depend for survival on the number of people who read them because this influences income from sales and advertising. Publishing is a competitive field, and editors more readily accept papers with a positive outcome than a negative one. The demonstration that a drug is not better than another, or as good as placebo, is less likely to be published than a positive result. Furthermore, the enthusiasm of researchers and their sponsors for publishing negative results is less than for positive ones and it is probable that fewer negative results are submitted for publication. These factors may bias the literature towards a view that drugs are more effective than they are. This problem is made worse by the current vogue for undertaking meta-analyses in areas in which the effectiveness of drug treatment may be borderline.

### THE ART OF MEDICINE

A drawback to reliance on evidence based medicine is that it is only possible to analyse studies that have been performed, not those that should have been performed. The practice of medicine is an art as well as a science. The difference between outcomes in the surgical field may relate to the skill of the surgeon (or lack of it). The same applies in the management of patients with medical disease, especially that of a functional nature and particularly when the symptom complained of may not be the real reason for attendance.<sup>2</sup> A carefully taken history may be more important than tests. An ability to explain the nature and causation of the symptoms and the gravitas to convincingly reassure the patient that there is nothing wrong may be most important of all. In modern medicine, tests and drugs may be used to reinforce a more general approach to the management of the disease but they are often of secondary importance compared with a good "bedside manner". Unfortunately, these factors are difficult to study and are unlikely to attract the financial support necessary to enable them to be investigated effectively. When this approach has been researched, it has usually been in the form of assessing the effect of specially trained paramedical personnel rather than doctors.

### INITIAL APPROACH TO DYSPEPSIA

When a doctor is consulted by a patient with dyspepsia, the concern is to avoid the misdiagnosis of serious disease, to provide effective treatment, to stay within budget, and to discharge a satisfied patient. Many patients presenting in primary care have minor symptoms or ones that have been present for a short period. In these cases, a carefully taken history, reassurance that the problem is likely to be temporary, and the provision of symptomatic treatment such as an antacid will often be sufficient, provided that the patient is followed up to ensure a satisfactory outcome. A different approach is necessary in patients who have more severe symptoms or ones that have been present for a longer period. Here there is a choice of three strategies. The first strategy is to

provide empirical treatment with, for example, a proton pump inhibitor. The second strategy is to refer for endoscopy. The third strategy, now commonly used in primary care, is to test for *H pylori*, treating those who test positive and reassuring those who are negative. Patients with dyspepsia are individuals, each with their own particular symptoms and concerns, and it is not possible to lay down a set of management protocols that will satisfy all patients and all doctors. Nevertheless, certain basic principles can be followed which should enable a satisfactory outcome in nearly all cases.

### Who should have endoscopy?

It is unnecessary and indeed impractical to refer all dyspeptic patients for endoscopy. Nevertheless, the most important principle for both the patient and doctor is to avoid the misdiagnosis of serious disease and, in this regard, endoscopy is the gold standard. Organic disease in the upper gastrointestinal tract increases with age. Most consensus groups have therefore adopted the view that all patients over a certain age and those with so-called "alarm symptoms" should undergo endoscopy. Thus patients of any age who present with gastrointestinal haemorrhage, dysphagia, odynophagia, significant weight loss, or intractable pain should be referred for endoscopy. Cancer of the upper gastrointestinal tract is uncommon in Western countries under the age of 50 years. Most authorities have therefore taken 45 years of age as a cut off point, above which endoscopy should be performed in order not to miss gastric cancer. Early gastric cancer, which carries a good prognosis if diagnosed, usually presents with symptoms indistinguishable from those of peptic ulcer or functional dyspepsia.<sup>8</sup> To make matters more difficult, symptoms of early gastric cancer have usually been present for a longer period than in individuals presenting with advanced cancer.<sup>9</sup> It is for these reasons that older patients with dyspepsia merit endoscopic examination. The cut off age must be determined by local epidemiological and economic factors. One difficult area is in patients who complain of typical symptoms of gastro-oesophageal reflux disease but who are above the cut off age. Should these patients be referred for endoscopy? Cancer arising in Barrett's oesophagus is uncommon under the age of 50 years but it is much more frequent today than previously, so an argument can be made that all patients over the cut off age with any form of dyspepsia should be referred for endoscopy.

Dyspepsia is common in patients treated with non-steroidal anti-inflammatory drugs and these drugs may cause chronic peptic ulcer. In view of medico-legal responsibilities, it is wisest in these patients to discontinue treatment with non-steroidal anti-inflammatory drugs. In the event that these drugs have to be taken in spite of symptoms, upper digestive endoscopy is desirable.

Apart from patients with alarm symptoms, those over a certain age, and those taking non-steroidal anti-inflammatory drugs, there remains a large number of patients with symptoms of gastro-oesophageal reflux disease and dyspepsia. Patients in whom symptoms have been present for a significant length of time are the ones for whom dyspepsia management strategies are designed. The aim should be to exclude peptic ulcer, to provide an explanation for symptoms, to provide reassurance and, where appropriate, to prescribe treatment. Endoscopy is unnecessary in approximately 75% of young dyspeptics according to a series of recent studies.<sup>10-13</sup> Initial endoscopy is therefore not recommended. The alternatives are either to prescribe empirical treatment or to test for *H pylori*.

### The test and treat approach

The reason to test for *H pylori* is to avoid mistreating peptic ulcer and to prevent future serious peptic disease. A number of studies have shown that patients under the age of 45 years

who are not taking non-steroidal anti-inflammatory drugs and who are negative for *H pylori* are very unlikely to have peptic ulcer at endoscopy.<sup>14–17</sup> Conversely, patients who are *H pylori* positive have an incidence of peptic ulcer ranging from approximately 20% to 60%.<sup>18–20</sup> Those who believe that *H pylori* is not a dangerous organism (in the absence of peptic ulcer disease) recommend that dyspeptics who test positive should undergo endoscopy in order to identify peptic ulcer so that they are not treated unnecessarily. A different view is that any patient infected with the organism should undergo therapy to prevent future cancer or peptic ulcer. As most infected patients usually demand treatment, the advantage of endoscopic this group of patients is limited. For this reason, a number of consensus panels have taken the view that patients testing positive should be treated for their infection.<sup>21–22</sup>

If a test and treat policy is adopted, a group of *H pylori* negative “young” dyspeptics are left. These can be confidently reassured that they are unlikely to have a serious underlying cause for their symptoms. A proportion can be discharged without further investigation or treatment but a significant number remain. These are patients troubled by their symptoms and others who are still unconvinced that nothing is seriously wrong with them. At this point it may be reasonable to employ empirical therapy. The data presented during this symposium<sup>23–25</sup> show that if empirical proton pump inhibitor therapy (omeprazole 10–20 mg once or twice daily) is used in patients with functional dyspepsia (as opposed to gastro-oesophageal reflux disease), 54–65% will have sufficient control of symptoms which includes 31–38% who will have complete resolution of symptoms. It is worth noting however that placebo provides equivalent success in 33–53% and 16–28%, respectively, so the advantage of the proton pump inhibitor is about 10%. The fact that symptoms are greatly ameliorated by, or disappear on, treatment may provide the added reassurance needed by the patient that nothing is seriously wrong. A reasonable explanation for symptoms can also be advanced by the doctor. In those patients (probably a greater number) who have predominant reflux, 70% will respond positively to a proton pump inhibitor within one month.<sup>26</sup> For those who fail to respond to treatment, a switch to a prokinetic agent may be successful.

If the patient is reassured by the response to treatment, the treatment should be stopped and the patient encouraged to modify their lifestyle or, where appropriate, to take intermittent symptomatic therapy, such as alginates, antacids, or H<sub>2</sub> receptor antagonists. For those patients who require long term acid suppression with a proton pump inhibitor, it is probably wisest to refer for endoscopy before restarting medication. The purpose of this is to detect *H pylori* negative peptic ulcer, Barrett's oesophagus, and rare conditions that could be causing dyspepsia.

If the test and treat protocol for *H pylori* eradication is followed, it provides reassurance for the patient and doctor that serious disease has not been missed, it treats appropriately nearly all peptic ulcer disease, it utilises the placebo response and the acid suppression response in such a way as to provide added reassurance to the patient, and also enables the doctor to provide an explanation for the cause of symptoms. If empirical treatment is needed, it should be prescribed on the understanding that it is a therapeutic trial rather than a treatment. This protocol protects the patient against future *H pylori* associated diseases and avoids invasive and expensive investigation in over 75% of the patients.

#### Drawbacks of the test and treat approach

There have been a number of objections to the test and treat approach. Some doctors take the view that *H pylori* should not be treated unless it is associated with peptic ulcer. For these, the test and treat approach is inappropriate because patients will usually request treatment if they know that they are

infected. The controlled trials presented during this symposium indicate that *H pylori* treatment in patients with non-ulcer dyspepsia provides little, if any, relief from symptoms.<sup>27–29</sup> An important finding however is that treatment does not increase the incidence or severity of gastro-oesophageal reflux symptoms.<sup>30</sup> This is important because earlier work suggested that eradication therapy might precipitate reflux oesophagitis.<sup>31</sup> A major concern today is the over use of antibiotics and the possibility that the widespread use of these drugs may lead to the development of resistance. In fact, when considered in the context of all the antibiotics that are currently prescribed, the amount used for *H pylori* eradication represents a tiny proportion. Far from avoiding treatment because of resistance, a case can be made that *H pylori* should be eradicated now rather than wait until more patients develop resistance as a result of the indiscriminate use of antibiotics for other purposes.

A test and treat policy means that young dyspeptic patients will not undergo endoscopy unless they need to receive long term proton pump inhibitor treatment. This means inevitably that certain patients with Barrett's oesophagus will be missed, as will patients with *H pylori* negative peptic ulcer. This criticism however can also be levelled at a policy of empirical treatment. The only way to avoid missing these diseases is to advocate universal endoscopy for all patients with dyspepsia. Even then, the majority of patients in the community with Barrett's oesophagus will not be diagnosed because reflux symptoms can be mild or absent in patients with this condition. The bulk of Barrett's oesophagus probably exists in the part of the community that does not seek medical advice.

If a test and treat policy is to be pursued, it is relevant to draw attention to the importance of an accurate non-invasive method for the diagnosis of *H pylori* infection. At present, most primary health doctors use serology. Most serological tests have a sensitivity and specificity of approximately 90%. This means that if 50% of a dyspeptic population is infected, 45/50 will be identified and treated appropriately, five will be missed, and five false positives will be inappropriately treated. It is different however if only 20% of a dyspeptic population is infected; under these circumstances, 18/20 positive patients will be identified, but with a specificity of 90%, 8/80 negative patients will actually be false positives and will also receive treatment, while two false negatives will not. Thus 10/28 patients will be inappropriately managed under these circumstances. It follows therefore in populations in which there is a relatively low percentage of infection that a more accurate test is desirable. The <sup>13</sup>C urea breath test, although more expensive, has a sensitivity and specificity of about 98% and hence under these circumstances is the investigation of choice.

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