REVIEW

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Management Issues in Dyspepsia: Current Consensus and Controversies

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Dyspepsia is a common condition in primary care (1). Endoscopy is of limited value in targeting therapy, as most patients do not have any abnormalities (1–3). Several empirical strategies have been proposed for the management of patients in primary care, the principal goal of which is to reduce the cost of therapy while avoiding delays in the diagnosis of serious disorders that occasionally present as dyspepsia (1). Patients likely to have malignancy should have endoscopic and not empirical management (1–3). Empirical strategies that have been proposed include: 1) the test-and-treat strategy: non-invasive testing for *Helicobacter pylori* is carried out first and infected patients are treated with antimicrobials; *H pylori*-negative patients receive symptomatic therapy. 2) The test-and-endoscope strategy: patients undergo non-invasive testing for *H. pylori* and those testing positive are examined endoscopically. 3) Acid suppression alone.

Paradoxically, the test-and-endoscope strategy could increase costs by causing more patients to be referred for endoscopy than is usually the case (4) and has largely fallen from use, being replaced by the 'test-and-treat' strategy in most countries. The management of dyspepsia represents a classic medical decision-making problem. Any investigation has to be justified in terms of cost-effectiveness. In both Europe and North America, dyspepsia is a common symptom and the costs of both upper gastrointestinal (GI) endoscopy and drug therapy for dyspepsia are substantial (1–3, 5).

Methods

During the 16th International Workshop of the European *Helicobacter pylori* Study Group held in Stockholm in September 2003, a group of experts reviewed management strategies based on the available literature. The authors all contributed to evidence-based debates on various aspects of the management of dyspepsia and these were organized and summarized by three of the authors (NT, NV, BD) to provide a review of the controversies in dyspepsia.

Results

There is still controversy about optimal management for dyspepsia. Expert guidelines have been produced in Sweden (6) and elsewhere (1–3), but European guidelines have not been concordant (6–9). For example, the Swedish guidelines for the West Coast recommend non-invasive testing for *H. pylori* with endoscopy for those who test positive (7). In contrast, the European *H. pylori* group guidelines recommend non-invasive testing followed by treatment for those infected with *H. pylori* (8). Current testing strategies, the evidence in support of available management strategies, the role of antibiotic resistance, and future directions were all considered, and will be summarized in this review.

Should 'uninvestigated dyspepsia' and 'uninvestigated gastroesophageal reflux disease' be managed by the same strategy?

Management trials have used different definitions of dyspepsia and recruited slightly different populations, which in turn has potentially confounded interpretation of the literature (10, 11). In primary care, predominant reflux symptoms and upper abdominal symptoms are typically not clearly distinguished, partly because there is significant overlap between heartburn and epigastric pain or discomfort (12, 13). In specialist practice, it has been more usual to identify patients with predominant heartburn and classify these patients as having gastroesophageal reflux disease (GERD) until proven otherwise (14). The Rome diagnostic criteria for functional dyspepsia exclude predominant heartburn as a symptom of dyspepsia, but these criteria were primarily designed for randomized clinical trials and physiological studies rather than utilization in clinical practice (15).

New insights have been obtained as a result of recent studies. In a large Canadian study, the prevalence of peptic ulcer in patients who presented in primary care with epigastric symptoms was similar to the prevalence of peptic ulcer in those who presented with typical or predominant reflux

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symptoms (12). Hence, distinguishing reflux symptoms from other upper abdominal complaints may not be helpful in practice in terms of deciding which management strategy to consider. However, application of a *H. pylori* testing and treatment strategy in people with typical reflux symptoms remains highly controversial (8, 14). Definitions of dyspepsia also impact on the prevalence of underlying non-ulcer dyspepsia, which remains essentially a diagnosis of exclusion (15). For example, in the US householder study of volunteers, the prevalence of functional dyspepsia defined clinically was 13% in this population; 33% of the population had heartburn (16). However, if heartburn and irritable bowel symptoms were excluded from the non-ulcer dyspepsia category, only 3% of the population would have this diagnosis (16). Hence, non-ulcer dyspepsia can almost disappear depending on how it is defined. At the present time, patients with upper abdominal pain or discomfort with or without heartburn are the target population for dyspepsia management strategies, while patients with heartburn only are best treated with acid suppression.

Why have empirical treatment strategies been developed?

If patients presenting to primary care physicians are referred for endoscopy, only a small proportion of patients have findings at endoscopy. Most of the abnormalities detected are not serious. Approximately 12% of patients (95% CI 2%–31%) will have esophagitis, 17% peptic ulcer disease (95% CI 13%–28%), 1.6% malignancy (95%, CI 0.2%–4.0%) and 70% normal or only minor changes (95% CI 35%–89%) (17). At least a further 20% will have non-erosive reflux disease (15). The findings will reflect the prevalent disorders in the population being studied and how they were recruited for the study. A Canadian study recently reported much higher rates of esophagitis in primary care (36%) (12). With the widespread availability of anti-secretory drugs over the counter, pre-endoscopy use of anti-secretory therapy may have confounded many of the results, obscuring esophagitis and peptic ulcer disease.

The test-and-treat strategy

Bytzer undertook a European survey for this meeting on the availability and use of *H. pylori* testing in primary care. A short questionnaire was sent to experts and opinion leaders in European countries, with responses from 19 countries. It was reported that there were national regional guidelines for *H. pylori* testing for primary care in 15 out of 19 countries, and serology was the most available test (in 13 of 19 countries) closely followed by urea breath testing (in 12 of 19 countries). Fecal antigen testing and rapid office-based testing were only available in 4 and 6 countries, respectively. Test-and-treat strategies were recommended in 12 countries, while test-and-endoscope or prompt endoscopy was recommended only in Sweden. No countries currently recommended empiric acid suppression as first-line management, although draft UK guidelines from the National Institute of Clinical Excellence recommend either acid suppression or test and treat. Non-invasive *H. pylori*-based management strategies have been challenged, however, on the basis of poor performance. This is due to the decreasing prevalence of *H. pylori* and of *H. pylori*-associated ulcer disease as well as a lack of availability of more accurate tests, such as urea breath tests in many primary care settings (18).

The aim of the test-and-treat strategy is to separate *H. pylori*-negative from -positive dyspepsia using non-invasive diagnostic testing. Test and treat will resolve symptoms caused by an underlying peptic ulcer (19). There is also a small benefit of eradication over placebo in non-ulcer dyspepsia (with a number needed to treat of 15) (20). Other evidence suggests that patients with GERD that present with epigastric symptoms are unlikely to have worsening of their symptoms with a test-and-treat strategy (21). A Cochrane review concluded that the test-and-treat approach is equivalent to an endoscopic management strategy in terms of symptom improvement, saves endoscopies, and is therefore cost effective (10). It is also associated with similar satisfaction with management although the results here have been less conclusive (10). There have been no trials of empirical *H. pylori* therapy alone, without testing. In view of concerns about antibiotic resistance, and the increasing availability of inexpensive non-invasive tests, this does not look an attractive option. However, it is one that might be used where primary-care physicians have restricted access to testing and the background prevalence of *H. pylori* is high.

The benefits of test-and-treat include the possibility that this may decrease the incidence of gastric cancer, although this has not been established in randomized controlled trials (22). It has also been argued that test-and-treat will reduce transmission of infection amongst family members and may make future use of non-steroidal anti-inflammatory drugs (NSAIDs) safer in terms of preventing ulcer disease, although this is also controversial (8). Both *H. pylori* and NSAIDs are independent, but synergistic, risk factors for ulcer disease (23). For patients who will start off with NSAIDs, it remains controversial whether testing-and-treating for *H. pylori* should be considered (24, 25). The European *Helicobacter pylori* Study Group has suggested that it is advisable in *H. pylori*-positive patients when their ongoing NSAID therapies are planned to consider eradication (8). However, in recent studies conflicting conclusions have been reached on this issue and probably *H. pylori* eradication alone is insufficient to prevent ulcers and ulcer complications in high-risk patients (26–30).

However, there are potential disadvantages of test-and-treat which have led to this management approach not being universally accepted. In recent US studies, the test-and-treat approach was not found superior to usual care (31, 32), although in one of these studies only patients on long-term acid suppression therapy were evaluated and was open-label (31). Moreover, usual care may be the wrong comparator to consider. Serological testing is often suboptimal but is widely

used in primary care (18). The positive predictive value of diagnostic tests in low prevalence regions remains an issue. There are concerns about the increased use of antibiotics in patients who will not derive any benefit, with the associated risk of side effects as well as increased antibiotic resistance. Moreover, the majority of patients after a test-and-treat strategy will remain symptomatic, which may frustrate both clinician and patient. While gastric and esophageal adenocarcinoma are rare presentations in primary care, diagnosis of cancer can be missed or delayed with a test-and-treat strategy. For example, in Hong Kong, Sung et al. reported that of 1017 patients under 45 years of age without alarm features, 0.3% had gastric cancer and 0.1% esophageal cancer (33).

Problems with test-and-treat

Poor performance of the diagnostic test for H. pylori. Recent reviews of the sensitivity and specificity of non-invasive *H. pylori* tests in primary care suggest that serology has a sensitivity and specificity of 85% and 79%, respectively, compared with office-based tests that have a sensitivity and specificity of 71% and 88%, respectively (34). In contrast, urea breath testing and fecal antigen testing have sensitivities and specificities that are considerably higher, around 93% to 95% each (34). However, the value of a positive test also depends on the background prevalence of the infection and this will affect the local utility of testing. For example, if the prevalence of *H. pylori* infection is only 10% in the patients being seen in a particular practice, then even with urea breath testing approximately 15% of patients who have a positive test will be falsely positive, although the absolute number of fake positives will still be low (1–2 cases out of 100 patients in this scenario). Most importantly, almost everybody who is negative will truly be negative in this setting. While testing in low-prevalence areas can be misleading if positive when only one test is used, serial testing can increase the specificity (at the expense of sensitivity) (35).

The emergence of antibiotic resistance. One reason for the lack of enthusiasm for test-and-treat relates to the possibility of increased antibiotic resistance from widespread, indiscriminate application of a test-and-treat strategy. Currently, antibiotic resistance to *H. pylori* from macrolides varies from 2% to 22% and from metronidazole from 7% to 70% around the world (36, 37). There is limited evidence for *H. pylori* antibiotic-resistant mutations occurring because of antibiotic pressure (38). The exact impact of widespread test-and-treat strategies in terms of antibiotic resistance has as yet to be documented. However, in a recent study it was shown that antibiotic treatment selects for resistance not only in *H. pylori* but also in the indigenous microflora, and that highly resistant bacteria of this flora can persist for years without further selection (39). In addition, failure of clarithromycin-based treatments is associated with clarithromycin resistance in *H. pylori*, although this may vary depending on the combination used (37).

Endoscopy-driven management

Endoscopy allows targeted diagnosis and management. However, the most common finding will be esophagitis (12); current evidence suggests that the management of symptoms will not be changed by endoscopy, as most patients have been given acid suppression treatment prior to endoscopy and will either have this continued or possibly increased after endoscopy (40). Endoscopy is unable to diagnose non-erosive reflux disease (14). A Cochrane review of direct randomized controlled trials comparing endoscopy with acid suppression in terms of cost-effectiveness found 5 trials, 2 based in secondary care, and 3 in primary care, where 1125 patients were randomized (10). Although there was a trend towards endoscopy-based management yielding better symptom relief, this was not significant, and may have been related to the trials not including *H. pylori* eradication in the 'empirical therapy' arm (10). It can be argued that detection of a peptic ulcer or esophagitis allows appropriate use of *H. pylori* eradication therapy or proton pump inhibitors (PPIs). *H. pylori* eradication therapy increases duodenal ulcer healing in *H. pylori*-positive patients, with an NNT for one patient to benefit from eradication of 18 (95% CI: 13 to 32), but does not increase gastric ulcer healing compared to acid suppression treatment (41). *H. pylori* eradication therapy reduces duodenal ulcer recurrence in *H. pylori*-positive patients. After 3–12 months, 39% of patients receiving short-term acid suppression therapy were without ulcer: eradication increased this by 52% with an NNT of 1.9 (95% CI: 1.7 to 2.3). *H. pylori* eradication also reduces gastric ulcer recurrence in *H. pylori*-positive patients (NNT 3.1, 95% CI: 2.3 to 5.0) (41). *H. pylori* eradication therapy is a cost-effective treatment for *H. pylori*-positive patients with peptic ulcer disease. Eradication therapy provides additional time free from dyspepsia at acceptable cost in conservative models and is cost saving in more optimistic models (41).

Endoscopy and targeted therapy for GERD

During the meeting a point of discussion was, if endoscopy defines a particular subgroup of patients with esophagitis, might these patients benefit from having more effective treatment? PPIs are more effective than H_2-receptor antagonists at healing esophagitis (14, 42). In randomized controlled trials, healing occurred in 22% of patients on placebo, 39% of patients on H_2-receptor antagonists (a number needed to treat of 6), and 76% of patients on PPIs (a number needed to treat of 2) (42). Limited evidence shows that antacids are no more effective at healing esophagitis than placebo. PPIs are also more effective than H_2-receptor antagonists in protecting a patient against relapse. In randomized, controlled trials, relapse occurred in 59% of patients on H_2-receptor antagonists and 20% of patients on PPI (a number needed to treat of 3). PPIs at full dose are more effective than PPIs at low dose. In randomized, controlled trials, relapse occurred in 28% of patients on low-dose PPI and 15% of patients on full-dose PPI (a number needed to treat of 8) (42).

Endoscopy and targeted therapy of non-ulcer dyspepsia

Endoscopy-negative GERD and functional dyspepsia are often treated, at least initially, with a PPI (2). PPIs appear to be more effective than H_2-receptor antagonists in endoscopy-negative reflux disease. In head-to-head randomized controlled trials, 53% of patients became symptom free on PPI compared with 42% receiving H_2-receptor antagonists, although the difference was not statistically significant (42). The same pattern of benefit was apparent in placebo-controlled trials (42). For functional dyspepsia, *H. pylori* eradication is modestly effective. Symptoms will naturally improve in 36% of patients, 7% will improve due to eradication therapy, and in 57% of patients substantial symptoms will remain over a 3–12-month period (NNT 15) (20). Full-dose PPIs are no more effective than low-dose PPIs in the management of functional dyspepsia but are more costly to prescribe, while low-dose PPIs are more expensive to prescribe than H_2-receptor antagonists, although the quality of evidence supporting PPIs is stronger (43). On this basis, it can be concluded that if empirical therapy with either PPIs or *H. pylori* eradication is employed, the endoscopy adds little more than, possibly, reassurance. Unfortunately, there are very few head-to-head studies of test-and-treat versus institution of a PPI. Secondary care data from Italy suggested that test-and-treat was superior (44). Primary care data are limited, but two preliminary reports support test and treat over using PPI empirically (45, 46).

Endoscopy in excluding malignancy and the role of age in selection

One approach that has been taken has been that of only referring patients for endoscopy who are older or have alarm features (1). On the other hand, the majority of patients with alarm features who are referred for endoscopy will have normal findings. Currently, there is increasing controversy concerning the issue of an age threshold. A number of the management trials have included adult patients of all ages and very few malignancies were identified (10). Alarm features (e.g. weight loss, dysphagia, vomiting, bleeding) are present in 10% of patients presenting with dyspepsia in primary care (47). Since cancers of the upper GI tract are rare, this means that the positive predictive value of alarm symptoms is low and the negative predictive value high.

Retrospective cohorts of patients in whom upper GI cancers were detected have been reported. In two studies conducted in the UK it was found that cancer was rarely detected in patients under the age of 55 years without alarm symptoms, and, when found, the cancer was usually inoperable (48, 49). The rate of presentation of malignancy in patients of less than 55 years without alarm symptoms was at 1 per million of the population per year. Data from the USA and Canada have shown similar findings (50, 51). All of these studies have limited value, since patients were not referred until they had developed the signs of late disease, as earlier investigation may have permitted surgery.

Two studies in primary-care populations provide more applicable evidence. In a Dutch study, weight loss (Odds Ratio, OR: 4.4), dysphagia (OR: 6.1), male sex (OR: 1.4) and smoking (OR: 2.6) were the only independent factors increasing the likelihood of malignancy (52). Nocturnal dyspepsia (OR: 0.3), daytime heartburn (OR: 0.2) and a history of dyspepsia longer than a year (OR: 0.4) featured a lower-than-average likelihood of malignancy. In a Danish primary-care study of 2479 patients, there were 13 upper GI cancers; only 1.5% of patients with dysphagia and 1.5% of those with weight loss had upper GI malignancy (47). A similar rate of colorectal cancers and upper GI cancer was diagnosed in dyspeptic patients with weight loss. Although changes such as intestinal metaplasia or Barrett's esophagus may be detected by endoscopy, the cost-effectiveness of surveillance and of treatment of these conditions is controversial (53, 54).

As gastric cancer is rare in dyspeptic patients, randomized, controlled trials to evaluate different referral thresholds are unfeasible. Simulation modeling can be used to extrapolate from existing knowledge and explore different referral rules. A Discrete Event Simulation of the management of dyspepsia in primary care has been adapted to compare the cost per life-year saved by prompt endoscopy-based management and an *H. pylori* 'test-and-treat' strategy for patients above different age thresholds (55). In this simulation model of endoscopy versus test-and-treat, the test-and-treat approach saved more life-years up to the age of 60 years and was equally effective up to the age of 70 years. It was only above the age of 70 that upper endoscopy potentially saved more life-years, although in the model this appeared only to be cost effective in men, not women. Hence, endoscopy-based management, even if there is no waiting list delay, is unlikely to be cost effective in Europe.

Conclusions

The available data support the test-and-treat strategy as an initial approach in the management of dyspepsia in primary care settings. Early endoscopy may help target therapy but no specific findings are found in the majority of patients and the cost is high. In uninvestigated dyspepsia, primary-care physicians tend not to distinguish between reflux and other upper GI tract symptoms (13). Based on limited evidence, the prevalence of ulcer disease may be similar in those with and without typical heartburn in primary care, which suggests that distinguishing these entities may not be useful (12). However, this needs to be further investigated in regions with varying *H. pylori* prevalence rates to confirm the findings. Recommending a test-and-treat strategy for patients with typical or predominant reflux symptoms is as yet not well accepted. Non-ulcer dyspepsia and functional dyspepsia are poor terms that refer to heterogeneous disorders that cannot be diagnosed without resorting to other disease exclusion. In functional dyspepsia, *H. pylori* eradication should be offered as first-line therapy if patients are infected, despite the limited benefits

(20). A number of questions remain, including whether the patient should be retested after eradication therapy to help guide subsequent management, as the majority of patients will continue to be symptomatic or may suffer relapse. Acid suppression remains the first-line therapy for *H. pylori*-negative functional dyspepsia. However, little second-line therapy has established efficacy. Functional dyspepsia can fall on the continuum between irritable bowel syndrome and GERD, and therapy remains limited because the correct pathophysiological targets are still poorly defined.

The evidence overall strongly supports the view that patients presenting with alarm features of new onset do deserve prompt endoscopy (10). However, age thresholds as a specific alarm feature in Europe are now controversial and, certainly, based on the available evidence, if an age threshold is used, it appears to be able to be raised to at least 60 years.

The current data suggest there is a toss-up amongst the various non-invasive strategies available. Test-and-treat appears to be the 'gold standard' non-invasive management strategy. However, there is insufficient evidence to determine whether empiric PPI therapy may be as cost effective. However, the background prevalence of *H. pylori* is an important driver of the assumptions here. If there is a low background prevalence of *H. pylori* (under 20%), then test-and-treat becomes less attractive and acid suppression strategies tend to dominate. On the other hand, with higher background prevalences of *H. pylori* and ulcer disease, test-and-treat probably dominates over blind empiric acid suppression therapy. One potential concern surrounding prolonged empiric PPI therapy in those with uninvestigated dyspepsia or reflux relates to the risk of accelerating the progression of *H. pylori* gastritis to intestinal metaplasia and atrophy with potent acid suppression (56–58). This topic remains a major area of unresolved debate. Endoscopy strategies overall cannot be supported by the current evidence in the absence of alarm features.

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