REVIEW

A rational approach to uninvestigated dyspepsia in primary care: review of the literature

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In this paper the rationale and limitations of the four most important approach strategies to dyspepsia in primary care (empiric treatment, prompt endoscopy, "test-and-scope", and "test-and-treat") are analysed. It is concluded that in the absence of alarm symptoms, a "test-and-treat" approach is currently the most rational approach provided that three conditions are met: (1) a highly accurate test should be used, (2) the prevalence of *Helicobacter pylori* in the population should not be too low, and (3) an effective anti-*H pylori* regimen should be prescribed taking sufficient time to instruct and motivate the patient.

Dyspepsia is not a diagnosis, but merely a cluster of symptoms believed to be referable to the upper gastrointestinal tract.¹⁻⁴ It is very common in the adult Western population with prevalence rates ranging from 19% up to 41% in several epidemiological studies.⁵⁻¹⁷ Although most dyspeptics do not seek medical attention, half of them regularly use over the counter drugs.^{10 12 16} About one out of every four subjects with dyspepsia consults his general practitioner,^{9 10 13 16 18} and these visits account for 1%-4% of all consultations in primary care.^{9 12 19} Twenty five per cent of these patients are referred for further investigations (that is, endoscopy, ultrasonography, etc) or to a secondary care physician (about 10%) but the majority of patients are managed empirically by their general practitioner.^{9 10 20-22} Altogether, dyspepsia is an important health issue and constitutes a significant clinical problem in primary care.

The objective of general practitioners when dealing with dyspeptic patients is to abolish or reduce symptoms, either by the detection and treatment of underlying disease or by symptomatic treatment or mere reassurance of the patient. Secondary objectives are the timely diagnosis of significant disease, avoidance of over-treatment, and containment of costs (box 1). The optimal approach to achieve these goals, however, is still a matter of discussion, even though several guidelines have been formulated.²³⁻²⁵ This current lack of agreement is related to several points, starting with the definition of dyspepsia. According to the recent Rome consensus the term dyspepsia refers to persistent or recurrent upper abdominal pain or discomfort, supposed to be referable to the upper gastrointestinal tract.²⁶ The consensus meeting excluded patients with heartburn or acid regurgitation as the predominant

symptom, as these symptoms were thought to be predictive of gastro-oesophageal reflux disease (GORD).^{27 28} Nevertheless, many studies on dyspepsia used other definitions and some do include patients with predominant heartburn.^{9-11 13 16} Secondly, the optimal approach of the dyspeptic patient depends on the prevalences of the underlying causes of dyspepsia. These prevalences differ between various parts of the world. For example, in South East Asia, where gastric cancer is a common condition,²⁹ the optimal approach is likely to be different from that in the Western world.³⁰ Thirdly, the role of some conditions in causing dyspeptic symptoms is still debated. This is especially true for the relationship between *Helicobacter pylori* gastritis and dyspepsia without an endoscopically identifiable cause (functional dyspepsia). Finally, what is the most cost effective approach largely depends on the local availability and costs of medical provisions (especially endoscopy).

The primary care physician can choose between the following strategies when dealing with uninvestigated dyspepsia: (1) symptom guided empirical treatment, (2) direct referral for endoscopy, (3) non-invasive testing for *H pylori* and subjecting the *H pylori* positive patients to endoscopy ("test-and-scope"), and (4) non-invasive testing for *H pylori* and treatment of the infection in *H pylori* positive patients ("test-and-treat"). The aim of this review is to evaluate the rationale behind each strategy and to weigh the available clinical evidence. It focuses on dyspepsia as encountered in primary care and the situation in the Western world. It does not discuss the approach of the patients with mild symptoms of short duration, which usually can be managed by reassurance and simple lifestyle advice. Nor does it consider the approach of patients with heartburn or acid regurgitation as the only or predominant symptom. It is recognised, however, that heartburn is frequently part of the dyspeptic syndrome.²⁶ Finally, patients with "alarm" symptoms (box 2) and patients using non-steroidal anti-inflammatory drugs (NSAIDs) are not subjects of this review. Patients with alarm symptoms should be subjected to endoscopy without delay. In patients using NSAIDs, this drug should be discontinued if at all possible before considering further steps.

Abbreviations: GORD, gastro-oesophageal reflux disease; NSAID, non-steroidal anti-inflammatory drug

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Box 1: Objectives in dealing with the dyspeptic patient in primary care

- Abolishment or reduction of symptoms.
- Timely diagnosis of significant disease.
- Avoidance of over-treatment.
- Containment of medical and non-medical costs.

Box 2: Sinister symptoms in the dyspeptic patient that necessitate endoscopy

- Unintentional weight loss.
- Iron deficiency anaemia.
- Gastrointestinal bleeding.
- Dysphagia.
- Odynophagia.
- Previous gastric surgery.
- Persistent vomiting.
- Epigastric mass.

DIFFERENTIAL DIAGNOSIS IN UNINVESTIGATED DYSPESPSIA

Dyspepsia can be ascribed to several conditions. Only a few studies have examined their relative prevalences in a primary care population. In three studies all patients consulting their general practitioner for dyspeptic symptoms were referred for endoscopy. Reflux oesophagitis was found in 6%–24%, peptic ulcer disease in 13%–16%, malignant disease in 1%–2%, and in more than 60% of the patients no abnormalities were found at endoscopy,^{31–33} the latter patients being usually diagnosed as having functional dyspepsia. More data are available from studies evaluating “open access endoscopy”. In “open access endoscopy” the general practitioner directly refers the patients for upper gastrointestinal endoscopy without prior evaluation by a specialist. Data from these studies should, however, be considered with caution. The patients represent a selected population, as no more than 25% of the patients in primary care are referred for further investigations.^{9–10} In these studies oesophagitis was diagnosed in 2%–31%, peptic ulcer disease in 13%–28%, a malignancy in 0.2%–4.0%, and endoscopy revealed no visible disease in 35%–89%. In table 1 the data from the three primary care studies and the “open access endoscopy” studies with over 400 participating patients each are summarised.^{31–50} Considering these data, it is noteworthy that the ranges of frequencies of the various endoscopic diagnoses in the studies evaluating “open access endoscopy” are very much alike those in the primary care studies. This suggests that clinical judgment does not adequately select patients at higher risk for underlying pathology, which is in line with other studies showing that it is impossible to predict endoscopic lesions in dyspeptic patients only from the clinical presentation.^{16–47–51–52} It is recognised, however, that in daily practice clinical judgment is not the only consideration to refer a patient for endoscopy, and other reasons, like a patient’s fear of cancer, may be involved. It is also noteworthy that the prevalences of endoscopic diagnoses vary considerably among the studies. This is probably explained by differences in inclusion criteria and by geographic differences, but prevalences are also changing. Several studies have shown that during the last decades the prevalences of GORD and adenocarcinoma of the oesophagus and cardia have been increasing rapidly in the Western world, together with decreasing prevalences of peptic ulcer disease and distal gastric cancer.^{53–55} The decreasing prevalence of *H pylori* infection is generally considered to contribute to these epidemiological changes.⁵⁶ Considering these varying and changing prevalences of underlying conditions in dyspepsia, it is obvious that the optimal approach of

the dyspeptic patient may be different between the various geographic regions and may also change with time.

ROLE OF *H PYLORI* IN DYSPESPSIA

In the years after the first description of *H pylori* by Warren and Marshall in 1983⁵⁷ it has become clear that this Gram negative curved bacterium plays a major part in several conditions of the upper gastrointestinal tract. There is ample evidence showing a causal relationship between *H pylori* infection and peptic ulcer disease. When patients using NSAIDs are excluded, the large majority of patients with peptic ulcer disease carry the infection⁵⁸ and eradication of *H pylori* heals the disease^{59–66} and prevents its recurrence.^{61–64–66–69} Moreover, *H pylori* gastritis is the most important risk factor for the subsequent development of peptic ulcer disease,^{70–71} a risk that has been estimated to be about 10% in a lifetime.^{72–73} On the other hand, several recent studies show that not all peptic ulcer disease is caused by *H pylori*, even after exclusion of patients using NSAIDs.^{74–78} The decreasing prevalence of *H pylori* in the Western world is likely to cause a relative increase in the proportion of these “idiopathic” peptic ulcers.^{76–79}

In addition to the causal relation with peptic ulcer disease, it has been shown that there is also a strong association between *H pylori* gastritis and the occurrence of gastric cancer^{80–89} and the International Agency for Research on Cancer has classified *H pylori* as a class I risk factor for gastric cancer.⁹⁰ Moreover, gastric MALT lymphoma (mucosa associated lymphoid tissue lymphoma)^{91–93} and Ménétrier’s disease of the stomach have been associated with *H pylori*.^{94–96} These conditions, however, are rare, and therefore this association will not be a major factor influencing decision making in the dyspeptic patient.

The relationship between *H pylori* and functional dyspepsia has been debated for a long time and is still not entirely clarified.^{97–98} Several studies have suggested a higher prevalence of *H pylori* in functional dyspepsia, but others came to dissimilar conclusions.^{99–100} Decisive evidence could be expected from studies evaluating the effect of *H pylori* eradication on symptoms in functional dyspepsia. Early studies were flawed by methodological problems,^{101–102} but recently four large well conducted randomised placebo controlled clinical trials with a follow up period of 12 months have been published as full papers.^{103–106} The results, however, are contradictory (table 2). A recent meta-analysis included these studies as well as five other studies^{107–111} and suggested that there is a small but significant benefit of about 10% of *H pylori* eradication over placebo.¹¹² Another meta-analysis, however, included other studies^{109–113–117} apart from the ones listed in table 2 and did not show any benefit.¹¹⁸

H pylori infection does not seem to be a causal factor in the pathogenesis of GORD.^{119–121} Epidemiological data even suggest that the infection protects against this condition. While the prevalence of *H pylori* gastritis is declining in the Western world, GORD and Barrett’s carcinoma are becoming more common.^{53–122–123} Moreover, some studies suggest that eradication of *H pylori* can induce GORD,^{124–125} although this has not been confirmed by others.^{126–128}

IMMEDIATE ENDOSCOPY OR SYMPTOM GUIDED EMPIRICAL TREATMENT

Endoscopy is the most appropriate investigation to detect pathological lesions in the upper alimentary tract as well as the presence of *H pylori*.^{129–130} Immediate endoscopy in patients with dyspepsia results in a definite diagnosis from the outset and ensures that the patient receives the most appropriate treatment. It is evident that in most patients with dyspepsia no underlying disease can be identified. Several studies, however, have shown that even then an endoscopy may have its merits. A negative endoscopy may have a significant reassuring effect and may result in a decreased use of medication and

Table 1 Prevalences of endoscopically encountered diseases in dyspeptic patients

	No	Reflux oesophagitis (%)	Peptic ulcer disease (%)	Malignancy (%)	Functional dyspepsia (%)
Unselected primary care patients					
Heikinen <i>et al</i> ^{B1} *	400	15	13	2.3	70
Kagevi <i>et al</i> ^{B2} *	172	6	13	1.2	79
Hansen <i>et al</i> ^{B3}	612	24	16	0.7	59
Range		6–24	13–16	0.7–2.3	59–79
Weighted mean		18	15	1.3	66
Open access endoscopy studies with >400 patients					
Ayoola <i>et al</i> ^{B4} *	10112	11	17	1.5	70
Hungin <i>et al</i> ^{B5}	6744	17	15	0.6	67
Hallisey <i>et al</i> ^{B6}	2659	19	16	2.7	62
Fedail <i>et al</i> ^{B7}	2500	8	18	2.2	71
Mansi <i>et al</i> ^{B8}	2086	5	13	1.5	81
Holdstock <i>et al</i> ^{B9}	1805	9	14	2.0	75
Fjosne <i>et al</i> ^{B10} *	1275	10	23	4.0	62
Capurso <i>et al</i> ^{B11}	1153	3	8	0.6	89
Stanghellini <i>et al</i> ^{B12}	1057	9	21	0.6	69
Davenport <i>et al</i> ^{B13}	1041	NA	24	2.6	NA
Nyren <i>et al</i> ^{B14}	972	3	23	0.3	74
Gear <i>et al</i> ^{B15}	968	5	17	2.3	76
Johannessen <i>et al</i> ^{B16} *	930	15	17	1.0	67
Bytzer <i>et al</i> ^{B17}	878	2	15	1.4	82
Talley <i>et al</i> ^{B18}	820	14	23	3.4	60
Williams <i>et al</i> ^{B19}	686	14	28	2.5	56
Saunders <i>et al</i> ^{B20} *	559	31	23	0.2	46
Range (%)		2–31	13–28	0.2–4.0	35–89
Weighted mean (%)		12	17	1.6	70

NA, data not available.

*In these studies more than one diagnosis was allowed in a single patient. Therefore, as functional dyspepsia was defined as the absence of either reflux oesophagitis, peptic ulcer disease or malignancy, this may have led to an underestimation of the percentage of patients with functional dyspepsia (within a total of 100%).

in fewer medical consultations.^{131–133} Investigating all dyspeptic patients by endoscopy, however, is not feasible in view of the high incidence of dyspepsia and the limited availability of endoscopic facilities. Therefore, alternative approaches have been suggested.

Many dyspeptic patients consult their general practitioner mainly because of fear of possible serious disease and sometimes mere reassurance may be sufficient.^{13 18 46 134} If the symptoms do not abolish spontaneously, it has been proposed to prescribe a trial of treatment, reserving endoscopy for those patients who do not respond or whose symptoms recur after stopping treatment.^{20–22 135} This strategy has been promoted by several organisations of both primary and secondary care physicians.^{2 25 49 129 136} The choice of the drug may be dictated by the predominant symptom² but treatment most often consists of an acid suppressing drug given during a fixed period. H₂-receptor blocking agents are used predominantly, although they are being gradually replaced by the more powerful proton pump inhibiting drugs. Acid suppression is effective in GORD and peptic ulcer disease and a few studies have shown some efficacy in functional dyspepsia.^{137–140} Besides acid suppressive

drugs, prokinetics, especially cisapride, have been advocated for the empirical treatment of uninvestigated dyspepsia. This drug is shown to be of benefit in GORD^{141–152} and functional dyspepsia,^{153–160} and may have some efficacy in peptic ulcer disease.^{161–164} Recently, however, serious cardiac side effects of cisapride were reported and, for that reason, the drug has been withdrawn from the US market.¹⁶⁵

SELECTION FOR ENDOSCOPY BY NON-INVASIVE TESTING FOR *H PYLORI*: THE “TEST-AND-SCOPE” AND “TEST-AND-TREAT” STRATEGIES

The incorporation of the *H pylori* concept in the approach of uninvestigated dyspepsia has led to the development of two major strategies: “test-and-scope” and “test-and-treat”.

The “test-and-scope” strategy was first suggested by Sobala *et al* in 1991.¹⁶⁶ They reasoned that dyspeptic patients under the age of 45 without alarm symptoms or NSAID use and testing negative for *H pylori* by non-invasive means have a very low probability for serious underlying disease. Therefore, they postulated that these patients could safely be treated empirically, without the need for an endoscopy. When this strategy was tested retrospectively in a group of 293 patients referred for endoscopy, they found that the total number of endoscopies performed would have been reduced by 25% in all age groups and by 48% in the age group below 45 years, without missing any peptic ulcer or malignancy. Other retrospective studies showed comparable results with a reduction in the number of endoscopies between 11% and 35% when all patients referred for endoscopy were considered, but at the cost of missing up to 2% of the peptic ulcers.^{167–175} Patel *et al* were the first to evaluate this strategy prospectively in 183 consecutive patients.¹⁷⁶ Seventy patients below the age of 45 without sinister symptoms or NSAID use and testing *H pylori* negative by serology were referred back to their general practitioner for symptomatic treatment without an endoscopy

Table 2 Effect of *H pylori* eradication on symptom improvement in patients with functional dyspepsia: results of double blind placebo controlled studies with one year follow up published as full papers

	No	Anti- <i>H pylori</i> treatment (% symptom improvement)	Placebo (% symptom improvement)
Blum <i>et al</i> ^{I06}	328	27.4	20.7
McColl <i>et al</i> ^{I05}	318	21	7*
Talley <i>et al</i> ^{I04}	275	24.1	21.8
Talley <i>et al</i> ^{I03}	337	46	50

*p=0.03.

Box 3: Factors with significant impact on the cost effectiveness of the various approaches in patients with dyspepsia

- Cost of endoscopy.
- Cost of treatment.
- Cost of physician visit.
- Prevalence of *H pylori* in the dyspeptic population.
- Prevalence of peptic ulcer disease in *H pylori* positive patients.
- Prevalence of underlying diseases in dyspepsia.
- Benefit of *H pylori* eradication in patients with functional dyspepsia.
- Recurrence of dyspeptic symptoms in patients with (functional) dyspepsia after treatment.

performed. Only three of these patients eventually underwent endoscopy, resulting in an overall reduction in the number of endoscopies by 37%. Moreover, endoscopy did not seem to influence subsequent symptom severity, quality of life, and number of days lost from work when these non-endoscoped patients were compared with a historic control group of *H pylori* negative endoscoped subjects. The number of physician visits and medication use were even less in these non-endoscoped patients. This is in accordance with the study of Asante *et al*, who showed that endoscopy in seronegative patients does not influence quality of life, number of visits to the general practitioner, or number of days lost from work.¹⁷⁷

A further reduction in the number of endoscopies could possibly be reached if *H pylori* positive dyspeptic patients were not subjected to endoscopy, but received immediate anti-*H pylori* treatment: the “test-and-treat” strategy. In this way, patients with *H pylori* related peptic ulcer disease would be treated adequately without the need for an endoscopy. If the symptoms persisted, the patient could still be referred for endoscopy.

STUDIES COMPARING THE VARIOUS STRATEGIES

In several studies the various strategies to approach the dyspeptic patient were compared by computer assisted decision analysis.^{178–185} Decision analysis is a quantitative method for estimating the outcome, both clinical and financial, of alternative management strategies. In such an analysis calculations are based on data from the literature and on estimates by expert opinion. Data in the model are often uncertain but recalculation of the outcome after varying a single assumption over a reasonable range can be used to show to what extent different parameters influence the conclusions. In that way these studies have identified factors, summarised in box 3, that have a significant impact on the cost effectiveness of any approach of dyspepsia. Most studies concluded that a non-invasive approach, especially by a “test-and-treat” strategy, is likely to be the most cost effective,^{178–185} although this conclusion was heavily influenced by the costs of endoscopy.¹⁷⁹ In these decision analytic studies, however, not all variables were incorporated in the model and, some aspects with a possible impact on the outcome of a strategy were not studied. Such aspects include a positive family history (peptic ulcer disease, cancer), the possible reassuring effect of a negative endoscopy, and the significance of detecting Barrett’s oesophagus, to name a few. Therefore, such mathematical studies cannot replace prospective clinical trials.

Just a few randomised trials have evaluated the various approaches of the dyspeptic patient in a clinical setting.^{131–186–190} Most of them compared a non-invasive approach, either the “test-and-treat” strategy or empirical acid suppressive treatment, with prompt endoscopy. The “test-and-treat” strategy was evaluated in a limited number of

studies.^{186–188–191} Heaney *et al* randomised *H pylori* positive patients as determined by the ¹³C-urea breath test to either anti-*H pylori* treatment or prompt endoscopy.¹⁸⁶ In the endoscopy group only the patients with peptic ulcer disease received anti-*H pylori* treatment. At one year follow up, only 27% of the patients who were not endoscoped initially had undergone endoscopy. The dyspepsia scores had improved significantly more in the non-endoscoped patients than in those subjected to endoscopy. Jones *et al* compared the “test-and-treat” strategy with standard clinical care in primary care.¹⁸⁷ In standard clinical care, only patients with proved peptic ulcer disease received anti-*H pylori* treatment. It was shown that during a follow up of one year, only 12% of the patients in the “test-and-treat” group eventually underwent endoscopy, compared with patients receiving standard clinical care. Clinical outcome was comparable in both groups, but medical costs in the “test-and-treat” group were only about half of that in the control group. Lassen *et al* compared the “test-and-treat” strategy using the ¹³C-urea breath test with prompt endoscopy.¹⁸⁸ Again, in the endoscopy arm, only the patients with peptic ulcer disease received anti-*H pylori* treatment. At the end, 40% of the patients in the “test-and-treat” group had been referred for endoscopy. Symptom resolution, changes in quality of life, the use of resources (medication, visits to outpatient clinics, days in hospital, visits to general practitioner), and the number of sick leave days were comparable in both study groups. Patients in the endoscopy group, however, were more satisfied with the treatment and were more often prescribed proton pump inhibitors. It was concluded that the “test-and-treat” strategy is as efficient and safe as prompt endoscopy. Finally, Arents *et al* compared the “test-and-treat” strategy using *H pylori* serology with prompt endoscopy.¹⁹¹ In contrast to other studies, all *H pylori* positive patients received anti-*H pylori* treatment in both study arms. At one year of follow up, 40% of the patients in the “test-and-treat” group had been referred for endoscopy. Symptom resolution, improvement in quality of life, and patient satisfaction were comparable in both study groups.

The most important study comparing acid suppression to prompt endoscopy was performed by Bytzer *et al*.¹³¹ In that study, patients were randomised to prompt endoscopy or to a trial of empirical treatment with H₂-receptor blocking agents. Prompt endoscopy proved to be more cost effective and to cause more patient satisfaction than empirical treatment with an H₂-receptor blocking agents. Laheij *et al* compared prompt endoscopy with an approach in which patients initially received empirical treatment with omeprazole, followed by a “test-and-treat” strategy if symptoms persisted.¹⁸⁹ After one year of follow up, 31% of the patients in the group receiving empirical treatment had been referred for endoscopy. Clinical outcome was the same in both groups, but medical costs were lower in the group at first subjected to empirical treatment. Finally, in one study, all four different strategies were compared: initial treatment with acid suppression, “test-and-treat”, “test-and-scope”, and immediate endoscopy.¹⁹⁰ In that study, prompt endoscopy was initially the most expensive approach, but after a one year follow up period it became the most cost effective one as subsequent costs were reduced.

Like the decision analytic studies, these clinical studies also have their limitations. They were performed in a specific setting in which the factors, listed in box 3, all have their significant influence on the outcome. These factors may have a diverse impact in different regions or clinical settings. For instance, all studies, except the study by Arents *et al*, were performed in a secondary care setting and the results may not be applicable for the dyspeptic patient visiting his primary care physician. Moreover, all studies used a specific treatment protocol. For example, in the two trials comparing a “test-and-treat” strategy with prompt endoscopy, all patients testing positive for *H pylori* in the “test-and-treat” group received anti-*H pylori* treatment whereas *H pylori* positive patients in

the endoscopy group only received such treatment if they had endoscopic evidence of peptic ulcer disease denying functional dyspepsia patients any possible benefit of anti-*H. pylori* treatment. Such a study design may have biased the results.

RATIONALE AND LIMITATIONS OF THE VARIOUS APPROACHES OF THE DYSPEPTIC PATIENT

The optimal approach to the dyspeptic patient in primary care is the one that best serves the objectives listed in box 1. Frequently, none of the aforementioned strategies will positively serve all these objectives and in clinical practice none of the strategies is always clearly superior to the others. What is the most cost effective strategy is determined by the factors enumerated in box 3 and the significance and impact of most of these factors may vary considerably between different regions of the world. Even within a single region, however, it is not likely that a single strategy is the best one in every patient. Sometimes a different approach should be chosen as dictated by the characteristics of the individual patient (age, family history, comorbidity, fear of cancer, etc). Therefore, it is the authors' view that, in order to be able to treat the dyspeptic patient in the most cost effective way, the primary care physician should be aware of the factors listed in box 3 and understand the rationale and limitations of the various approaches of uninvestigated dyspepsia.

If one chooses to prescribe empirical treatment with an acid suppressive agent, what can be expected? It is evident that acid suppressive therapy will be beneficial in patients with peptic ulcer disease and GORD.¹⁹²⁻¹⁹⁷ In functional dyspepsia the benefit of acid suppressive drugs is less clear. Studies examining the efficacy of acid suppressive agents in this condition are difficult to evaluate,^{153 157 198-203} but about half of the studies examining H₂-receptor blocking agents show a modest positive effect. Only a few randomised placebo controlled trials studied the efficacy of proton pump inhibitors in functional dyspepsia and showed a benefit of about 10% over placebo.^{137-140 204} Taken together with the well known large placebo effect of any drug in functional dyspepsia,^{153 157} these data explain that a trial of treatment with an acid suppressive agent reduces symptoms in a fair number of patients with uninvestigated dyspepsia. Nevertheless, several objections can be made to such an approach. The benefit of an attempt to treat the patient empirically depends on the number of patients becoming permanently symptom-free afterwards or at least for a long period. Unfortunately, in patients with peptic ulcer disease and GORD, symptoms usually recur after stopping the treatment.^{61 193 205 206} It is very likely that the same can be said about many patients with functional dyspepsia, as this is also often a chronic condition with the majority of the patients still experiencing symptoms after one year.^{7 15 207-209} Therefore, it can be anticipated that, unless one is willing to continue acid suppression without a definite diagnosis, a trial with such medication just postpones endoscopy in most patients. This assumption is supported by the study of Bytzer *et al* who showed that 67% of dyspeptic patients who received empirical treatment with H₂-receptor blocking agents underwent endoscopy within a year.¹³¹ The second objection that can be made against this approach is a practical one. If endoscopy is performed after all, signs of peptic ulcer disease or GORD may be obscured if the medication has not been withdrawn for a sufficiently long period before endoscopy as commonly occurs in clinical practice. A trial with a prokinetic drug (cisapride) will be of benefit in patients with GORD and probably in some with peptic ulcer disease and functional dyspepsia and will also have a considerable placebo effect in patients with functional dyspepsia.^{153 157} Therefore, it can be anticipated that, like acid suppression, a trial of such treatment will have a favourable response in a fair number of patients. Most drawbacks mentioned above for acid suppression, however, are also pertinent for this class of drugs, although prokinetic agents are

probably less likely to obscure endoscopic signs of GORD and peptic ulcer disease. The recently described cardiac side effects of cisapride will now limit its use.

What about continuing treatment without a definite diagnosis? Although this is an option, several objections can be made to such an approach. First, patients with peptic ulcer disease will be effectively treated, but a far more cost effective treatment (*H. pylori* eradication) is to be preferred.²¹⁰ Second, if patients with GORD, who are likely to respond well to potent acid suppression, are not subjected to endoscopy, Barrett's metaplasia will not be detected. This condition occurs in about 10%-15% of all patients with GORD,²¹¹⁻²¹³ and is associated with an increased risk for oesophageal cancer,²¹⁴⁻²¹⁶ although it was recently suggested that this relative risk has been exaggerated.²¹⁷ Recent studies have indeed confirmed the latter.^{218 219} Whether or not failure to diagnose Barrett's oesophagus is significant depends on one's view on the necessity of endoscopic surveillance of these patients. This is still an unsettled issue.^{214 215 216 220-226} Finally, it has been argued that empirical treatment with acid suppressive agents may lead to a significant delay in diagnosing malignant disease.²²⁷ In the Western world, however, this contention does not seem to hold as gastrointestinal malignancy is extremely rare in dyspeptic patients below 45-50 years if alarm symptoms are not present.²²⁸⁻²³⁰

If one chooses to test for *H. pylori* one should first have knowledge of the reliability of the test results (its positive and negative predictive value). This is not only dependent on the characteristics of the test (sensitivity and specificity) but also on the prevalence of the infection in the population. For instance, as the prevalence of *H. pylori* infection is decreasing in the younger age group, the likelihood of a false positive test in this age group increases. This may be acceptable if a "test-and-scope" strategy is followed as the test can be confirmed by one or more biopsy based methods, but it is certainly not acceptable if one follows a "test-and-treat" strategy. In that case, only highly accurate tests (with very high specificity) are acceptable and serology will soon not be suitable anymore. Urea breath tests^{231 232} and stool antigen tests²³³⁻²³⁵ may be valuable alternatives.

Screening for *H. pylori* will provide one of two possibilities: a positive test result or a negative test result. A negative test result leads to the same approach in both the "test-and-scope" and "test-and-treat" strategies. In such a patient peptic ulcer disease is highly unlikely, leaving functional dyspepsia and GORD as the most likely diagnoses. In the absence of alarm symptoms malignancies are extremely rare under the age of 50.²²⁸⁻²³⁰ Most patients can, therefore, safely be treated blindly with acid suppression. Endoscopy will not change the management in most of these patients.¹⁷⁷

In case of a positive test result the "test-and-scope" strategy will detect most patients with peptic ulcer disease. Anti-*H. pylori* treatment can be limited to these patients as the benefit of such a treatment is only shown decisively in peptic ulcer disease.²³⁶ Treatment can be guided by susceptibility testing based on *H. pylori* culture. In the "test-and-treat" strategy, however, all *H. pylori* positive patients receive anti-*H. pylori* treatment. This approach will be beneficial in most patients with peptic ulcer disease and possibly a few patients with functional dyspepsia, but in the large majority of patients there will be no short term benefit. Nevertheless, two additional arguments support the eradication of *H. pylori* in all patients with uninvestigated dyspepsia. First, in contrast to all other therapeutic options, anti-*H. pylori* treatment only takes one to two weeks and, if successful, eliminates a potential cause of dyspepsia for lifetime, as reinfection is rare in the Western world.^{69 237-242} Second, it may have a positive effect by preventing future disease, especially peptic ulcer disease.⁷¹⁻⁷³ Whether gastric cancer is prevented by eradication of *H. pylori* is still highly uncertain,²⁴³ but some have advocated prophylactic anti-*H. pylori* treatment for patients on long term acid suppressive therapy as these patients may be at increased risk of

Box 4: Arguments for and against *H pylori* treatment in uninvestigated dyspepsia

For

- A single short term treatment, with lifelong effects when beneficial.
- Prevents future disease.

Against

- No benefit in most patients.
- Exposes patients to side effects.
- Induces antibiotic resistance (*H pylori* and other gastrointestinal bacteria).
- Possibly induces GORD after *H pylori* eradication.

developing gastric cancer.^{244–246} This issue is still debated^{247–248} but it may support *H pylori* eradication in dyspeptic patients.

On the other hand, several arguments have been cited against treatment of the infection in all patients with uninvestigated dyspepsia in whom *H pylori* is detected. First of all, it will not diminish symptoms in the large majority of patients and just expose them to the side effects of the anti-*H pylori* regimen,^{249–253} even though these are usually mild and in a trial setting form a reason to discontinue treatment in less than 5% of all patients.^{250–254} Second, treating *H pylori* infection in all these patients may induce antibiotic resistance. To what extent this occurs in clinical practice is not known. Antibiotic resistance in *H pylori* is indeed a major problem^{254–258} and its prevalence seems to be increasing.^{259–260} Whether this increase is caused by anti-*H pylori* treatment or by the prescription of antibiotics for other indications, however, is not known. As the current anti-*H pylori* regimens are so effective, with eradication rates of >95% in susceptible strains,²⁵⁵ induction of resistance should be a rare event, as long as the regimen is properly prescribed and time is taken to instruct and motivate the patient.²⁶¹ Third, eradication of *H pylori* may induce other diseases, especially GORD,^{124–125–262} but this does not seem to be a clinically significant problem in the majority of patients.^{110–263} Considering all these arguments favouring and renouncing *H pylori* treatment in uninvestigated dyspepsia (box 4), it is the authors' view that the weight of the evidence favours treatment of the infection when it is diagnosed.

CONCLUSIONS AND RECOMMENDATIONS

It is unlikely that a single strategy will be applicable in all dyspeptic patients in primary care. Nevertheless, in our view, the "test-and-treat" strategy is currently a rational way to deal with many patients with uncomplicated dyspepsia, provided that the following conditions are met. First, the positive predictive value of the test should be adequate. Therefore, an accurate test should be used and the prevalence of the infection should be monitored. Second, an effective anti-*H pylori* treatment regimen should be used and time should be taken to instruct the patient in order to improve compliance. If the prevalence of *H pylori* gets low, as is the case in the younger age group in Western countries, the "test-and-treat" strategy becomes less suitable. "Test-and-scope" becomes more appropriate as the positive non-invasive *H pylori* test can be confirmed by two or more biopsy based tests. In our view, if the infection is confirmed, it should be treated even if no peptic ulcer disease is detected as such an approach may prevent future diagnostic dilemmas and possibly future disease. In both strategies all patients testing negative for *H pylori* can safely be treated with acid suppression (or prokinetics if symptomatology suggests a motility disorder). If this treatment is successful, the medication should gradually be stopped if possible. If this approach fails and the patient remains symptomatic endoscopy should be considered mainly to reassure the patient, as it is unlikely to reveal underlying

disease or change treatment. If the prevalence of *H pylori* gets very low, as is likely to be the case in the future in Western societies, non-invasive testing for the micro-organism is probably not appropriate any more. In that situation empirical treatment may be the way to proceed, even though it may just postpone endoscopy in some patients. Acid suppressive drugs, especially proton pump inhibitors, are then the drugs of choice. Prokinetics may become an alternative but cisapride has recently been withdrawn from the market and other comparably effective prokinetic drugs, both in patients with functional dyspepsia and GORD, are not yet available. In some patients, however, the approach should be individualised as dictated by their personal history. Any alarm symptom should urge for an immediate endoscopy. A strong family history for peptic ulcer disease may be a persuasive argument in favour of a "test-and-treat" approach even if the prevalence of *H pylori* is low. If fear of cancer is deep rooted early endoscopy should be considered. Therefore, the taking of an adequate medical history remains the mainstay of the approach of every patient. This holds no less for the dyspeptic patient in primary care.

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