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 overtreatment, 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.

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

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 DYSPEPSIA

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 DYSPEPSIA

In the years after the first description of *H pylori* by Warren and Marshall in 1983[57] 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 infection[58] 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					
Heikinnen et al[31]*	400	15	13	2.3	70
Kagevi et al[32]*	172	6	13	1.2	79
Hansen et al[33]	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 acces endoscopy studies with >400 patients					
Ayoola et al[34]*	10112	11	17	1.5	70
Hungin et al[35]	6744	17	15	0.6	67
Hallisey et al[36]	2659	19	16	2.7	62
Fedail et al[37]	2500	8	18	2.2	71
Mansi et al[38]	2086	5	13	1.5	81
Holdstock et al[39]	1805	9	14	2.0	75
Fjosne et al[40]*	1275	10	23	4.0	62
Capurso et al[41]	1153	3	8	0.6	89
Stanghellini et al[42]	1057	9	21	0.6	69
Davenport et al[43]	1041	NA	24	2.6	NA
Nyren et al[44]	972	3	23	0.3	74
Gear et al[45]	968	5	17	2.3	76
Johannessen et al[46]*	930	15	17	1.0	67
Bytzer et al[47]	878	2	15	1.4	82
Talley et al[48]	820	14	23	3.4	60
Williams et al[49]	686	14	28	2.5	56
Saunders et al[50]*	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 symptom[2] but treatment most often consists of an acid suppressing drug given during a fixed period. H_2-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-*H pylori* treatment (% symptom improvement)	Placebo (% symptom improvement)
Blum et al[106]	328	27.4	20.7
McColl et al[105]	318	21	7*
Talley et al[104]	275	24.1	21.8
Talley et al[103]	337	46	50

*p=0.03.

> **Box 3: Factors with significant impact on the cost effectiveness of the various approaches in patients with dyspepsia**
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> - 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,[178 181–185] 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 ^{13}C-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 ^{13}C-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 H_2-receptor blocking agents. Prompt endoscopy proved to be more cost effective and to cause more patient satisfaction than empirical treatment with an H_2-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 H_2-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 H_2-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 tests[233–235] 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**
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> **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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REFERENCES

1 **Crean GP**, Card WI, Beatti AD, *et al*. Ulcer-like dyspepsia. *Scand J Gastroenterol* 1982;**17**(suppl 79):9–15.
2 **Colin-Jones DG**. Management of dyspepsia: report of a working party. *Lancet* 1988;**i**:576–9.
3 **Barbara L**, Camilleri M, Corinaldesi R, *et al*. Definition and investigation of dyspepsia. *Dig Dis Sci* 1989;**34**:1271–6.
4 **Heading RC**. Definitions of dyspepsia. *Scand J Gastroenterol* 1991;**26**(suppl 182):1–6.
5 **Doll R**, Jones AF, Bucjatzsch MM. Occupational factors in the aetiology of gastric and duodenal ulcers, with an estimate of their incidence in the general population. *Medical Research Council Reports Series* 1951;**276**:1–9.
6 **Tibblin G**. Ulcusfrekvens bland 50-ariga man. *Lakartidningen* 1966;**63**:4825–9.
7 **Weir RD**, Backett EM. Studies of the epidemiology of peptic ulcer in a rural community: prevalence and natural history of dyspepsia and peptic ulcer. *Gut* 1968;**9**:75–83.
8 **Johnsen R**, Straume B, Forde OH. Peptic ulcer disease and non-ulcer dyspepsia—a disease and a disorder. *Scand J Prim Health Care* 1988;**6**:239–43.
9 **Jones R**, Lydeard S. Prevalence of symptoms of dyspepsia in the community. *BMJ* 1989;**298**:30–32.
10 **Jones RH**, Lydread SE, Hobbs FDR, *et al*. Dyspepsia in England and Scotland. *Gut* 1990;**31**:401–5.
11 **Bernersen B**, Johnsen R, Straume B, *et al*. Towards a true prevalence of peptic ulcer: the Sorreisa gastrointestinal disorder study. *Gut* 1990;**31**:989–92.
12 **Knill-Jones RP**. Geographical differences in the prevalence of dyspepsia. *Scand J Gastroenterol* 1991;**26**(suppl 182):17–24.
13 **Talley NJ**, Zinsmeister AR, Schleck CD, *et al*. Dyspepsia and dyspepsia subgroups: a population-based study. *Gastroenterology* 1992;**102**:1259–68.
14 **Agreus L**, Svardsudd K, Nyren O, *et al*. The epidemiology of abdominal symptoms: prevalence and demographic characteristics in a Swedish adult population. *Scand J Gastroenterol* 1994;**29**:102–9.
15 **Kay L**, Jorgensen T. Epidemiology of upper dyspepsia in a random population. Prevalence, incidence, natural history, and risk factors. *Scand J Gastroenterol* 1994;**29**:2–6.
16 **Penston JG**, Pounder RE. A survey of dyspepsia in Great Britain. *Aliment Pharmacol Ther* 1996;**10**:83–9.
17 **Nyren O**. Functional dyspepsia—a disorder of the stomach ? *The Stomach* 1990: 385–415.
18 **Holtmann G**, Goebell G, Talley NJ. Dyspepsia in consulters and non-consulters: prevalence, health-care seeking behaviour and risk factors. *Eur J Gastroenterol Hepatol* 1994;**6**:917–24.
19 **Heikkinen M**, Pikkarainen P, Takala J, *et al*. General practitioners' approach to dyspepsia. *Scand J Gastroenterol* 1996;**31**:648–53.
20 **Muris JWM**, Starmans R, Fijten GH, *et al*. Abdominal pain in general practice. *Fam Pract* 1993;**10**:387–90.
21 **Warndorff DK**, Knottnerus JA, Huijnen LGJ, *et al*. How well do general practitioners manage dyspepsia ? *J R Coll Gen Pract* 1989;**39**:499–502.

22 **Bodger K**, Daly MJ, Heatly RV. Prescribing patterns for dyspepsia in primary care: a prospective study of selected general practitioners. *Aliment Pharmacol Ther* 1996;**10**:889–5.

23 **Anonymous**. American Gastroenterology Association medical position paper: evaluation of dyspepsia. *Gastroenterology* 1997;**114**:579–81.

24 **British Society of Gastroenterology**. Dyspepsia Management Guidelines. *Guidelines in Gastroenterology* 1996;**1**:1–8.

25 **Numans ME**, de Wit NJ, Geerdes RHM, *et al*. NHG-standaard maagklachten, eerste herziening. *Huisarts en Wetenschap* 1996;**39**:565–77.

26 **Talley NJ**, Colin-Jones D, Koch KL, *et al*. Functional dyspepsia: a classification with guidelines for diagnosis and management. *Gastroenterology Intl* 1991;**4**:145–60.

27 **Klauser AG**, Schindlbeck NE, Muller-Lissner SA. Symptoms in gastro-oesophageal reflux disease. *Lancet* 1990;**335**:205–8.

28 **Silverstein BD**, Pope CE. Role of diagnostic tests in esophageal evaluation. *Am J Surg* 1980;**139**:744–8.

29 **International Agency for Research on Cancer**. Cancer incidence in five continents. *IARC Monograph on the Evaluation of Carcinogenic Risks to Humans* 1987;**88**:1–970.

30 **Lam SK**, Talley NJ. Report of the 1997 Asia pacific consensus conference on the management of Helicobacter pylori infection. *J Gastroenterol Hepatol* 1997;**13**:1–12.

31 **Heikinnen M**, Pikkarainen P, Takala J, *et al*. Etiology of dyspepsia: four hundred unselected consecutive patients in general practice. *Scand J Gastroenterol* 1995;**30**:519–23.

32 **Kagevi I**, Lofstedt S, Persson LG. Endoscopic findings and diagnoses in unselected dyspeptic paptients at a primary health care center. *Scand J Gastroenterol* 1989;**24**:145–50.

33 **Hansen JM**. Dyspepsia in primary care. Clinical decision making and pharmacotherapy in non-organic dyspepsia. (Thesis, Odense University, Odense, Danmark, 1995.)

34 **Ayoola EA**, al Rashed RS, al Mofleh IA, *et al*. Diagnostic yield of upper gastrointestinal endoscopy in relation to age and gender: a study of 10112 Saudi patients. *Hepato-Gastroenterology* 1996;**43**:409–15.

35 **Hungin P**. Open access gastroscopy. (Thesis, University of Newcastle upon Tyne, Newcastle upon Tyne, UK, 1995.)

36 **Hallissey MT**, Allum WH, Jewkes AJ, *et al*. Early detection of gastric cancer. *BMJ* 1990;**301**:513–15.

37 **Fedail SS**, Araba BM, Homeida MM, *et al*. Upper gastrointestinal fibreoptic endoscopy experience in the Sudan. Analysis of 2500 endoscopies. *Lancet* 1983;**ii**:897–9.

38 **Mansi C**, Mela GS, Pasini D, *et al*. Patterns of dyspepsia in patients with no clinical evidence of organic diseases. *Dig Dis Sci* 1990;**35**:1452–8.

39 **Holdstock G**, Wiseman M, Loehry CA. Open-access endoscopy service for general practitioners. *BMJ* 1979;**i**:457–9.

40 **Fjosne U**, Kleveland PM, Waldum H, *et al*. The clinical benefit of routine upper gastrointestinal endoscopy. *Scand J Gastroenterol* 1986;**21**:433–40.

41 **Capurso L**, Koch M, Dezi A, *et al*. Towards a quantitative diagnosis of dyspepsia: the value of clinical symptoms. *Ital J Gastroenterol* 1988;**20**:191–202.

42 **Stanghellini V**, Tosetti C, Paternico A, *et al*. Risk indicators of delayed gastric emptying of solids in patients with functional dyspepsia. *Gastroenterology* 1996;**110**:1036–42.

43 **Davenport PM**, Morgan AG, Darnborough A, *et al*. Can preliminary screening of dyspeptic patients allow more effective use of investigational techniques? *BMJ* 1985;**290**:217–20.

44 **Nyren O**, Adami HO, Gustavsson S, *et al*. The epigastric distress syndrome—a possible disease entity identified by history and endoscopy in patients with nonulcer dyspepsia. *J Clin Gastroenterol* 1987;**9**:303–9.

45 **Gear MW**, Ormiston MC, Barnes RJ, *et al*. Endoscopic studies of dyspepsia in the community: an "open-access" service. *BMJ* 1980;**280**:1135.

46 **Johannessen T**, Petersen H, Kleveland PM, *et al*. The predicitve value of history in dyspepsia. *Scand J Gastroenterol* 1990;**25**:689–97.

47 **Bytzer P**, Schaffalitzky de Muckadell OB. Prediction of major pathologic conditions in dyspeptic patients referred for endoscopy. A prospective validation study of a scoring system. *Scand J Gastroenterol* 1992;**27**:987–92.

48 **Talley NJ**, Weaver AL, Tesmer DL, *et al*. Lack of discriminant value of dyspepsia subgroups in patients referred for upper endoscopy. *Gastroenterology* 1993;**105**:1378–86.

49 **Williams B**, Luckas M, Ellingham JH, *et al*. Do young patients with dyspepsia need investigation? *Lancet* 1988;**ii**:1349–51.

50 **Saunders JH**, Oliver RJ, Higson DL. Dyspepsia: incidence of a non-ulcer disease in a controlled trial of ranitidine in general practice. *BMJ* 1986;**292**:665–8.

51 **The Danish Dyspepsia Study Group**. Value of the unaided clinical diagnosis in dyspeptic patients in primary care. *Am J Gastroenterol* 2001;**96**:1417–21.

52 **Adang RP**, Ambergen AW, Talmon JL, *et al*. The discriminative value of patient characteristics and dyspeptic symptoms for upper gastrointestinal endoscopic findings: a study on the clinical presentation of 1,147 patients. *Digestion* 1996;**57**:118–34.

53 **El-Seraq HB**, Sonnenberg A. Opposing time trends of peptic ulcer and reflux disease. *Gut* 1997;**43**:327–33.

54 **Baldi F**, GISMAD. Prevalence of reflux esophagitis (RE) in Italy. *Gastroenterology* 1997;**112**:A63.

55 **Prach AT**, MacDonald TA, Hopwood DA, *et al*. Increasing incidence of Barrett's oesophagus: education, enthusiasm, or epidemiology? *Lancet* 1997;**350**:933.

56 **Blaser MJ**. Helicobacter pylori and gastric diseases. *BMJ* 1998;**316**:1507–10.

57 **Warren JR**, Marshall BJ. Unidentified curved bacillus on the gastric epithelium in active chronic gastritis. *Lancet* 1983;**i**:1273–5.

58 **Kuipers EJ**, Thijs JC, Festen HPM. Helicobacter pylori and peptic ulcer disease. *Aliment Pharmacol Ther* 1995;**9**(suppl 2):59–69.

59 **Coghlan JG**, Gilligan D, Humphries H, *et al*. Campylobacter pylori and recurrence of duodenal ulcers: a 12 month follow-up study. *Lancet* 1987;**ii**:1109–11.

60 **Lam SK**, Ching CK, Lai KC, *et al*. Does treatment of Helicobacter pylori with antibiotics alone heal duodenal ulcer? A randomised double blind placebo controlled study. *Gut* 1997;**41**:43–8.

61 **Marshall BJ**, Goodwin CS, Warren JR. Prospective double-blind trial of duodenal ulcer relapse after eradiction of Campylobacter pylori. *Lancet* 1988;**ii**:1437–42.

62 **Hentschel E**, Brandstatter G, Dragosics B, *et al*. Effect of ranitidine and amoxicilline plus metronidazole on the eradicition of Helicobacter pylori and the recurrence of duodenal ulcer. *N Engl J Med* 1993;**328**:308–12.

63 **Mantzaris GJ**, Hatzis A, Tamvakologos G, *et al*. Prospective randomised investigator-blind trial of Helicobacter pylori infection treatment in patients with refractory duodenal ulcers. Healing and long term relapse rates. *Dig Dis Sci* 1993;**38**:1132–6.

64 **Seppala K**, Pikkarainen P, Karvonen AL, *et al*, group Fgus. The role of Helicobacter pylori eradication in gastric ulcer healing and relapses. *Gastroenterology* 1992;**102**:A162.

65 **Seppala K**, Pikkarainen P, Sipponen P, *et al*. Cure of peptic gastric ulcer associated with eradication of Helicobacter pylori. Finnish Gastric Ulcer Study Group. *Gut* 1995;**36**:834–7.

66 **Labenz J**, Borsch G. Evidence for the essential role of Helicobacter pylori in gastric ulcer disease. *Gut* 1994;**35**:19–22.

67 **Rauws EA**, Tytgat GN. Cure of duodenal ulcer associated with eradication of Helicobacter pylori. *Lancet* 1990;**335**:1233–5.

68 **Unge P**, Gad A, Eriksson K, *et al*. Amoxicillin added to omeprazole prevents relapse in the treatment of duodenal ulcer patients. *Eur J Gastroenterol Hepatol* 1993;**5**:325–31.

69 **Forbes GM**, Glaser ME, Cullen DJE, *et al*. Duodenal ulcer treated with Helicobacter pylori eradication: seven year follow-up. *Lancet* 1994;**343**:258–60.

70 **Nomura A**, Stemmermann GN, Chyou PH, *et al*. Helicobacter pylori infection and the risk for duodenal and gastric ulceration. *Ann Intern Med* 1994;**120**:977–81.

71 **Sipponen P**, Seppala K, Aarynen M, *et al*. Chronic gastritis and gastroduodenal ulcer: a case control study on risk of coexisiting duodenal or gastric ulcer in patients with gastritis. *Gut* 1989;**30**:922–9.

72 **Sipponen P**, Varis K, Fraki O, *et al*. Cumulative 10 year risk of symptomatic duodenal and gastric ulcer disease in patients with or without chronic gastritis. *Scand J Gastroenterol* 1990;**25**:966–73.

73 **Cullen DJE**, Collins J, Christiansen KJ, *et al*. Long term risk of peptic ulcer disease in people with Helicobacter pylori infection—a community based study. *Gastroenterology* 1993;**104**(suppl 2):A60.

74 **Jyotheeswaran S**, Shah AN, Jin HO, *et al*. Prevalence of Helicobacter pylori in peptic ulcer patients in greater Rochester, NY: is empirical triple therapy justified? *Am J Gastroenterol* 1998;**93**:574–8.

75 **Sprung DJ**. The natural history of duodenal ulcer disease and how it relates to Helicobacter pylori. *Am J Gastroenterol* 1997;**92**:1655.

76 **Ciociola AA**, McSorley DJ, Turner K, *et al*. Helicobacter pylori infection rates in duodenal ulcer patients in the United States may be lower than previously estimated. *Am J Gastroenterol* 1999;**94**:1834–40.

77 **Peterson WL**, Ciociola AA, Sykes DL, *et al*, The RBC H pylori study group. Ranitidine bismuth citrate plus clarithromycin is effective for healing duodenal ulcers, eradicating Helicobacter pylori and reducing ulcer recurrence. *Aliment Pharmacol Ther* 1996;**10**:251–61.

78 **Schubert M**, De Witt JM, Taylor CA. Prospective evaluation of the prevalence of H pylori in duodenal abd gastric ulcer: is its role overestimated? *Gastroenterology* 1999;**116**:A305.

79 **Higuchi K**, Arakawa T, Fuijwara Y, *et al*. Is Helicobacter pylori-negative duodenal ulcer masked by the high prevalence of H pylori infection in the general population ? *Am J Gastroenterol* 1999;**94**:3083–4.

80 **EUROGAST study group**. An international association between Helicobacter pylori infection and gastric cancer. *Lancet* 1993;**341**:1359–62.

81 **Hansen S**, Melby KK, Aase S, *et al*. Helicobacter pylori infection and risk of cardia cancer and non-cardia gastric cancer. A nested case-control study. *Scand J Gastroenterol* 1999;**34**:353–60.

82 **Jaskiewicz K**, Louwrens HD, Woodroof CW, *et al*. The association of Campylobacter pylori with mucosal pathological changes in a population at risk for gastric cancer. *S Afr Med J* 1989;**75**:417–19.

83 **Sipponen P**, Kosunen TU, Valle J, *et al*. Helicobacter pylori infection and chronic gastritis in gastric cancer. *J Clin Pathol* 1992;**45**:319–23.

84 **Hansson LE**, Engstrand L, Nyren O, *et al*. Helicobacter pylori infection: independent risk indicator of gastric adenocarcinoma. *Gastroenterology* 1993;**105**:1098–103.

85 **Kuipers EJ**, Gracia-Casanova M , Pena AS, *et al*. Helicobacter pylori serology in patients with gastric carcinoma. *Scand J Gastroenterol* 1993;**28**:433–7.

86 **Parsonnet J**, Friedman GD, Vandersteen DP, *et al*. Helicobacter pylori infection and the risk of gastric carcinoma. *N Engl J Med* 1991;**325**:1127–31.

87 **Forman D**, Newell DG, Fullerton F, *et al*. Association between infection with Helicobacter pylori and risk of gastric cancer: evidence from a prospective investigation. *BMJ* 1991;**302**:1302–5.

88 **Nomura A**, Stemmermann GN, Chyou PH, *et al*. Helicobacter pylori and gastric carcinoma among Japanese Americans in Hawaii. *N Engl J Med* 1991;**325**:1132–6.

89 **Talley NJ**, Zinsmeister AR, Weaver A, *et al*. Gastric adenocarcinoma and Helicobacter pylori infection. *J Natl Cancer Inst* 1991;**83**:1734–9.

90 **International Agency for Research on Cancer**. Schistosomes, liver flukes and Helicobacter pylori. *IARC Monograph on the evaluation of carcinogenic risks to humans* 1994;**61**:1–241.

91 **Wotherspoon AC**, Ortiz-Hidalgo C, Falzon MR, *et al*. Helicobacter pylori-associated gastritis and primary B-cell gastric lymphoma. *Lancet* 1991;**338**:1175–6.

92 **Stolte M**. Helicobacter pylori gastritis and gastric MALT-lymphoma. *Lancet* 1992;**339**:745–6.

93 **Du MQ**, Isaacson PG. Recent advances in our understanding of the biology and pathogenesis of gastric mucosa-associated lymphoid tissue (MALT) lymphoma. *Forum Genova* 1998;**8**:162–73.

94 **Lepore MJ**, Smith FB, Bonanno CA. Campylobacter-like organisms in patients with Menetriers disease. *Lancet* 1988;**i**:466.

95 **Bayerdorffer E**, Ritter MM, Hatz R, *et al*. Menetriers disease and Helicobacter pylori disease. *N Engl J Med* 1993;**329**:60.

96 **Bayerdorffer E**, Ritter MM, Hatz R, *et al*. Healing of protein losing hypertrophic gastropathy by eradication of Helicobacter pylori infection—is Helicobacter pylori a pathogenic factor in Menetriers disease? *Gut* 1994;**35**:701–4.

97 **Lambert JR**. The role of Helicobacter pylori in nonulcer dyspepsia: a debate for. *Gastroenterol Clin North Am* 1993;**22**:141–51.

98 **Talley NJ**. The role of Helicobacter pylori in nonulcer dyspepsia. A debate against. *Gastroenterol Clin North Am* 1993;**22**:153–67.

99 **Armstrong D**. Helicobacter pylori and dyspepsia. *Scand J Gastroenterol* 1996;**215**:38–47.

100 **Jaakkimainen RL**, Boyle E, Tudiver F. Is Helicobacter pylori associated with non-ulcer dyspepsia and will eradication improve symptoms? A meta-analysis. *BMJ* 1999;**319**:1040–4.

101 **Talley NJ**. A critique of therapeutic trials in Helicobacter pylori positive functional dyspepsia. *Gastroenterology* 1994;**106**:1174–83.

102 **Veldhuyzen van Zanten SJO**. A systematic overview (meta-analysis) of outcome measures in Helicobacter pylori gastritis trials and functional dyspepsia. *Scand J Gastroenterol* 1993;**28**(suppl 199):40–3.

103 **Talley NJ**, Vakil N, Ballard ED, *et al*. Absence of benefit of eradicating Helicobacter pylori in patients with nonulcer dyspepsia. *N Engl J Med* 1999;**341**:1106–11.

104 **Talley NJ**, Janssens J, Lauritsen K, *et al*. H pylori eradication therapy for non-ulcer dyspepsia. A randomized double-blind placebo controlled longterm trial. *Gut* 1998;**43**(suppl 2):A79.

105 **McColl K**, Murray L, El-Omar E, *et al*. Symptomatic benefit from eradicting Helicobacter pylori infection in patients with nonulcer dyspepsia. *N Engl J Med* 1998;**339**:1869–74.

106 **Blum AL**, Talley NJ, O'Morain C, *et al*. Lack of effect of treating Helicobacter pylori infection in patients with nonulcer dyspepsia. *N Engl J Med* 1998;**339**:1875–81.

107 **Bruley des Varannes S**, Flejou JF, Colin R, *et al*. Helicobacter pylori eradication in non-ulcer dyspepsia: a randomized, double-blind, placebo-controlled study with a 12-month follow-up. *Gastroenterology* 2000;**118**:A468.

108 **Froehlich F**, Convers JJ, Wietlisbach V, *et al*. Helicobacter pylori eradication treatment does not benefit patients with non-ulcer dyspepsia. *Gastroenterology* 2000;**118**:A469.

109 **Koelz HR**, Arnold R, Stolte M, *et al*, FROSCH Study Group. Treatment of *Helicobacter pylori* (Hp) does not improve symptoms of functional dyspepsia (FD). *Gastroenterology* 1998;**114**:A182.

110 **Malfertheiner P**, Fischbach W, Layer P, *et al*. Elan study proves symptomatic benefit of Helicobacter pylori eradication in functional dyspepsia (FD). *Gastroenterology* 2000;**118**:A440.

111 **Miwa H**, Hirose M, Kikuchi S, *et al*. How useful is the detection kit for antibody to Helicobacter pylori in urine (urinalisa) in clinical practice. *Am J Gastroenterol* 1999;**94**:3460–3.

112 **Moayyedi P**, Soo S, Deeks J, *et al*. Systematic review and economic evaluation of Helicobacter pylori eradication treatment for non-ulcer dyspepsia. *BMJ* 2000;**321**:659–64.

113 **Dhali GK**, Garg PK, Sharma MP. Role of anti-Helicobacter pylori treatment in H pylori-positive and cytoprotective drugs in H pylori-negative, non-ulcer dyspepsia: results of a randomized, double-blind, controlled trial in Asian Indians. *J Gastroenterol Hepatol* 1999;**14**:523–8.

114 **Greenberg PD**, Cello JP. Lack of effect of treatment for Helicobacter pylori on symptoms of nonulcer dyspepsia. *Arch Intern Med* 1999;**159**:2283–8.

115 **David J**, Lee A, Forbes N, *et al*. Helicobacter pylori eradication for non-ulcer dyspepsia: a prospective, double-blind, randomized, placebo controlled study. *Gastroenterology* 1996;**110**:A91.

116 **Passos MCF**, Coelho LGV, Gloria ALF, *et al*. H pylori eradication for functional dyspepsia: a long-term, randomised, prospective, double-blind, placebo-controlled study. *Gut* 1998;**43**(suppl 2):A81.

117 **Sheu BS**, Lin CY, Lin XZ, *et al*. Long-term outcome of triple therapy in Helicobacter pylori-related nonulcer dyspepsia: a prospective controlled assessment. *Am J Gastroenterol* 1996;**91**:441–7.

118 **Laine L**, Schoenfeld P, Fennerty MB. Therapy for Helicobacter pylori in patients with nonulcer dyspepsia. A meta-analysis of randomized, controlled trials. *Ann Intern Med* 2001;**134**:361–9.

119 **Vicari JJ**, Falk GW, Goldblum JR, *et al*. Helicobacter pylori is not a pathogenic factor in GERD or its complications. *Gastroenterology* 1997;**112**:A322.

120 **Werdmuller BF**, Loffeld RJ. Helicobacter pylori infection has no role in the pathogenesis of reflux esophagitis. *Dig Dis Sci* 1997;**42**:103–5.

121 **O'Connor HJ**. Helicobacter pylori and gastro-oesophageal reflux disease—clinical implications and management. *Aliment Pharmacol Ther* 1999;**13**:117–27.

122 **Graham DY**, Malaty HM, Evans DG, *et al*. Epidemiology of Helicobacter pylori in an asymptomatic population in the united states. Effect of age race, and socioeconomic status. *Gastroenterology* 1991;**100**:1495–501.

123 **Banatvala N**, Mayo K, Megraud F, *et al*. The cohort effect and Helicobacter pylori. *J Infect Dis* 1993;**168**:219–21.

124 **Labenz J**, Blum AL, Bayerdorffer E, *et al*. Curing Helicobacter pylori infection in patients with duodenal ulcer may provoke reflux esophagitis. *Gastroenterology* 1997;**112**:1442–7.

125 **Fallone CA**, Barkun AN, Friedman GD, *et al*. Is Helicobacter pylori eradication associated with gastroesophageal reflux disease? *Am J Gastroenterol* 2000;**95**:914–20.

126 **Vakil N**, Hahn B, McSorley D. Recurrent symptoms and gastro-oesophageal reflux disease in patients with duodenal ulcer treated for Helicobacter pylori infection. *Aliment Pharmacol Ther* 2000;**14**:45–51.

127 **Schwizer W**, Thumshirn M, Dent J, *et al*. Helicobacter pylori and symptomatic relapse of gastro-oesophageal reflux disease: a randomised controlled trial. *Lancet* 2001;**357**:1738–42.

128 **McColl KEL**, Dickson A, El-Nujumi A, *et al*. Symptomatic benefit 1–3 years after H pylori eradication in ulcer patients: impact of gastroesophageal reflux disease. *Am J Gastroenterol* 1999;**95**:101–5.

129 **Kahn K**, Greenfield S. Endoscopy in the evaluation of dyspepsia. United States 1984. Health and Public Policy Committee, American College of Physicians, Philadelphia, Pennsylvania. *Ann Intern Med* 1985;**102**:266–9.

130 **Talley NJ**, Silverstein MD, Agreus L, *et al*. AGA technical review: evaluation of dyspepsia. *Gastroenterology* 1998;**114**:582–95.

131 **Bytzer P**, Hansen JM, Schaffalitzky de Muckadell OB. Empirical H2-blocker therapy or prompt endoscopy in management of dyspepsia. *Lancet* 1994;**343**:811–16.

132 **Hungin APS**, Thomas PR, Bramble MG, *et al*. What happens to patients following open access gastroscopy? An outcome study from general practice. *Br J Gen Pract* 1994;**44**:519–21.

133 **Jones R**. What happens to patients with non-ulcer dyspepsia after endoscopy? *Practitioner* 1988;**232**:75–8.

134 **Lydeard S**, Jones R. Factors affecting the decision to consult with dyspepsia: comparison of conslters and non-consulters. *J R Coll Gen Pract* 1989;**39**:495–8.

135 **Nyren O**, Adami HO, Gustavsson S, *et al*. Social and economic effects of non-ulcer dyspepsia. *Scand J Gastroenterol* 1985;**20**(suppl 109):41–5.

136 **Brown C**, Rees WD. Dyspepsia in general practice. *BMJ* 1990;**300**:829–30.

137 **Talley NJ**, Meineche-Schmidt V, Pare P, *et al*. Efficacy of omeprazole in functional dyspepsia: double-blind, randomized, placebo-controlled trials (the Bond and Opera studies). *Aliment Pharmacol Ther* 1998;**12**:1055–65.

138 **Lauritsen K**, Aalykke C, Havelund T, *et al*. Effect of omeprazole in functional dyspepsia: a double-blind, randomized, placebo-controlled study. *Gastroenterology* 1996;**110**:A702.

139 **Blum AL**, Arnold R, Koelz HR, *et al*, FROSCH Study Group. Treatment of functional dyspepsia (FD) with omeprazole and ranitidine. *Gastroenterology* 1997;**112**:A73.

140 **Peura DA**, Kovacs TO, Metz D, *et al*. Low-dose lansoprazole: effective for non-ulcer dyspepsia (NUD). *Gastroenterology* 2000;**113**:A2418.

141 **Richter JE**, Long JF. Cisapride for gastroesophageal reflux disease: a placebo-controlled, double-blind study. *Am J Gastroenterol* 1995;**90**:423–30.

142 **Castell DO**, Sigmund C Jr, Patterson D, *et al*. Cisapride 20 mg bid provides symptomatic relief of heartburn and related symptoms of chronic mild to moderate gastroesophageal reflux disease. CIS-USA-52 Investigator Group. *Am J Gastroenterol* 1998;**93**:547–52.

143 **Vigneri S**, Termini R, Leandro G, *et al*. A comparison of five maintenance therapies for reflux esophagitis. *N Engl J Med* 1995;**333**:1106–10.

144 **Galmiche JP**, Fraitag B, Filoche B, *et al*. Double-blind comparison of cisapride and cimetidine in treatment of reflux esophagitis. *Dig Dis Sci* 1990;**35**:649–55.

145 **Inauen W**, Emde C, Weber B, *et al*. Effects of ranitidine and cisapride on acid reflux and oesophageal motility in patients with reflux oesophagitis: a 24 hour ambulatory combined pH and manometry study. *Gut* 1993;**34**:1025–31.

146 **Koelz HR**. Treatment of reflux esophagitis with H2-blockers, antacids and prokinetic drugs. An analysis of randomical clinical trials. *Scand J Gastroenterol* 1989;**156**:25–36.

147 **McCallum RW**, Ippoliti AF, Cooney C, *et al*. A controlled trial of metoclopramide in symptomatic gastroesophageal reflux. *N Engl J Med* 1977;**296**:354–7.

148 **Toussaint J**, Gossuin A, Deruyttere M, *et al*. Healing and prevention of relapse of reflux oesophagitis by cisapride. *Gut* 1991;**32**:1280–5.

149 **Baldi F**, Bianchi PG, Dobrilla G, *et al*. Cisapride versus placebo in reflux esophagitis. A multicenter double- blind trial. *J Clin Gastroenterol* 1988;**10**:614–18.

150 **Arvanitakis C**, Nikopoulos A, Theoharidis A, *et al*. Cisapride and ranitidine in the treatment of gastro-oesophageal reflux disease—a comparative randomized double-blind trial. *Aliment Pharmacol Ther* 1993;**7**:635–41.

151 **Geldof H**, Hazelhoff B, Otten MH. Two different dose regimens of cisapride in the treatment of reflux oesophagitis: a double-blind comparison with ranitidine. *Aliment Pharmacol Ther* 1993;**7**:409–15.

152 **Dakkak M**, Jones BP, Scott MG, *et al*. Comparing the efficacy of cisapride and ranitidine in oesophagitis: a double-blind, parallel group study in general practice. *Br J Clin Pract* 1994;**48**:10–14.

153 **Talley NJ**. Drug treatment of functional dyspepsia. *Scand J Gastroenterol* 1991;**182**:47–60.

154 **Finney JS**, Kinnersley N, Hughes M, *et al*. Meta-analysis of antisecretory and gastrokinetic compounds in functional dyspepsia. *J Clin Gastroenterol* 1998;**26**:312–20.

155 **Dobrilla G**, Comberlato M, Steele A, *et al*. Drug treatment of functional dyspepsia. A meta-analysis of randomized controlled clinical trials. *J Clin Gastroenterol* 1989;**11**:169–77.

156 **Archimandritis A**, Tzivras M, Fertakis A, *et al*. Cisapride, metoclopramide, and ranitidine in the treatment of severe nonulcer dyspepsia. *Clin Ther* 1992;**14**:553–61.

157 **Veldhuyzen van Zanten SJ**, Cleary C, Talley NJ, *et al*. Drug treatment of functional dyspepsia: a systematic analysis of trial methodology with recommendations for design of future trials. *Am J Gastroenterol* 1996;**91**:660–73.

158 **Carvalhinhos A**, Fidalgo P, Freire A, *et al*. Cisapride compared with ranitidine in the treatment of functional dyspepsia. *Eur J Gastroenterol Hepatol* 1995;**7**:411–17.

159 **Miazza B**, Halter F, Brignoli R. A multicentre comparative trial in functional dyspepsia: cisapride versus cimetidine. *Gastroenterology* 1993;**104**:A18.

160 **Halter F**, Miazza B, Brignoli R. Cisapride or cimetidine in the treatment of functional dyspepsia. Results of a double-blind, randomized, Swiss multicentre study. *Scand J Gastroenterol* 1994;**29**:618–23.

161 **Simon B**, Bergemann W, Bouzo H, *et al*. Prokinetic drug treatment (cisapride) is as effective as H2-blocking agent (ranitidine) in the treatment of gastric ulcer. *Hepato-Gastroenterology* 1991;**38**(suppl 1):41–5.

162 **Testoni PA**, Bagnolo F, Buizza M, *et al*. Effectiveness of cisapride in gastric ulcer. Results of a double-blind randomized trial versus ranitidine and versus cisapride plus ranitidine. *J Clin Gastroenterol* 1993;**17**:5–9.

163 **Stubberod A**, Glise H, Hallerback B, *et al*. The effect of cisapride and ranitidine as monotherapies and in combination in the treatment of uncomplicated gastric ulceration. *Scand J Gastroenterol* 1995;**30**:106–10.

164 **Kerrigan DD**, Taylor ME, Read NW, *et al*. Acid, motility, and ulcers: a comparison of cisapride with placebo in the prevention of duodenal ulcer relapse. *Gut* 1993;**34**:1042–6.

165 **Food and Drug Administration**. *FDA warnings for cisapride*. Rockville, MD: Department of Public Health and Human Services, 2000: 24:(Jan).

166 **Sobala GM**, Crabtree JE, Pentith JA, *et al*. Screening dyspepsia by serology to Helicobacter pylori. *Lancet* 1991;**338**:94–6.

167 **Mendall MA**, Goggin PM, Marrero JM, *et al*. Role of Helicobacter pylori serology in screening prior to endoscopy. *Eur J Gastroenterol Hepatol* 1992;**4**:713–17.

168 **Mendall MA**, Jazrawi RP, Marrero JM, *et al*. Serology for Helicobacter pylori compared with symptom questionnaires in screening before direct access endoscopy. *Gut* 1995;**36**:330–3.

169 **Tham TC**, McLaughlin N, Hughes DF, *et al*. Possible role of Helicobacter pylori serology in reducing endoscopy workload. *Postgrad Med J* 1994;**70**:809–12.

170 **Patel P**, Mendall MA, Khulusi S, *et al*. Salivary antibodies to Helicobacter pylori: screening dyspeptic patients before endoscopy. *Lancet* 1994;**344**:511–12.

171 **Collins JSA**, Bamford KB, Sloan JM, *et al*. Screening for Helicobacter pylori antibody could reduce endoscopy workload in young dyspeptic patients. *Eur J Gastroenterol Hepatol* 1992;**4**:991–3.

172 **Vyas SK**, Sharpstone D, Treasure J, *et al*. Pre-endoscopy screening using serodiagnosis of Helicobacter pylori infection. *Eur J Gastroenterol Hepatol* 1994;**6**:783–5.

173 **Werdmuller BF**, der Putten AB, Veenendaal RA, *et al*. Can screening for IgG antibodies against Helicobacter pylori be used in clinical practice? Omit endoscopy in seropositive or seronegative patients? *Dig Dis Sci* 1998;**43**:2296–300.

174 **Vaira D**, Stanghellini V, Menegatti M, *et al*. Prospective screening of dyspeptic patients by Helicobacter pylori serology: a safe policy? The Italian Helicobacter pylori Study Group. *Endoscopy* 1997;**29**:595–601.

175 **Reilly TG**, Stone D, Poxon V, *et al*. H. pylori serology in the investigation of dyspepsia: a general practice based follow-up study. *Gut* 1996;**38**(suppl 1):A65.

176 **Patel P**, Khulusi S, Mendall MA, *et al*. Prospective screening of dyspeptic patients by Helicobacter pylori serology. *Lancet* 1995;**346**:1315–18.

177 **Asante AA**, Mendall M, Patel P, *et al*. A randomized trial of endoscopy vs no endoscopy in the management of seronegative Helicobacter pylori dyspepsia. *Eur J Gastroenterol Hepatol* 1998;**10**:983–9.

178 **Fendrick AM**, Chernew ME, Hirth RA, *et al*. Alternative management strategies for patients with suspected peptic ulcer disease. *Ann Intern Med* 1995;**123**:260–8.

179 **Silverstein MD**, Petterson T, Talley NJ. Initial endoscopy or empirical therapy with or without testing for Helicobacter pylori for dyspepsia: a decision analysis. *Gastroenterology* 1996;**110**:72–83.

180 **Sonnenberg A**. Cost-benefit analysis of testing for Helicobacter pylori in dyspeptic subjects. *Am J Gastroenterol* 1996;**91**:1773–7.

181 **Briggs AH**, Sculpher MJ, Logan RP, *et al*. Cost effectiveness of screening for and eradication of Helicobacter pylori in management of dyspeptic patients under 45 years of age. *BMJ* 1996;**312**:1321–5.

182 **Ebell MH**, Warbasse L, Brenner C. Evaluation of the dyspeptic patient: a cost-utility study. *J Fam Pract* 1997;**44**:545–55.

183 **Ofman JJ**, Etchason J, Fullerton S, *et al*. Management strategies for Helicobacter pylori-seropositive patients with dyspepsia: clinical and economic consequences. *Ann Intern Med* 1997;**126**:280–91.

184 **Laheij RJ**, Severens JL, Jansen JB, *et al*. Management in general practice of patients with persistent dyspepsia. A decision analysis. *J Clin Gastroenterol* 1997;**25**:563–7.

185 **Olson AD**, Deutsch D. Combined empiric treatment and specific Hp screening and treatment decrease the cost of evaluating epigastric abdominal pain. *Gastroenterology* 1998;**114**:A248.

186 **Heaney A**, Collins JSA, Watson RGP, *et al*. A prospective randomised trial of a test- and-treat policy versus endoscopy based management in young Helicobacter pylori positive patients with ulcer-like dyspepsia, referred to a hospital clinic. *Gut* 1999;**45**:186–90.

187 **Jones R**, Tait C, Sladen G, *et al*. A trial of a test-and-treat strategy for Helicobacter pylori positive dyspeptic patients in general practice. *Int J Clin Pract* 1999;**53**:413–16.

188 **Lassen AT**, Pedersen FM, Bytzer P, *et al*. Helicobacter pylori test-and-eradicate versus prompt endoscopy for management of dyspeptic patients: a randomised trial. *Lancet* 2000;**356**:455–60.

189 **Laheij RJ**, Severens JL, van de Lisdonk EH, *et al*. Randomized controlled trial of omeprazole or endoscopy in patients with persistent dyspepsia: a cost-effectiveness analysis. *Aliment Pharmacol Ther* 1998;**12**:1249–56.

190 **Duggan A**, Elliot C, Tolley K, *et al*. Randomised controlled trial of four dyspepsia management strategies in primary care with 12 months follow-up. *Gastroenterology* 2000;**118**:A438.

191 **Arents NLA**, Thijs JC, Zwet van AA, The SENSE Study Working Party. Screening and treating for Helicobacter pylori ("test-and-treat" strategy) in dyspepsia reduces the number of endoscopies and leads to a similar clinical outcome as prompt endoscopy. *Gastroenterology* 2001;**120**:A89.

192 **Klinkenberg-Knol EC**, Jansen JM, Festen HP, *et al*. Double-blind multicentre comparison of omeprazole and ranitidine in the treatment of reflux oesophagitis. *Lancet* 1987;**i**:349–51.

193 **Hetzel DJ**, Dent J, Reed WD, *et al*. Healing and relapse of severe peptic esophagitis after treatment with omeprazole. *Gastroenterology* 1988;**95**:903–12.

194 **Hunt RH**. The relationship between the control of pH and healing and symptom relief in gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 1995;**9**(suppl 1):3–7.

195 **Lauritsen K**, Rune SJ, Bytzer P, *et al*. Effect of omeprazole and cimetidine on duodenal ulcer. A double-blind comparative trial. *N Engl J Med* 1985;**312**:958–61.

196 **Bardhan KD**, Bianchi PG, Bose K, *et al*. A comparison of two different doses of omeprazole versus ranitidine in treatment of duodenal ulcers. *J Clin Gastroenterol* 1986;**8**:408–13.

197 **Lanza F**, Goff J, Scowcroft C, *et al*. Double-blind comparison of lansoprazole, ranitidine, and placebo in the treatment of acute duodenal ulcer. Lansoprazole Study Group. *Am J Gastroenterol* 1994;**89**:1191–200.

198 **Farup PG**, Larsen S, Ulshagen K, *et al*. Ranitidine for non-ulcer dyspepsia. A clinical study of the symptomatic effect of ranitidine and a classification and characterization of the responders to treatment. *Scand J Gastroenterol* 1991;**26**:1209–16.

199 **Johannessen T**, Kristensen P, Petersen H, *et al*. The symptomatic effect of 1-day treatment periods with cimetidine in dyspepsia. Combined results from randomized, controlled, single-subject trials. *Scand J Gastroenterol* 1991;**26**:974–80.

200 **Johannessen T**, Fjosne U, Kleveland PM, *et al*. Cimetidine responders in non-ulcer dyspepsia. *Scand J Gastroenterol* 1988;**23**:327–36.

201 **Smith PM**, Troughton AH, Gleeson F, *et al*. Pirenzepine in non-ulcer dyspepsia: a double-blind multicentre trial. *J Int Med Res* 1990;**18**:16–20.

202 **Talley NJ**, McNeil D, Hayden A, *et al*. Randomized, double-blind, placebo-controlled crossover trial of cimetidine and pirenzepine in nonulcer dyspepsia. *Gastroenterology* 1986;**91**:149–56.

203 **Gad A**, Dobrilla G. Campylobacter pylori and non-ulcer dyspepsia. The final results of a double-blind multicentre trial for treatment with pirenzepine in Italy. *Scand J Gastroenterol* 1989;**167**:39–43.

204 **Rabeneck L**, Souchek J, Wristers K, *et al*. Management of uninvestigated dyspepsia: a randomized, double-blind, placeo-controlled trial of proton pump inhibitor therapy. *Gastroenterology* 2001;**119**:A468.

205 **Koelz HR**, Birchler R, Bretholz A, *et al*. Healing and relapse of reflux esophagitis during treatment with ranitidine. *Gastroenterology* 1986;**91**:1198–205.

206 **Graham DY**, Colon-Pagan J, Morse RS, *et al*. Ulcer recurrence following duodenal ulcer healing with omeprazole, ranitidine, or placebo: a double-blind, multicenter, 6-month study. The Omeprazole Duodenal Ulcer Study Group. *Gastroenterology* 1992;**102**:1289–94.

207 **Jones R**, Lydeard S. Dyspepsia in the community: a follow-up study. *Br J Clin Pract* 1992;**46**:95–7.

208 **Talley NJ**, Weaver AL, Zinsmeister AR, *et al*. Onset and disappearance of gastrointestinal symptoms and functional gastrointestinal disorders. *Am J Epidemiol* 1992;**136**:165–77.

209 **Agreus L**, Svardsudd K, Nyren O, *et al*. Irritable bowel syndrome and dyspepsia in the general population: overlap and lack of stability over time. *Gastroenterology* 1995;**109**:671–80.

210 **Unge P**, Jonsson B, Stalhammar NO. The cost effectiveness of Helicobacter pylori eradication versus maintenance and episodic treatment in duodenal ulcer patients in Sweden. *Pharmacoeconomics* 1995;**8**:410–27.

211 **Hameeteman W**. Columnar-lined (Barrett's) esophagus. (Thesis, University of Amsterdam, Amsterdam, The Netherlands, 1989.)

212 **Mann NS**, Tsai MF, Nair PK. Barrett's esophagus in patients with symptomatic reflux esophagitis. *Am J Gastroenterol* 1989;**84**:1494–6.

213 **Winters C Jr**, Spurling TJ, Chobanian SJ, *et al*. Barrett's esophagus. A prevalent, occult complication of gastroesophageal reflux disease. *Gastroenterology* 1987;**92**:118–24.

214 **van der Burgh A**, Dees J, Hop WC, *et al*. Oesophageal cancer is an uncommon cause of death in patients with Barrett's oesophagus. *Gut* 1996;**39**:5–8.

215 **Spechler SJ**, Robbins AH, Rubins HB, *et al.* Adenocarcinoma and Barrett's esophagus. An overrated risk? *Gastroenterology* 1984;**87**:927–33.

216 **Van der Veen AH**, Dees J, Blankensteijn JD, *et al.* Adenocarcinoma in Barrett's oesophagus: an overrated risk. *Gut* 1989;**30**:14–18.

217 **Shaheen NJ**, Crosby MA, Bozymski EM, *et al.* Is there publication bias in the reporting of cancer risk in Barrett's esophagus? *Gastroenterology* 2000;**119**:333–8.

218 **Rudolph RE**, Vaughan TL, Storer BE, *et al.* Effect of segment length on risk for neoplastic progression in patients with Barrett esophagus. *Ann Intern Med* 2000;**132**:612–20.

219 **Bytzer P**, Christensen PB, Damkier P, *et al.* Adenocarcinoma of the esophagus and Barrett's esophagus: a population-based study. *Am J Gastroenterol* 1999;**94**:86–91.

220 **220 Smith AM**, Maxwell-Armstrong CA, Welch NT, *et al.* Surveillance for Barrett's oesophagus in the UK. *Br J Surg* 1999;**86**:276–80.

221 **van Sandick JW**, Bartelsman JF, van Lanschot JJ, *et al.* Surveillance of Barrett's oesophagus: physicians' practices and review of current guidelines. *Eur J Gastroenterol Hepatol* 2000;**12**:111–17.

222 **Richter JE**, Falk GW. Barrett's esophagus and adenocarcinoma. The need for a consensus conference. *J Clin Gastroenterol* 1996;**23**:88–90.

223 **Spechler SJ**, Lee E, Ahnen D, *et al.* Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: follow-up of a randomized controlled trial. *JAMA* 2001;**285**:2331–8.

224 **Johansson KE**, Tibbling L. Maintenance treatment with ranitidine compared with fundoplication in gastro-oesophageal reflux disease. *Scand J Gastroenterol* 1986;**21**:779–88.

225 **Negre JB**, Markkula HT, Keyrilainen O, *et al.* Nissen fundoplication. Results at 10 year follow-up. *Am J Surg* 1983;**146**:635–8.

226 **Spechler SJ**. Comparison of medical and surgical therapy for complicated gastroesophageal reflux disease in veterans. The Department of Veterans Affairs Gastroesophageal Reflux Disease Study Group. *N Engl J Med* 1992;**326**:786–92.

227 **Griffin SM**, Raimes SA. Proton pump inhibitors may mask early gastric cancer. Dyspeptic patients over 45 should undergo endoscopy before these drugs are started. *BMJ* 1998;**317**:1606–7.

228 **Breslin NP**, Thomson ABR, Bailey RJ, *et al.* Gastric cancer and other endoscopic diagnoses in patients with benign dysplasia. *Gut* 2000;**46**:93–97.

229 **Christie J**, Shepherd NA, Codling BW, *et al.* Gastric cancer below the age of 55: implications for screening patients with uncomplicated dyspepsia. *Gut* 1997;**41**:513–17.

230 **Gillen D**, McColl KE. Does concern about missing malignancy justify endoscopy in uncomplicated dyspepsia in patients aged less than 55? *Am J Gastroenterol* 1999;**94**:75–9.

231 **Leodolter A**, Dominguez-Munoz JE, von Arnim U, *et al.* Validity of a modified 13C-urea breath test for pre- and posttreatment diagnosis of Helicobacter pylori infection in the routine clinical setting. *Am J Gastroenterol* 1999;**94**:2100–4.

232 **Savarino V**, Mela GS, Zentilin P, *et al.* Comparison of isotope ratio mass spectrometry and nondispersive isotope-selective infrared spectroscopy for 13C-urea breath test. *Am J Gastroenterol* 1999;**94**:1203–8.

233 **Vaira D**, Malfertheiner P, Megraud F, *et al.* Diagnosis of Helicobacter pylori infection with a new non-invasive antigen-based assay. *Lancet* 1999;**354**:30–3.

234 **Vaira D**, Malfertheiner P, Megraud F, *et al.* Noninvasive antigen-based assay for assessing Helicobacter pylori eradication: a European multicenter study. *Am J Gastroenterol* 2000;**95**:925–9.

235 **Arents NLA**, van Zwet AA, Thijs JC, *et al.* The accuracy of the Helicobacter pylori stool antigen test in diagnosing H pylori in treated and untreated patients. *Eur J Gastroenterol Hepatol* 2001;**13**:383–6.

236 **NIH Consensus Conference**. Helicobacter pylori in peptic ulcer disease. *JAMA* 1994;**272**:65–9.

237 **van der Wouden EJ**, Thijs JC, van Zwet AA, *et al.* Six year follow-up after successful triple therapy for Helicobacter pylori infection in patients with peptic ulcer disease. *Gut* 1998;**43**(suppl 2):A100.

238 **Bell GD**, Powell KU, Burridge SM, *et al.* Reinfection or recrudescence after apparently successful eradication of Helicobacter pylori infection: implications for treatment of patients with duodenal ulcer disease. *Q J Med* 1993;**86**:375–82.

239 **Abu-Mahfouz MZ**, Prasad VM, Santogade P, *et al.* Helicobacter pylori recurrence after successful eradication: 5-year follow-up in the United States. *Am J Gastroenterol* 1997;**92**:2025–8.

240 **Borody TJ**, Andrews P, Mancuso N, *et al.* Helicobacter pylori reinfection rate, in patients with cured duodenal ulcer. *Am J Gastroenterol* 1994;**89**:529–32.

241 **Borody T**, Andrews P, Mancuso N, *et al.* Helicobacter pylori reinfection 4 years post- eradication. *Lancet* 1992;**339**:1295.

242 **van der Hulst RW**, Rauws EA, Koycu B, *et al.* Prevention of ulcer recurrence after eradication of Helicobacter pylori: a prospective long-term follow-up study. *Gastroenterology* 1997;**113**:1082–6.

243 **Uemura N**, Mukai T, Okamoto S, *et al.* Helicobacter pylori eradication inhibits the growth of intestinal type of gastric cancer in initial stage. *Gastroenterology* 1996;**110**:A282.

244 **Kuipers EJ**, Lundell L, Klinkenberg-Knol EC, *et al.* Atrophic gastritis and Helicobacter pylori infection in patients with reflux esophagitis treated with omeprazole or fundoplication. *N Engl J Med* 1996;**334**:1018–22.

245 **Lamberts R**, Creutzfeldt W, Struber HG, *et al.* Long-term omeprazole therapy in peptic ulcer disease: gastrin, endocrine cell growth, and gastritis. *Gastroenterology* 1993;**104**:1356–70.

246 **Mowat C**, Williams C, Gillen D, *et al.* Omeprazole, Helicobacter pylori status, and alterations in the intragastric milieu facilitating bacterial N-nitrosation. *Gastroenterology* 2000;**119**:339–47.

247 **Uemura N**, Okamoto S, Yamamoto S, *et al.* Changes in Helicobacter pylori-induced gastritis in the antrum and corpus during long-term acid-suppressive treatment in japan. *Aliment Pharmacol Ther* 2000;**14**:1345–52.

248 **Genta RM**. Atrophy, acid suppression and Helicobacter pylori infection: a tale of two studies. *Eur J Gastroenterol Hepatol* 1999;**11**(suppl 2):S29-S33.

249 **Bell GD**, Powell K, Burridge SM, *et al.* Experience with "triple" anti-Helicobacter pylori eradication therapy: side effects and the importance of testing the pre-treatment bacterial isolate for metronidazole resistance. *Aliment Pharmacol Ther* 1992;**6**:427–35.

250 **Thijs JC**, van Zwet AA, Oey HB. Efficacy and side effects of a triple drug regimen for the eradication of Helicobacter pylori. *Scand J Gastroenterol* 1993;**28**:934–8.

251 **Thijs JC**, van Zwet AA, Moolenaar W, *et al.* Triple therapy vs. amoxicillin plus omeprazole for treatment of Helicobacter pylori infection: a multicenter, prospective, randomized, controlled study of efficacy and side effects. *Am J Gastroenterol* 1996;**91**:93–7.

252 **Marshall BJ**, Hoffman SR, McCallum RW. Incidence of side effects during bismuth subsalicylate and antibiotic therapy for H pylori (HP). *Gastroenterology* 1992;**100**:A117.

253 **de Boer WA**, Tytgat GN. The best therapy for Helicobacter pylori infection: should efficacy or side-effect profile determine our choice? *Scand J Gastroenterol* 1995;**30**:401–7.

254 **Houben MH**, van de Beek D, Hensen EF, *et al.* Helicobacter pylori eradication therapy in The Netherlands. *Scand J Gastroenterol* 1999;**34**(suppl 230):17–22.

255 **van der Wouden EJ**, Thijs JC, van Zwet AA, *et al.* The influence of in vitro nitroimidazole resistance on the efficacy of nitromidazole containing anti-Helicobacter pylori regimens: a meta-analysis. *Am J Gastroenterol* 1999;**94**:1751–9.

256 **Laheij RJ**, Rossum LG, Jansen JB, *et al.* Evaluation of treatment regimens to cure Helicobacter pylori infection—a meta-analysis. *Aliment Pharmacol Ther* 1999;**13**:857–64.

257 **Schmid CH**, Whiting G, Cory D, et al. Omeprazole plus antibiotics in the eradication of Helicobacter pylori infection: a meta-regression analysis of randomized, controlled trials. *Am J Ther* 1999;**6**:25–36.

258 **Unge P**, Berstad A. Pooled analysis of anti-Helicobacter pylori treatment regimens. *Scand J Gastroenterol* 1996;**220**:27–40.

259 **van der Wouden EJ**, van Zwet AA, Vosmaer GD, *et al.* Rapid increase in the prevalence of metronidazole-resistant Helicobacter pylori in the Netherlands. *Emerg Infect Dis* 1997;**3**:385–9.

260 **Megraud F**. Epidemiology and mechanism of antibiotic resistance in Helicobacter pylori. *Gastroenterology* 1998;**115**:1278–82.

261 **de Boer WA**. How to achieve a near 100% cure rate for H pylori infection in peptic ulcer patients. A personal viewpoint. *J Clin Gastroenterol* 1996;**22**:313–16.

262 **Schutze K**, Hentschel E, Dragosics B, *et al.* Helicobacter pylori reinfection with identical organisms: transmission by the patients' spouses. *Gut* 1995;**36**:831–3.

263 **Graham DY**. The only good Helicobacter pylori is a dead Helicobacter pylori. *Lancet* 1997;**350**:70–1.