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Review article: the continuing dilemma of dyspepsia

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SUMMARY

Dyspepsia drains a substantial proportion of healthcare resources in industrialized countries and an appropriate management strategy is needed. An aetiological role for *Helicobacter pylori* infection has been demonstrated in a number of pathological conditions associated with dyspepsia, such as peptic ulcer and gastric malignancies, but not in functional dyspepsia. Endoscopy and diagnosis-based treatment, *H. pylori* testing and eradication therapy, history taking and empirical therapy, are the main tools that are currently available for managing patients with upper gastrointestinal symptoms. Endoscopy identifies malignancies and organic diseases of the proximal gut and therefore provides reassurance to both doctors and patients. It should be recommended in older patients with suspicious symptoms and it has proven to be more cost-effective than empirical H_2-receptor antagonists in patients with ulcer-like symptoms. Empirical eradication in all dyspeptics without suspicious symptoms is a cost-effective approach that cures the majority of peptic ulcers. Nevertheless, it does not control symptoms in the majority of patients, it may exacerbate gastro-oesophageal reflux disease, and it encourages antibiotic resistance. The realities of current clinical practice require empirical therapy in most, if not all, the dyspeptics seen by general practitioners. A detailed history taking can help to diagnose gastro-oesophageal reflux disease and to identify suspicious symptoms. Furthermore, identification of dyspepsia subgroups may provide guidance for empirical therapy. Nevertheless, even analysis of individual symptoms does not provide a sufficient diagnostic yield to differentiate functional from organic dyspepsia and appropriate investigations are needed in patients with poor response to short-term therapy or frequent relapses.

INTRODUCTION

Dyspepsia is an important and demanding clinical problem. The syndrome affects 20–40% of the population of industrialized countries and, despite the fact that only 20–25% of affected individuals seek medical help, it accounts for 5% of the everyday workload of general practitioners.[1] Therefore, dyspepsia drains a substantial proportion of healthcare resources and an appropriate management strategy is needed. In patients who have not undergone diagnostic tests, dyspepsia is termed 'uninvestigated'.

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Dyspepsia can be secondary to a variety of organic, systemic and metabolic diseases, but in most cases no potential cause of symptoms is identified even after extensive investigations. Dyspepsia in these cases is termed 'functional' or 'idiopathic'. 'Non-ulcer dyspepsia' is an alternative term that can be misleading, since some doctors and investigators believe that functional dyspepsia should include only patients with symptoms suggestive of gastric or duodenal ulcer (namely different types of epigastric pain), in the absence of an ulcer crater at endoscopy. In patients complaining of dyspepsia who have not undergone diagnostic tests, dyspepsia is termed 'uninvestigated'. The pathogenesis of functional dyspepsia remains largely unknown. Many theories have been advanced including gastric acid hypersecretion,

disturbed gastrointestinal motility, somatization-psychological factors, visceral hypersensitivity to normal or abnormal mechanical or chemical stimuli, and *Helicobacter pylori* infection.[2] So far, an aetiological role for *H. pylori* infection has been demonstrated for gastritis, duodenal ulcer, gastric ulcer, gastric lymphoma, gastric carcinoma, but not for functional dyspepsia. Nevertheless, a relationship between *H. pylori* and dyspeptic symptoms has not been disproved. Furthermore, the realities of current clinical practice mean that doctors face the dilemma of whether or not to eradicate *H. pylori* in symptomatic patients.

Management of dyspepsia is a challenge that has major clinical as well as socio-economic implications. In fact, due to the enormity of the problem and the current economic restrictions, referral of every patient for endoscopy is not practical. On the other hand, symptoms in patients with uninvestigated dyspepsia may signal the presence of a variety of serious (and sometimes lethal) organic diseases. Functional dyspepsia may also precipitate substantial loss in the quality of life of affected patients with consequent costs for society. Identification and eradication of *H. pylori* infection may substantially decrease the need for endoscopy. However, uncertainties concerning the pathogenetic mechanisms through which *H. pylori* infection may cause dyspeptic symptoms, the conflicting results of therapeutic trials on *H. pylori* eradication, and the potentially dangerous effects of widespread eradication, do not provide a solid background for unrestricted *H. pylori* eradication in dyspepsia.[3]

Endoscopy and diagnosis-based treatment, *H. pylori* testing and eradication therapy, history taking and empirical therapy are the main tools that are currently available for managing patients with upper gastrointestinal symptoms. More sophisticated tests such as 24-h pH-metry, gastric emptying studies, and manometry are available only in referral centres with a specific interest in the field, may be useful in a limited number of selected patients, and will not be herein discussed.

This article reviews the most recent studies regarding the relationship between dyspepsia and *H. pylori*, with a particular interest in the practical and economic issues relative to the different options for the management of patients, highlighting potential drawbacks of available studies and, hopefully, providing some useful suggestions for future research.

CURRENT CONCEPTS IN THE DIAGNOSIS OF DYSPEPSIA

One of the main problems encountered when evaluating the role of *H. pylori* in dyspepsia is to compare the patients included in the published studies with those sitting in the doctor's office. There is an international agreement that dyspepsia refers to pain or discomfort centred in the upper abdomen.[2] However, this apparently straightforward definition has been the cause of substantial disagreement among investigators. The main reason for this misunderstanding is the interpretation of the apparently innocent word '*discomfort*'. Is it different from pain? Or almost synonymous indicating a certain type of pain, or a mild degree of pain? Many investigators interpret discomfort as a mild pain and therefore the cardinal feature of all patients included in their studies is pain of different degrees of severity (with or without associated symptoms). Other investigators semantically closer to the origins of the word '*dyspepsia*' (from the Greek words *dus* = bad, and *peptein* = digestion) include patients who do not necessarily experience epigastric pain, but rather non-painful symptoms suggestive of deranged digestive functions such as post-prandial fullness, early satiety, bloating, nausea, in the definition of dyspepsia with the same relevance as pain.

Another area of controversy with important clinical implications is represented by the overlapping of digestive syndromes. Dyspeptic patients often present with concomitant symptoms suggestive of irritable bowel syndrome or gastro-oesophageal reflux disease (GORD). The former occurs in approximately 30% of patients with functional dyspepsia, but factor analysis studies confirm that the two syndromes are distinct entities.[4] A similar overlap also exists between dyspepsia and GORD, but, based on 24 h oesophageal pH testing, patients with predominant heartburn, particularly if associated with regurgitation, should be considered as affected by GORD and managed approriately.[5] Patients with predominantly dyspeptic symptoms often present with milder forms of GORD, but the natural history and response to single or combined therapies in these cases has not yet been appropriately investigated.

Finally, a major source of confusion is represented by dyspeptic subgroups. Symptoms included in the definition of dyspepsia are intuitively suggestive of different pathogenetic mechanisms and the existence of dyspepsia subgroups has become entrenched in clinical

practice,[6] although the techniques for identifying different subgroups and their clinical value have not been clearly established. Several studies carried out in the recent past have invariably failed to demonstrate any epidemiological, pathophysiological, and clinical utility of dyspepsia subgroups based on symptom clusters, both in functional and uninvestigated dyspepsia.[7] Conversely, recent studies carried out in referral centres on patients with strictly defined functional dyspepsia confirm the existence of these subgroups characterized by different predominant symptoms[8,9] as well as by different demographic[8] and pathophysiological features[8,9] and also by different responses to therapeutic strategies.[10] Whether these subgroups classified on the basis of the predominant symptoms bear some clinical relevance to uninvestigated dyspepsia, or can become useful in clarifying the relationship between *H. pylori* infection and dyspepsia, remains to be evaluated by appropriate studies.

UPPER GASTROINTESTINAL ENDOSCOPY AND DIAGNOSIS-BASED TREATMENT

Endoscopy is the ideal technique for identifying malignancies and organic diseases of the proximal gut in general, so that a negative investigation provides reassurance to both doctors and at least to some patients. Reassurance, however, has been found to be short-lived in patients with high pre-endoscopic anxiety levels.[11] A general agreement exists that endoscopy should be performed in all dyspeptic patients who present with suspicious symptoms. The Health and Public Policy Committee of the American College of Physicians identified the following suspicious features: anaemia, blood loss, anorexia, weight loss, early satiety.[12] A prospective audit among British doctors on the practical impact of these recommendations[13] confirmed that there was little controversy about performing endoscopy in patients presenting with haematemesis, dysphagia, weight loss, anorexia and early satiety. Nevertheless, evidence of the clinical value of recognizing alarm features is scarce. A positive diagnosis (oesophagitis, peptic ulcer, gastric cancer, cirrhosis, irritable bowel syndrome) was achieved in 14% of patients with anaemia, 21% with black stools, 9% with blood in stools, but also in 15% with dysphagia and 13% with weight loss.[14] Patients with low ferritin levels showed significant gastrointestinal pathology in 53% of cases, the majority being peptic ulcers.[15] Weight loss exceeding 3 kg is higher among patients with gastric cancer (85%), than gastric ulcer (61%), duodenal ulcer (44%) and functional dyspepsia (32%)[16] and has been prospectively found to be associated with the presence of a malignancy.[17] We are not aware of any scientific data that justifies inclusion of early satiety among alarm symptoms. On the other hand, clinical experience suggests that, beyond blood loss (anaemia) and weight loss, jaundice, chronic or recurrent vomiting and progressive dysphagia should be included as suspicious symptoms.[18] Some data support the hypothesis that older dyspeptic patients are at higher risk of having secondary dyspepsia, and onset of dyspeptic symptoms in individuals older than 45 years is the single strongest risk indicator of secondary dyspepsia in Western countries.[18] Furthermore, preliminary data show that being older than 40[19,20] or 45 years[21] is an independent risk indicator of secondary dyspepsia at endoscopy, but conflicting results have been published.[22]

Overall about 25% of dyspeptic patients take NSAIDs,[23] while the percentage is as low as 5% if only young (< 45 years) patients are considered.[24] NSAIDs intake is associated with dyspepsia[25] and must be carefully investigated in all patients since their complications are associated with greater mortality.[26]

Outcomes of prompt endoscopy and empirical H_2RA treatment have been compared by Bytzer *et al.* in previously uninvestigated patients of all ages complaining of dyspeptic symptoms in the absence of alarm features.[27] Notably, the study was restricted to patients with symptoms suggestive of peptic ulcer and severe enough to justify the use of anti-secretory treatment. At the end of a one-year monitoring period the groups were similar in terms of prevalence of organic diseases, symptoms and quality-of-life measures. However, the empirical treatment strategy was associated with higher costs, mainly due to a higher number of sick-leave days and ulcer-drug use. Furthermore, up to 60% of empirically treated patients eventually underwent endoscopy. In general, dyspeptic patients after endoscopy appear to be satisfied,[27] reassured[28] and to need fewer medical visits and prescriptions.[27–29] As previously mentioned, these positive effects may vanish rapidly in patients with high levels of anxiety,[11] and, due to the restricted inclusion criteria, they can eventually be extrapolated to patients with ulcer-like symptoms and not to dyspepsia in general.

H. PYLORI TESTING AND TREATMENT

The availability of reliable non-invasive techniques for determining *H. pylori* status has markedly influenced the philosophy that had originally driven the management of dyspepsia. Organic diseases are rare in young *H. pylori*-negative dyspeptic patients without alarm features. Breath tests or serology have been proposed to decrease referrals for upper gastrointestinal endoscopy without significantly increasing the risk of missing dangerous diseases. Office-based tests lack both sensitivity and specificity[20] and have not been tested in cost-effectiveness studies. McColl *et al.*[30] used the urea breath test for a pre-endoscopic analysis of *H. pylori* status and found that only 5% of *H. pylori*-negative dyspeptics had a peptic ulcer at endoscopy, compared with an astonishingly high 47% among *H. pylori*-positive patients, a figure that has not been more recently confirmed in the same geographical area.[31]

Several studies evaluated outcome and costs of different management strategies for dyspepsia through decision analysis. Fendrick *et al.*[32] compared five different strategies and concluded that the most cost-effective approach was empirical eradication in all dyspeptics, while the most expensive was prompt endoscopy with biopsies and eradication targeted to *H. pylori*-positive ulcer patients. Sensitivity analysis showed that the results were influenced by two variables: estimated endoscopy-related costs and estimated symptom recurrence rates. Since the former is highly variable in different countries and the latter is as yet unknown in non-ulcer patients, the conclusion of the study remains open to interpretation. Ofman *et al.*[33] failed to confirm these data, reporting that neither the response rate of 'non-ulcer' dyspepsia to *H. pylori* eradication nor any amount of endoscopy cost-cutting could make prompt endoscopy more cost-effective than a test and treat strategy in patients with uncomplicated dyspepsia. The decision analysis by Silverstein *et al.*[34] compared the direct costs in the first year after the onset of dyspepsia for patients managed by initial endoscopy or empirical therapy with and without serological *H. pylori* testing and came to different conclusions. The study failed to detect any substantial difference among management options. Non-invasive testing for *H. pylori* turned out to be more expensive only if eradication of serological positive cases was preceded by endoscopic confirmation. Sensitivity analysis indicated that costs were affected by dyspepsia recurrence rates and medical costs. Briggs *et al.*[35] extended the theoretical follow-up and found that it would take 8 years for a strategy aimed at identifying and eradicating *H. pylori*-positive ulcer patients to become more convenient than maintenance therapy with H_2-receptor antagonists maintenance. Sonnemberg quantified the level at which endoscopic screening by *H. pylori* serology becomes cost effective at a cost of $4000 US for each ulcer treated provided that peptic ulcers are responsible for the symptoms in 10% or more of all dyspeptic patients.[36] The controversy generated by these computer simulations, based on estimates of clinical probabilities and costs derived from the literature provides little guidance to the clinician in everyday practice. Indeed, some aspects of these decision analysis models are the cause of major misunderstandings and need to be clarified. Firstly, they have invariably taken into consideration patients 'suspected of having an ulcer' (i.e. patients with typical ulcer-like symptoms) who, as previously discussed, represent only a proportion of dyspeptic patients so that their results can not be extended to the management of dyspepsia as a whole. Secondly, many assumptions of these studies may prove inaccurate when applied in the 'real world', even if the widest range of published results is considered. For instance, serological *H. pylori* testing has been recently proven to be significantly less sensitive when applied in average endoscopic centres as compared with dedicated laboratories from which the vast majority of published material is produced.[37] Similar considerations may hold true for other diagnostic procedures, as well as for therapies as yet unsettled such as those for *H. pylori* eradication. Thirdly, dyspepsia is an extremely frequent condition and a uniform management strategy would result in a relevant impact on society at large.[38] Inappropriate overprescription of antibiotics, for instance, would inevitably contribute to the already serious problem of antibiotic resistance[39] not only among *H. pylori* strains, but also among other germs colonizing the human body, with potentially dramatic effects. Finally, there are also concerns about the long-term risks of GORD and, possibly, oesophageal cancer after *H. pylori* eradication.[40] Many studies have examined the effect of *H. pylori* eradication on dyspeptic symptoms, but the results have been conflicting and inconclusive, with as many studies yielding positive as negative results. In 1994, Talley reported that methodological flaws marred all the published trials.[41] Table 1 summarizes more recent placebo-controlled published

Table 1. Placebo-controlled trials on *H. pylori* eradication in functional dyspepsia published after 1994. Only studies including more than 100 patients with a follow up of at least 1 year are reported

Authors (reference)	Patients (% drop outs)	Patient selection		Outcomes		
		GORD	Predominant discomfort	Symptom improved vs. PLA	% pts improved vs. PLA	Notes
Gilvarry *et al.* 1977[42]	100(22%)	Excluded	Included	Yes	?	Dysmotility-like not improved
Blum *et al.* 1998[43]	328(25%)	Excluded	Excluded?	No	31% vs. 26%	Unique score for pain/ discomfort: erosions included
McColl *et al.* 1998[31]	318(3%)	Included	Included?	Yes	21% vs. 7%	Only 4/154 ulcers in placebo arm (47% in previous publication)
Talley *et al.* 1999[44]	278(15%)	Excluded	Included?	No	35% vs. 28%	No differences ulcer-like vs. dysmotility-like
Talley *et al.* 1999[45]	283(21%)	Excluded	Included?	No	45% vs. 50%	Unique score for pain/ discomfort: erosions included

GORD, Gastro-oesophageal reflux disease. PLA, placebo.

studies including at least 100 patients with functional dyspepsia and characterized by follow-up periods of at least 12 months. We could identify only five of these studies, with two showing a significant (although weak) symptomatic improvement after *H. pylori* eradication,[31–42] and three yielding negative results.[43–45] It is difficult to reconcile these apparently conflicting results since several aspects of the studies are difficult to interpret. McColl *et al.* adopted a definition of dyspepsia also including GORD.[31] They reported a particularly low percentage of drop outs which is at variance with other experiences in this field. Also very low was the number of patients who were found to have an ulcer at endocopy in the placebo arm (4/154), which is sharply in contrast with previous data from the same authors in the same area.[29] In the multicentre study by Blum and colleagues[43] and in the study by Talley and colleagues carried out in the USA,[45] patients with organic dyspepsia (i.e. up to five focal lesions in the gastrointestinal mucosa) were included, and no distinction was made between pain and discomfort that were analysed together by one symptom score.

Although difficult to interpret and reconcile, these apparently conflicting results agree in denying a significant role for *H. pylori* in the pathogenesis of functional dyspepsia in the majority of affected individuals. A recent meta-analysis study summarizing papers investigating the association between symptoms and gastric infection reported a summary odds-ratio of *H. pylori* infection in patients with non-ulcer dyspepsia of 1.6 (95% confidence interval 1.4–1.8), and a summary odds-ratio for symptom improvement after effective eradication of 1.9 (1.3–2.6).[46]

HISTORY TAKING AND EMPIRICAL THERAPY

At the beginning of the century, Lord Moynihan stated that secondary dyspepsia could be identified by the symptoms alone.[47] Indeed, some clinical features have been found to discriminate between functional and organic dyspepsia. Some studies reported a high sensitivity (0.78) of symptoms for ulcer disease in 'non-ulcer' dyspepsia, but this could be influenced by the high prevalence of peptic ulcers in that study setting.[48] In a group of 100 patients with meal-related 'chronic dyspepsia pain', a very high sensitivity (0.95) and a low specificity (0.23) were found for the diagnosis of organic dyspepsia.[49] In a Norwegian study, the diagnostic accuracy of a provisional pre-endoscopic diagnosis made by general practitioners showed a sensitivity of 0.68 and a specificity of 0.60.[50] These studies were carried out in patients complaining of symptoms suggestive of peptic ulcer, and failed to consider the severity of individual symptoms. More recently, two studies evaluated the predictive value of different types of upper gastrointestinal symptoms, taking into account

their severity. Hansen *et al.*[51] found that classification of Danish patients by predominant symptoms increased the *a priori* probability of ulcer and oesophagitis from 16 to 40% in the ulcer-like sub-group and from 23 to 52% in the reflux-like subgroups, respectively. Interestingly, classification of the dysmotility-like subgroups by the predominant symptom increased the *a priori* probability of functional dyspepsia from 60 to 80%. In keeping with these results, we have recently demonstrated that no mild dyspeptic symptom is of predictive value in organic dyspepsia, while both epigastric and retrosternal pain or burning severe enough to influence usual activities are indicators of positive endoscopic findings.[20] These results confirm that identification of a predominant symptom may help to predict not only the underlying pathophysiological mechanism, as previously mentioned, in functional dyspepsia, but also the underlying organic disease in uninvestigated dyspepsia. However, the predictive value of symptoms is too low to guide the management of uninvestigated dyspepsia in the individual patient.[20] Nevertheless, history taking provides important guidance in the management of upper gastrointestinal symptoms. As already discussed, a good history taking including the respective severity of individual symptoms is superior to endoscopy in identifying GORD, diagnosed by 24-h pH-metry.[4] Furthermore, other aspects of the patient's history are clinically relevant and should be carefully taken into consideration: presence of alarm features, age at onset of symptoms, NSAID use.[37] Recent audits among general practitioners confirm that history taking in general and symptom subgroups in particular are considered useful and commonly used to manage dyspeptic patients.[6]

The realities of current clinical practice require empirical therapy in most, if not all, the dyspeptics seen by general practitioners: (a) those who are seen for the first time before starting a diagnostic process; (b) those who failed to respond to *H. pylori* eradication therapy, and; (c) those who are known to have chronic functional dyspepsia. Anti-secretory agents and prokinetics are drugs that have some proven efficacy in the treatment of dyspepsia.

The majority of dyspeptics do not have abnormal gastric acid secretion, but many are receiving long-term antisecretory treatment, generally without a diagnosis.[52] A meta-analysis suggested that H_2-receptor antagonists produce a therapeutic benefit in functional dyspepsia approximately 20% greater than placebo,[53] although results of different trials are contradictory probably because only a sub-group of patients characterized by acid hypersecretion and/or symptoms suggestive of acid-related diseases respond to these drugs. Unfortunately, including criteria and description of symptoms in these studies are too poor to draw a meaningful conclusion on this important aspect. In a recent study, Talley *et al.* demonstrated that omeprazole at low doses is significantly superior in improving symptoms in patients with functional dyspepsia classified as having reflux-like or ulcer-like, but not dysmotility-like dyspepsia.[10] Interestingly, these results could be obtained by classifying dyspepsia subgroups by the predominant symptom, but not by symptom clusters. In keeping with these results, neither cimetidine[54] nor ranitidine[55] had been reported to exert any favourable effect in patients with dysmotility-like dyspepsia.

Abnormalities of gastrointestinal motility have been reported in 20–70% of patients with functional dyspepsia seen in referral centres[56] and prokinetics obtain a 46% benefit over placebo.[53] Whether the therapeutic effect of this class of drugs is more pronounced in a specific sub-group of dyspeptic patients can not be evinced from the published trials.

Thorough evaluation of the effects of drugs on individual symptoms and quality of life should characterize future trials in functional dyspepsia.

CONCLUSIONS

After 25 years of intense research, the role of *H. pylori* in upper gastrointestinal symptoms is far from being elucidated and 'believers' and 'non-believers' are still debating in the absence of sound evidence. Nevertheless, it is commonly accepted that an improvement of symptoms after successful *H. pylori* eradication can not be reasonably expected to exceed 10% and that therefore the role of the infection (if any) is minimal. Conversely, the management of 'uninvestigated' dyspepsia can be substantially influenced by *H. pylori* eradication, particularly in areas with a high prevalence of peptic ulcers.

There are three possible management strategies for patients with uninvestigated dyspepsia: (a) prompt endoscopy and diagnosis-driven therapy; (b) *H. pylori* testing and treatment; (c) history taking and empirical therapy.

Prompt endoscopy is mandatory in patients with alarm features or late onset dyspepsia, the cut-off being around 45 years in industrialized countries. Endoscopy

should also be performed in all patients who fear a serious disease, although it provides only short-lived reassurance in patients with high anxiety scores. Some patients try to avoid endoscopy because of its invasiveness and high costs or long waiting lists prevent in certain circumstances a widespread application of this technique.

Non-invasive *H. pylori* testing and treatment in positive cases have been proposed in an attempt to reduce the high numbers of negative endoscopies in young patients with uncomplicated uninvestigated dyspepsia. This strategy can indeed heal the majority of peptic ulcers, ultimately decreasing the need for endoscopy. It might also decrease the incidence of gastric cancer by healing gastritis that represents the first step of the cascade of events leading to the appearance of gastric malignancies. Possible shortcomings of widespread *H. pylori* eradication are: increased incidence of GORD, increased incidence of oesophageal and cardiac cancer, decreased response to antisecretory therapies and increased antibiotic resistance among both *H. pylori* and other germ strains.

History taking is being reconsidered as a potentially useful clinical tool in gastroenterology after a long period of domination by the apparently undisputed power of technology. In functional dyspepsia, analysis of the predominant symptom allows identification of subgroups with different demographic and pathophysiological features that correspond, at least to a certain extent, to different responses to pharmacological trials. In uninvestigated dyspepsia, analysis of the predominant symptom allows differentiation between dyspepsia and GORD and, if necessary, irritable bowel syndrome thus contributing to a more rational management of patients. Analysis of the predominant symptom also improves the predictive value of history taking for organic dyspepsia, although this predictive value remains too low to guide management in the individual dyspeptic patient.

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