

# How should *Helicobacter pylori* negative patients be managed?

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## Summary

Dyspepsia is a digestive syndrome distinct from (although frequently overlapping with) gastro-oesophageal reflux disease (GORD) and irritable bowel syndrome (IBS), which is characterised by various combinations of painful and non-painful symptoms arising from the epigastrium. Dyspepsia can be secondary to a variety of diseases, but in most instances it is idiopathic. *Helicobacter pylori* infection is responsible for the majority of peptic ulcers and of other diseases potentially associated with dyspepsia. Nevertheless, a causal role for *H pylori* infection in symptom occurrence has not been established. Experimental data indicate that *H pylori* eradication does not improve symptoms in the majority of dyspeptic patients. It has been proposed recently that *H pylori* negative patients should be managed according to their clinical presentation. Some reports suggest that taking into consideration the most relevant or "predominant" symptom may help to identify distinct subgroups among dyspeptic patients with different underlying pathophysiological abnormalities and different responses to treatment. Well designed and conducted prospective studies are needed to verify whether treatment of *H pylori* negative dyspeptic patients based on the predominant symptom actually is a cost effective approach.

## Introduction

Doctors and investigators have been puzzled by dyspepsia for decades. Two factors have recently occurred to stimulate further their interest in this field: understanding of the pathogenic role played by *H pylori* in gastro-duodenal diseases potentially associated

with dyspeptic symptoms; and the squeeze on health care budgets which prompts scrutiny of diagnostic and therapeutic decisions.

Organic diseases are rare among young *H pylori* negative dyspeptic patients without alarm features<sup>1</sup> and non-invasive *H pylori* testing has been proposed to decrease referrals for upper gastrointestinal endoscopy without significantly increasing the risk of missing dangerous diseases.<sup>2-4</sup> Both European<sup>5</sup> and North American guidelines<sup>6</sup> suggest that all young patients who are found to be *H pylori* positive by breath test or serology should be treated, whereas endoscopy should be performed only in patients with alarm features or non-responders to treatment. Young *H pylori* negative patients should be treated with antisecretory drugs or prokinetic agents.<sup>7</sup>

If *H pylori* plays a pathogenic role in the production of dyspeptic symptoms, a large scale eradication strategy should be associated with a remarkable decrease in dyspepsia in the population, but this does not seem to be the case. Despite effective healing of ulcer craters, *H pylori* eradication fails to control dyspeptic symptoms in over 30% of patients with ulcers,<sup>8</sup> and the effect of *H pylori* eradication on symptoms in patients with functional dyspepsia is even more disappointing. Unfortunately, many of the available eradication studies are flawed and therefore are difficult to interpret.<sup>9</sup> Even the most recent studies with appropriate follow up periods have produced conflicting results: patients with symptom improvement after *H pylori* eradication ranging between 0%<sup>10</sup> and 86%.<sup>11</sup> Furthermore, recent evidence suggests that *H pylori* might be associated with the onset of GORD,<sup>12</sup> although conflicting results have also been published.<sup>13</sup> Altogether these figures indicate that approximately 70% of young patients with uninvestigated dyspepsia would remain symptomatic if a large scale eradication programme was undertaken (fig 1). Management of dyspepsia, therefore, will be largely independent of the *H pylori* status of affected individuals. We propose a hypothetical management strategy based mainly on clinical features and summarise the current literature that may substantiate the proposed plan.

## Management of *H pylori* negative patients

Figure 2 shows a hypothetical algorithm for the management of uninvestigated dyspepsia. Factors other than *H pylori* status should initially guide clinical decisions. Patients with late onset

**Abbreviations used in this paper:** GORD, gastro-oesophageal reflux disease; IBS, irritable bowel syndrome.

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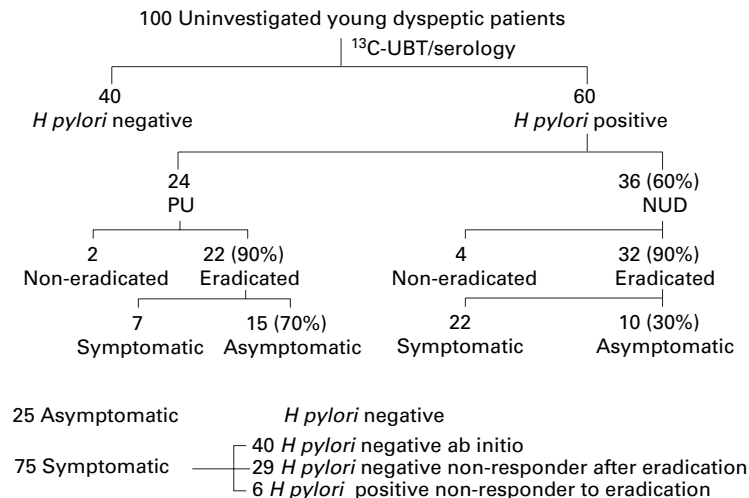


Figure 1 Expected effect of *H pylori* eradication on symptoms in 100 young patients with uninvestigated dyspepsia. PU, peptic ulcer; NUD, non-ulcer dyspepsia; UBT, urea breath test.

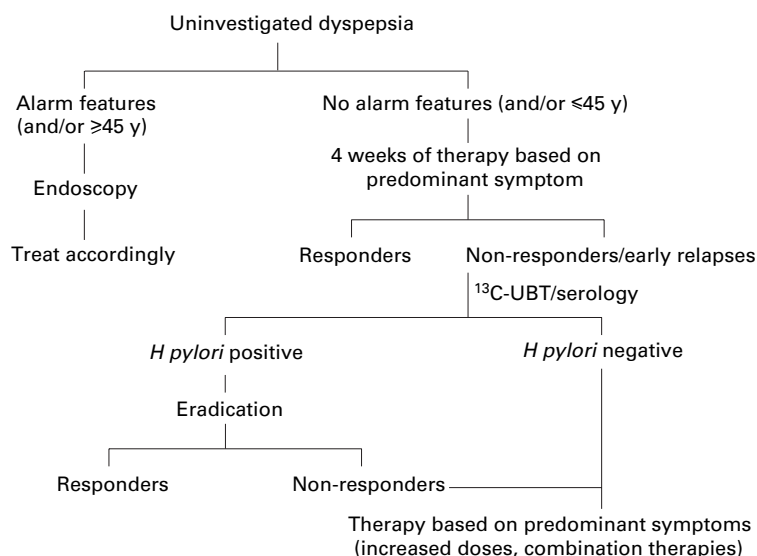


Figure 2 Management of uninvestigated dyspepsia. Short courses of medical treatment tailored to the predominant symptom should be prescribed initially. *H pylori* investigation and treatment of infected individuals should be considered for non-responders or in the case of frequent recurrences. UBT, urea breath test.

of symptoms and/or associated alarm features should be investigated immediately. The remainder, with a low probability of having an organic disease,<sup>1</sup> should be treated symptomatically. In those who fail to respond or have frequent relapses, *H pylori* testing followed by eradication in infected cases may be considered. If patients do not think that a serious disease—for example, cancer, is the cause of their symptoms, non-invasive diagnostic tests should be performed.

Three different types of *H pylori* negative dyspeptic patients can therefore be encountered in clinical practice:

- dyspeptic patients with no evidence of *H pylori* infection on non-invasive testing;
- dyspeptic patients with no evidence of *H pylori* infection at endoscopy; and
- dyspeptic patients with no evidence of *H pylori* infection after successful eradication.

As previously mentioned, there is a substantial overlap between the first two groups among young individuals, as organic diseases are rare in these subjects.<sup>1</sup> The third group may be more difficult to manage as patients may be frustrated by the experience of an unsuccessful therapeutic attempt to control their symptoms and by the objective evidence that the infection of their stomach was not the cause of their symptoms.

*H pylori* negative patients with chronic dyspepsia should be given short courses of medical treatment. Increasing evidence suggests that the choice of drug should be tailored to the clinical presentation,<sup>7</sup> and more specifically to the predominant symptom(s).<sup>14</sup> The validity of these guidelines relies on the hypothesis that the presence of a predominant symptom may help to identify dyspepsia subgroups characterised by distinct underlying pathophysiological mechanisms.

Indeed, many of the symptoms included in the definition of dyspepsia are intuitively suggestive of different pathogenic mechanisms

and the existence of distinct dyspepsia subgroups is already considered clinically useful by general practitioners.<sup>15</sup> Three working teams proposed definitions of dyspepsia subgroups with the endorsement of international experts in the field.<sup>16–18</sup> It is now generally accepted that dyspepsia is different from GORD and IBS,<sup>17, 18</sup> and that two main hypothetical subgroups can be identified<sup>16–18</sup>: ulcer-like and dysmotility-like. The former is characterised by several aspects of pain, the latter by distinct symptoms different from pain and suggestive of impaired gastroduodenal motility. None of these reports recommended investigation of the severity of symptoms. Investigating the presence or absence of symptoms without quantitating their severity may decrease the power of a symptom questionnaire, as digestive symptoms are very frequent in the general population and among individuals who do not seek medical help.<sup>19</sup> Adopting these criteria Talley and colleagues<sup>20</sup> failed to detect any difference among dyspeptic subgroups at upper gastrointestinal endoscopy.

Conversely, some data are available to support the validity of a classification which takes into account the severity of symptoms. Talley *et al* reported that low dose omeprazole is superior to placebo in controlling symptoms in patients with ulcer-like dyspepsia, provided that this subgroup is identified by predominant epigastric pain.<sup>21</sup> Cisapride has been reported to be particularly efficacious in controlling symptoms of patients with delayed gastric emptying<sup>22</sup> whose predominant complaint is discomfort.<sup>23, 24</sup> A theoretical economic model,<sup>25</sup> supported by experimental evidence,<sup>26</sup> suggested that identification of a predominant symptom may provide significant benefits and effective resource saving in the management of dyspeptic patients. Well designed and conducted studies are needed to confirm the validity of this hypothesis.

### Do *H pylori* infected and uninfected dyspeptic patients respond differently to symptomatic treatment?

Due to the scarce (if any) symptomatic effect of *H pylori* eradication, one may anticipate that treatment of dyspepsia should be unrelated to *H pylori* status. Whether *H pylori* negative and positive dyspeptic patients respond differently to symptomatic treatment has not been properly investigated. We will briefly compare demographic, pathophysiological, and clinical features of the two subgroups.

#### DEMOGRAPHIC FEATURES

When using non-invasive tests to identify *H pylori* status, infected and uninfected dyspeptic patients show very similar demographic features. Both groups are characterised by the prevalence of male sex and have similar smoking and eating habits; *H pylori* negative patients, however, are younger, more frequently involved in non-manual working activities, and less often have a positive family history of peptic ulcer disease.<sup>27, 28</sup>

## PATHOPHYSIOLOGICAL FEATURES

*H pylori/gastric acid hypersecretion*

The role of acid in the development of dyspeptic symptoms has not been clarified. Both basal and pentagastrin stimulated acid secretion are normal in patients with functional dyspepsia, regardless of their *H pylori* status.<sup>29</sup> Conversely, patients with *H pylori* infection and otherwise unexplained dyspepsia have gastrin releasing peptide stimulated gastric acid secretion that is lower than that of *H pylori* positive patients with duodenal ulcer, but higher than in *H pylori* negative controls.<sup>30</sup>

*H pylori/gut dysmotility*

Gastrointestinal dysmotility is a complex function characterised by myoelectrical smooth muscle activity, movement of the gut wall, intraluminal phasic and tonic pressure changes, and movement of intraluminal contents. No single technique is available to measure all of these events simultaneously and we have only fragmentary information both in health and disease. Regardless of the technique adopted, gastroduodenal motor abnormalities have been detected in the vast majority of studies on functional dyspepsia.<sup>31</sup> Nevertheless, their relation with symptoms and *H pylori* infection has only been partially explored. Testoni *et al* manometrically recorded decreased fasting and postprandial antral motility in *H pylori* infected dyspeptic patients, compared with both healthy controls and *H pylori* negative patients,<sup>32</sup> but this motor abnormality was not modified by *H pylori* eradication.<sup>33</sup> Pieramico and colleagues<sup>34</sup> confirmed previous data<sup>31</sup> by showing lower antral contractile activity in dyspeptic patients and failed to detect significant differences between *H pylori* positive and negative patients, but reported normalisation of interdigestive motility in *H pylori* positive patients after eradication. In keeping with these findings, preliminary data<sup>34</sup> reported increased antral contractility after eradication. Several studies investigating scintigraphic gastric emptying and *H pylori* status failed to detect any difference in gastric motility between *H pylori* positive and negative dyspeptic patients. However, recent studies done using appropriate methods, showed a higher prevalence of motility disturbances among uninfected patients.<sup>28 35 36</sup> Indeed, these two putative mechanisms of dyspepsia do not seem to interact as *H pylori* eradication does not influence gastric emptying.<sup>37-39</sup>

*H pylori/hypersensitivity*

Dyspeptic patients as a group have gastric<sup>40 41</sup> and duodenal<sup>42</sup> hypersensitivity which is not influenced by sex or age.<sup>40</sup> The gut wall contains three kinds of neural receptors: chemoreceptors, in the mucosa, which respond to chemical stimuli; mechanoreceptors, in the smooth muscle layer, which respond to stretch or compression; and nociceptors, the most numerous receptors, which are commonly silent, but can be "recruited" by any stimulus that is strong enough to induce pain.<sup>43</sup> *H pylori* infection has not been shown to be involved in the aetiology of gastric<sup>41</sup> or duodenal

hypersensitivity<sup>42</sup> in patients with functional dyspepsia.

## CLINICAL FEATURES

Whether *H pylori* negative patients have a peculiar symptom profile has not been established yet. A low prevalence of *H pylori* was observed in a group of patients with strictly selected functional dyspepsia whose predominant symptom was postprandial fullness.<sup>28</sup> In keeping with these findings, epigastric pain and heartburn were the symptoms most frequently associated with *H pylori* infection, as detected by breath test<sup>44</sup> or serology<sup>45</sup> in separate studies from Northern Italy, whereas the prevalence of infection in subjects complaining of postprandial fullness was lower and similar to that of asymptomatic subjects. Histological *H pylori* status, gastric acid secretion, gastrin concentrations, cutaneous electrogastrigraphy, and gastric emptying were evaluated in 144 Japanese patients with functional dyspepsia.<sup>46</sup> All the parameters were similar among the dyspepsia subgroups, with the exception of gastric emptying which was more frequently delayed in patients with dysmotility-like and reflux-like dyspepsia, whereas no association was detected between *H pylori* and symptoms. Hovelius *et al* explored the relation between serologically evaluated *H pylori* status and dyspeptic symptoms among patients seen by general practitioners in Sweden. *H pylori* positive patients presented with ulcer-like symptom scores significantly higher than *H pylori* negative patients.<sup>27</sup>

**Conclusions**

*H pylori* infection certainly plays a limited role in symptom generation in patients with functional dyspepsia and, therefore, treatments other than *H pylori* eradication are needed to control dyspeptic symptoms in most patients. It has been proposed that dysmotility-like dyspepsia should be distinguished from the ulcer-like form according to the predominant symptom, and that the two subgroups should be treated with prokinetic agents and antisecretory drugs, respectively. The validity and cost effectiveness of this hypothesis have still to be explored fully. Furthermore, it is necessary to clarify whether and to what extent *H pylori* negative and positive patients respond differently to symptomatic treatment. Nevertheless, testing for and treatment of *H pylori* infection is a possible option in patients who fail to respond to appropriate courses of symptomatic treatment or who have heard of the "bug" and want to get rid of it.

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