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Eradication of *Helicobacter pylori* Infection in the Management of Patients with Dyspepsia and Non-ulcer Dyspepsia

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Although *H. pylori* infection has been recognized as a major etiological agent for the development of chronic active gastritis, duodenal ulcer and benign non-NSAID related gastric ulcer, its role in the development of symptoms in patients with dyspepsia remains uncertain. Results from population-based epidemiological studies have been conflicting regarding a causal link between *H. pylori* infection and dyspepsia. Abnormalities in gastric acid secretion may exist in some dyspeptic patients. Whether disordered gastric motility seen in dyspeptic patients is related to the infection is not clear based on the results in the literature. Numerous clinical trials have been undertaken to eradicate *H. pylori* infection and improve the symptoms in dyspeptic patients; however, the results have been discrepant between studies. Many published studies suffer from methodological problems that have made interpretation difficult. Large, well-conducted, randomized, placebo-controlled, clinical trials with long-term follow-up are needed to justify the beneficial effect of *H. pylori* eradication treatment in dyspeptic patients seen in some small studies. *H. pylori* eradication therapy is cost-effective in *H. pylori*-infected dyspeptic patients although this benefit may take a long time to accrue, especially in younger patients.

INTRODUCTION

Dyspepsia, defined by an International Working Group as "persistent or recurrent abdominal pain or abdominal discomfort (a subjective, negative feeling) centered in (mainly localized to) the upper abdomen" [1], is very common in the developed and the developing world. Approximately one in four adults in the United States and Australia and 40 percent in the United Kingdom suffer from various dyspeptic symptoms [2-4]. The prevalence is higher in some developing countries [5, 6]. However, among the majority of patients, no evidence of organic disease will be found [7], and a diagnosis of non-ulcer dyspepsia (NUD)[b] will be made in these patients [8].

Helicobacter pylori infection also is very common in the general populations of western countries. Epidemiological studies have shown that about 30 to 60 percent of NUD patients are infected with *H. pylori* [9-11]. However, the results in the literature regarding a causal association between *H. pylori* infection and NUD are conflicting [12]. Moreover, whether treatment to eradicate the infection is beneficial to the improvement of dyspeptic symptoms remains inconclusive. Many clinical trials suffer from methodological problems making interpretation difficult [13]. This article aims to discuss whether *H. pylori* infection may have any causal link to the development of symptoms in patients with dyspepsia;

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[b]*Abbreviations:* NUD, non-ulcer dyspepsia; BSS, bismuth subsalicylate; CBS, colloidal bismuth subcitrate.

what the possible mechanisms might be; whether the infection should be eradicated and what management strategies should be considered to relieve symptoms in patients with dyspepsia and NUD.

IS THERE A CAUSAL LINK BETWEEN *H. PYLORI* INFECTION AND DYSPEPSIA

The published epidemiological studies provide equivocal results regarding a relationship between *H. pylori* infection and dyspepsia. Some studies report a difference in *H. pylori* prevalence between dyspeptics and controls [14-16], whereas others show the infection to be more common in asymptomatic controls [17, 18]. Unfortunately, many studies suffer from serious flaws in study design including the representativeness of the control group to the general population to which the dyspeptic patients belonged. Most studies have not used race, age- and sex- matched controls [12, 13], which are strongly related to the prevalence of *H. pylori* infection in the general population [19, 20]. This also is the case in dyspeptic patients in which the prevalence of *H. pylori* infection increases with advancing age [18, 21]. A recent review combined 19 epidemiological studies published between 1987 and 1994 and found a relative risk of 2.3 (95 percent confidence intervals 1.9-2.7) for a link between *H. pylori* infection and NUD irrespective of study quality [22].

An interesting study from Italy has shown a positive relation between *H. pylori* seroprevalence and the frequency of dyspeptic symptoms [23]. In 124 subjects, whose spouse had been diagnosed with *H. pylori* positive duodenal ulcer, 88 (71 percent) were found to be seropositive by IgG antibodies against *H. pylori* infection compared with 145 of 248 (58 percent) age- and sex-matched healthy controls. Of 88 *H. pylori*-positive spouses, 30 percent had a history of chronic or recurrent upper gastrointestinal symptoms, whereas only 11 percent of sero-negative spouses experienced similar symptoms [23]. Another prospective study also found that subjects who became infected with *H. pylori* were four times more likely to have upper gastrointestinal symptoms than *H. pylori*-negative controls although the sample size was small [24].

Dyspeptic symptoms have been divided into three general subgroups based on which symptoms are predominant: namely, ulcer-like, reflux-like and dysmotility-like symptoms. It has been suggested that *H. pylori* infection may be more commonly associated with ulcer-like dyspepsia than with dysmotility-like symptoms [15, 25]. However, most studies have failed to demonstrate any association between individual symptoms and *H. pylori* status [12, 26]. Furthermore, many symptoms overlap, and the severity of symptoms between individuals varies significantly, indicating a complex relationship between *H. pylori* infection and dyspepsia, if any.

PATHOPHYSIOLOGY OF DYSPEPTIC SYMPTOMS AND *H. PYLORI* INFECTION

The pathogenesis of dyspepsia remains uncertain, although abnormalities involving the regulation of gastric acid secretion, disordered gastric motility and altered visceral perception to gastric stimuli, gastric mucosal inflammation, psychological and environmental factors and *H. pylori* infection alone or together have all been considered possible candidates [22, 27-29]. It is likely that a constellation of factors leads to the development of the symptom complex of dyspepsia (Figure 1).

Could *H. pylori* infection be considered the trigger for the development of dyspepsia? There is evidence to show that a substantial proportion of NUD patients with *H. pylori*

infection have abnormalities of gastric acid secretion similar to duodenal ulcer patients [27]. In a well-designed study, El-Omar et al. compared 25 *H. pylori*-infected NUD patients with 25 *H. pylori*-positive asymptomatic subjects, 25 *H. pylori*-negative healthy controls and 25 *H. pylori*-infected duodenal ulcer patients. They found that gastrin-releasing peptide-stimulated gastric acid secretion in the infected NUD patients was 1.5 times that of the *H. pylori*-positive asymptomatic controls and five times that of the *H. pylori*-negative healthy controls, although the median acid output was lower than that of *H. pylori* infected duodenal ulcer patients [27]. However, since this study did not include *H. pylori*-negative NUD patients, the generalizability of the results needs to be confirmed. Furthermore, it is not known whether eradication of *H. pylori* infection will restore the abnormal response of acid secretion to GRP stimulation, although this would be anticipated from the results in duodenal ulcer patients [30].

Dyspeptic patients have a spectrum of motor disturbances including an increased gastric perception to distension, antral hypomotility and delayed gastric emptying [31-33]. However, results regarding the relation of *H. pylori* infection to the altered gastric motility in NUD patients have been conflicting. Some studies suggested that *H. pylori* infection is associated with delayed [34, 35] or accelerated gastric emptying [36]; however, the majority of studies have not shown any association between the *H. pylori* status of NUD patients and gastric motility [37-40]. This may be due to mild gastric mucosal inflammation with less dense *H. pylori* infection in dyspeptic patients, since there is some evidence to suggest that the degree of mucosal inflammation is associated with the number of bacteria [41], and sensory abnormalities have been linked to a subgroup of patients with high anti-*H. pylori* titers [33]. *H. pylori*-induced mucosal inflammation and the subsequent release of chemokines and cytokines may excite neurons and increase pain sensation through the release of mucosal prostaglandin E_2 as has been shown in a rabbit ear pain model [42]. IL-Iβ increases enteric neural sensitivity and stimulates IL-1, IL-6 and TNF-α secretion by intestinal smooth muscle cells (for review see [22]). Chronic inflammation

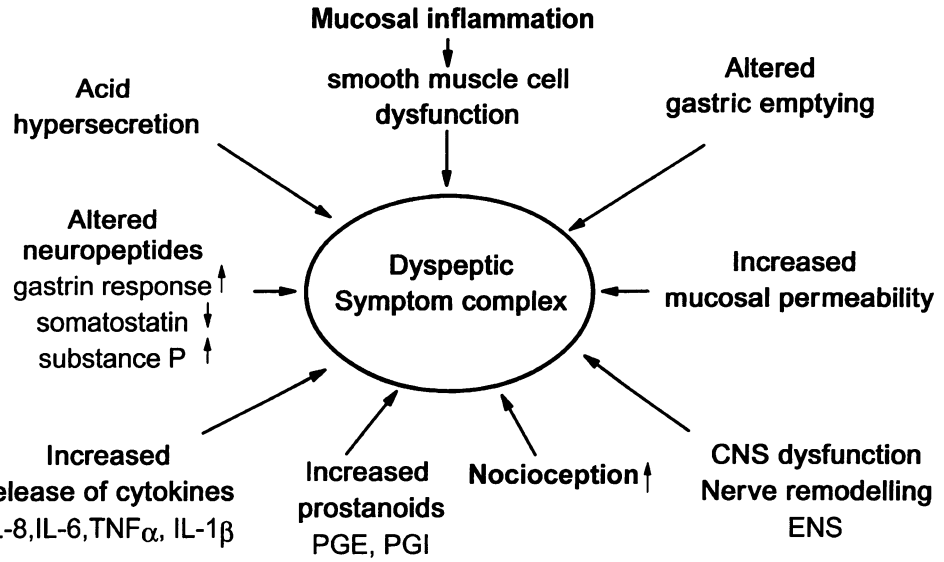

Figure 1. Postulated mechanisms for H. pylori-initiated inflammation to disturb antro-pyloro-duodenal function. (Reproduced from: Talley, N.J. and Hunt, R.H. Gastroenterology 113:S67-S77, 1997. (With permission).

of the gastric mucosa may alter enteric nerve and smooth muscle cell function [43]. Thus, a subgroup of *H. pylori*-infected dyspeptic patients with severe mucosal inflammation may be linked to dyspeptic symptoms.

Increased mucosal permeability permits the entry of antigens to the mucosa, not only *H. pylori* related antigens, but also food-derived antigens that could result in altered mucosal function even after *H. pylori* eradication [44].

RESULTS OF CLINICAL TRIALS

The NIH Consensus Conference in 1994 did not recommend eradication treatment for dyspeptic patients infected with *H. pylori* [45]. Indeed, the results of studies in the literature are conflicting regarding improvement in dyspeptic symptoms after treatment for *H. pylori* infection in dyspeptic patients. As critically reviewed by Talley and van Zanten [13, 46], previous studies have many methodological problems and provide data of variable quality, and it is difficult to draw a firm conclusion. A recent meta-analysis combining results from 10 studies, though open to criticism, showed that *H. pylori* eradication treatment improved dyspeptic symptoms [47]. Symptom improvement was more evident after a mean follow-up of longer than 12 months [47]. This is in agreement with the histological changes seen in patients after successful treatment of the infection [48]. These results suggest that a subgroup of dyspeptic patients might benefit from eradication treatment over a longer time period than has been observed in most studies to date.

Numerous clinical trials with different drug combinations have been undertaken in an attempt to relieve symptoms in dyspeptic patients. In studies that compared the effect of different bismuth salts with placebo on the improvement of dyspeptic symptoms, poor study quality and the difficulty of blinding studies in patients treated with bismuth have made the results difficult to interpret [13]. In a well-designed, placebo-controlled trial, Marshall et al. compared the effect of bismuth subsalicylate (BSS) 512 mg qid and placebo given for 3 weeks after a two-week placebo run-in period in 50 *H. pylori*-infected NUD patients [49]. They found that 70 percent of the infection was cleared in the BSS treatment group, and the histological improvement in gastritis paralleled *H. pylori* suppression. Lower symptom scores and fewer symptomatic days were seen in patients treated with BSS when compared to patients in the placebo group, but the difference was not significant due to a large overlap of confidence intervals between the two groups [49].

Most studies report that suppression of *H. pylori* infection with bismuth salts correlated with symptomatic improvement [13]. This may result from the improvement in histological gastritis. One study, reported by Kang, has shown that, in parallel with the suppression of *H. pylori* infection, significantly more patients benefitted from bismuth (De-Nol) treatment than from placebo when histological gastritis was present, whereas there was no difference between the two groups in patients without histological gastritis [50].

It may be argued that the poor effect of treatment with a single bismuth agent results from a lower eradication rate of *H. pylori* infection [51] since histological gastritis, together with an increase in the number of bacteria in the stomach, recurred rapidly after discontinuation of treatment [49]. Furthermore, many early studies only followed patients up to three months [47]. This may be too short a period of follow-up to see a possible difference between patients with and without *H. pylori* infection after eradication treatment. Several recent studies have prolonged the observation period up to nearly three years following cure of the infection [52-55]. McCarthy et al. prospectively studied the effect of eradication of *H. pylori* infection with colloidal bismuth subcitrate (CBS) or metronidazole plus amoxicillin or CBS plus metronidazole and amoxicillin on the symptoms of 83 *H. pylori*-positive NUD patients followed for one year [53]. They found that *H. pylori*

eradication therapy significantly improved symptom scores at four weeks after treatment compared to those at entry. This was more significant in patients in whom the infection was cured [53]. At one year, the symptom scores returned almost to baseline in patients with persistent infection, whereas a significant and continued fall in the scores was seen in patients cured [53]. Furthermore, the sustained symptom improvement correlated with the higher eradication rate of the infection in those treated with the three drug combination. These results suggest a possible role of *H. pylori* infection in the development of dyspeptic symptoms in NUD patients, although this study suffered from several methodological problems including lack of randomization and no placebo control group. In a better designed and randomized, placebo-controlled study, eradication of *H. pylori* infection did not improve dyspeptic symptoms in NUD patients when compared to placebo at six weeks or six months following treatment, although both groups showed a good response to treatment at week six [56]. However, this could have been due to the shorter time of follow-up.

In a study from Italy, Lazzaroni et al. randomized 41 NUD patients to treatment with either four-week CBS plus one-week metronidazole or placebo and compared the histological change in the severity of gastritis and clinical improvement in symptom scores [52]. Eradication of *H. pylori* infection was achieved in 64 percent (16/25) of the patients treated with dual therapy and 25 percent (6/24) with CBS plus placebo. In the dual therapy group, a significant improvement in the histological gastritis at eight and 24 weeks post-therapy was seen in patients cured, but not in those with persistent infection. This also was the case in the CBS plus placebo group [52]. Eradication of *H. pylori* infection correlated significantly with the decrease in symptom scores in NUD patients especially at 24 weeks after treatment compared to those with the infection [52]. However, there was no association between *H. pylori* status and symptom subgroups (ulcer-like and dysmotility-like) in symptom scores before or after treatment [52]. A similar result was reported by Sheu et al. who compared the long-term effect of *H. pylori* eradication on symptom relief and gastritis in 41 young NUD patients (< 45 years) treated with CBS-based triple therapy or H_2-receptor antagonist and confirmed that eradication of the infection improved in both symptom and gastritis scores [54]. Indeed, there seems to be a correlation between the suppression of *H. pylori* infection and an improvement in dyspeptic symptoms [22], although contrasting reports do exist in the literature [55, 57]. Large multicenter, well-conducted, randomized clinical trials with long-term follow-up (> 1 year) are needed to clarify this issue further.

MANAGEMENT STRATEGIES FOR *H. PYLORI* INFECTION IN PATIENTS WITH DYSPEPSIA

The optimal management of patients with dyspepsia is controversial. There is now evidence to show that eradication of *H. pylori* infection would benefit most dyspeptic patients infected with *H. pylori*. To test by serology for evidence of *H. pylori* infection first, or to use empirical antisecretory medications, or to undergo endoscopy are the key questions in daily practice. Several decision and cost-effective analysis studies have addressed this issue [58-61]. Silverstein et al. evaluated, by decision analysis and comprehensive simulation experiments, the long-term outcome of the two most frequent management strategies for patients with dyspepsia of unknown cause: initial endoscopy before medical therapy and empirical treatment with an H_2-receptor antagonist before endoscopy [58]. They found a difference of 1.8 percent of total cost between initial endoscopy and empirical treatment. However, initial non-invasive testing for *H. pylori* has lower charges than initial endoscopy if *H. pylori*- infected patients are treated with antimicrobials without prior endoscopy. In other words, if patients with *H. pylori* infection routinely have endoscopy,

the cost would be much higher than initial serological testing for the infection and antimicrobial treatment [58]. Ofman's study reported a similar result suggesting that initial anti-*H. pylori* therapy is the most cost-effective management strategy in *H. pylori*-seropositive patients with dyspepsia [59].

Few studies have examined the cost-effectiveness of testing for *H. pylori* infection and initial empiric treatment in patients with dyspepsia. Sonnenberg found that the cost-benefit relationship of serological screening for *H. pylori* in dyspeptic patients is influenced primarily by the response rate of nonulcer dyspepsia to *H. pylori* eradication and secondly by the monetary benefit of ulcer prevention in *H. pylori* positive patients [61]. A response to *H. pylori* eradication in 5 to 10 percent of all patients with dyspepsia would make screening and treatment for *H. pylori* a beneficial option [61]. Furthermore, potential benefits associated with *H. pylori* eradication may outweigh the risk of continued *H. pylori* exposure in some patients and may prevent progression to peptic ulcer disease, MALT lymphoma or gastric adenocarcinoma. Therefore, the decision to test for and treat *H. pylori* infection should be made on a case-by-case basis. Testing for *H. pylori* infection is only recommended if eradication treatment is planned. For patients who present with previously uninvestigated dyspepsia in whom a diagnosis of organic disease is possible, testing for *H. pylori* or together with other investigations to establish the clinical diagnosis should be considered. For those with alarm symptoms such as weight loss, bleeding, anemia or dysphagia, a formal diagnostic evaluation by endoscopy should be undertaken.

In conclusion, *H. pylori* infection and patients with dyspeptic symptoms are both widely prevalent in the general population. There is evidence to suggest that eradication of *H. pylori* may benefit dyspeptic patients over a long term. However, well-conducted, long-term clinical trials are needed to assess the effectiveness of such treatments, improvement of dyspeptic symptoms and cost.

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