

***Helicobacter pylori* and Dyspepsia**

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*It is clear that non-ulcer (or functional) dyspepsia is a heterogenous syndrome that includes a subset of patients with unrecognized gastroesophageal reflux. Patient heterogeneity combined with inadequate study methodology has led to enormous confusion in interpreting the relationship between *Helicobacter pylori* and non-ulcer dyspepsia. The possibility that *H. pylori* is associated with gastroesophageal reflux disease may explain, in part, the difficulty in establishing a link between non-ulcer dyspepsia and *H. pylori* infection. It is unclear whether the prevalence of *H. pylori* is increased in non-ulcer dyspepsia over and above the background population. *H. pylori* does not appear to be linked to heartburn or other specific upper gastrointestinal tract symptoms. The results of eradication trials in *H. pylori*-infected patients with non-ulcer dyspepsia have been equivocal and generally flawed. There is no doubt that *H. pylori* is not a sufficient cause of non-ulcer dyspepsia, because it is well documented in the literature that dyspepsia can occur in the absence of infection and infection can occur in the absence of symptoms. At this stage, there is insufficient evidence to support the hypothesis that *H. pylori* is etiologically linked to non-ulcer dyspepsia, but data from well designed large randomized controlled trials of eradication therapy are awaited with great interest.*

INTRODUCTION

Definitions of dyspepsia have often included upper abdominal as well as reflux symptoms, which has led to considerable confusion in the literature [1, 2]. In order to try and clarify the situation, consensus-based definitions have been developed. The most widely accepted definition of dyspepsia, commonly referred to as the "Rome" definition, defines the condition as chronic or recurrent pain or discomfort centered in the upper abdomen [1]; it was concluded that those with heartburn alone or those in whom heartburn is the predominant complaint are most likely to have gastroesophageal reflux disease and should not be labelled as having dyspepsia, although this is often ignored [1].

A vexing question is the relationship between *Helicobacter pylori* gastritis and dyspepsia. Only a minority with dyspepsia have an obvious structural explanation such as chronic peptic ulcer disease [1-3]; the remainder are generally labelled as having non-ulcer (or functional) dyspepsia. While there is no dispute that *H. pylori* is causally linked to chronic peptic ulcer disease, the association with non-ulcer dyspepsia is highly controversial [3-6]. Of course, non-ulcer dyspepsia is a very poor term: it implies the presence of a disorder based on the absence of a disease, namely peptic ulcer. However, non-ulcer dyspepsia remains one of the most widely used terms in practice. Here, the link between non-ulcer dyspepsia and reflux and their

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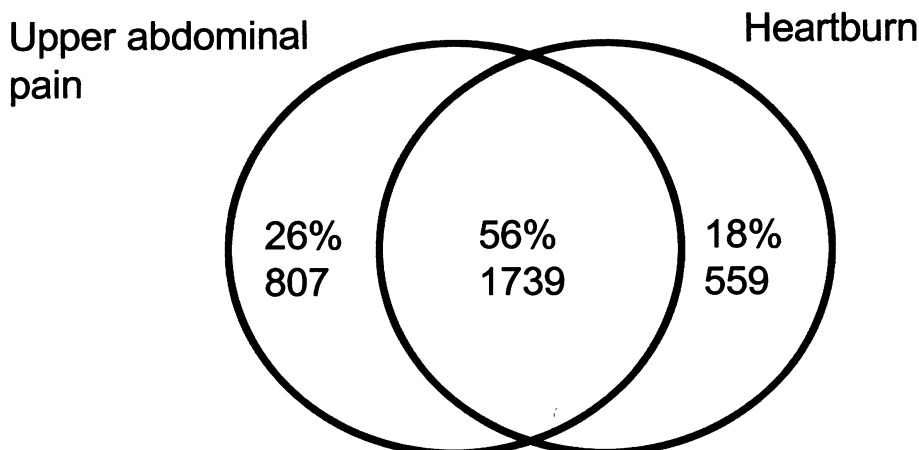


Figure 1. Distribution of upper abdominal pain (dyspepsia) and heartburn in a population-based study from the United Kingdom. From Reference [7] with permission.

association with *H. pylori* infection will be critically reviewed.

HOW MUCH OF DYSPEPSIA IS EXPLAINED BY GASTROESOPHAGEAL REFLUX DISEASE?

Whatever definition of dyspepsia is used, there is a considerable overlap of upper gastrointestinal tract symptoms in the general population. The majority of patients with upper abdominal symptoms who are labelled as having non-ulcer dyspepsia also have some heartburn [1]. Thus, Jones and Lydeard in a population-based survey from the United Kingdom reported that 56 percent of subjects with upper gastrointestinal symptoms had both heartburn and upper abdominal pain (Figure 1) [7], and these results have been confirmed in the United States and elsewhere [8-10]. There are surprisingly few data on the discriminant value of heartburn, but it has been reported that heartburn is an insensitive symptom for the detection of true gastroesophageal reflux disease. Klauser et al. found that heartburn had a sensitivity of only 38 percent for gastroesophageal

reflux disease based on abnormal 24-hour esophageal pH testing, indicating that many people with this symptom will not have the disease [11]. Unfortunately, this was a flawed study because only very selected patients were included (namely those referred for 24-hour pH monitoring); symptom events were not evaluated in relation to pH change in the esophagus, and measurement of symptoms may not have been optimal.

The value of heartburn in identifying reflux disease must critically depend on how it is defined and measured. In a recent study based on a questionnaire, patients with a burning sensation in the epigastrium or lower retrosternal region that radiated up towards the neck described their main symptom as epigastric pain rather than as heartburn in 56 percent of cases [12]. Yet a burning sensation in the epigastrium or retrosternum that travels up towards the neck has an excellent positive predictive value for an abnormal 24-hour esophageal pH test or the presence of erosive esophagitis, and also is highly predictive of the response to proton pump inhibitor therapy over placebo [13]. These preliminary data support the concept that

symptom-based definitions of dyspepsia and heartburn can be more rigorous, and appropriate history taking may help to differentiate reflux from dyspepsia [14], but the current non-ulcer dyspepsia literature is contaminated by reflux patients [15, 16].

IS *H. PYLORI* LINKED TO GASTROESOPHAGEAL REFLUX?

The relationship between *H. pylori* and gastroesophageal reflux is currently unclear and has been reviewed recently elsewhere [17-19]. However, there appears to be increasing evidence for the following. Firstly, *H. pylori* infection is probably negatively associated with the presence of reflux esophagitis, at least in some populations. Thus, Werdmuller and Loffeld identified the prevalence of *H. pylori* to be significantly lower in patients with reflux esophagitis (34 percent) compared with patients who had a normal upper endoscopy (51 percent) [20]. Other studies have supported these observations [21-23] although some investigators have failed to detect a significant difference in the prevalence of *H. pylori* infection between those with and without reflux esophagitis [24]. The major limitation of the current literature is that a number of patients with endoscopy negative (non-erosive) reflux disease have presumably been included in the control groups, which may have confounded the detection of a negative relationship in some studies. These observations are important, however, because if *H. pylori* is really less common in patients with true gastroesophageal reflux disease, then this may account for some of the confusion in the dyspepsia literature as described below.

There is also some evidence that cure of *H. pylori* infection in duodenal ulcer disease may result in an increased incidence of reflux esophagitis. Thus, a recent study found that reflux esophagitis developed in approximately 26 percent of duodenal ulcer patients cured of the infection compared with 13 percent in those with

persistent infection [25]. However, inclusion of adequate control groups has been lacking and both erosive and non-erosive changes have been lumped together, which may have confounded the observations [17, 25, 26].

Thus, *H. pylori* infection may protect against reflux esophagitis in a subset, perhaps because over the long term a proportion of infected patients have hypochlorhydria, which may or may not be related to atrophic gastritis [27-29] or because raised gastrin levels increase lower esophageal sphincter pressure [17]. Alternatively, the presence of the infection in the region of the gastric cardia may alter reflex responses that reduce the number of transient lower esophageal sphincter relaxations [17, 18]. On the other hand, patients with raised acid secretion from an antral-predominant infection may potentially be predisposed to reflux esophagitis [18, 19].

IS THE PREVALENCE OF *H. PYLORI* INCREASED IN NON-ULCER DYSPEPSIA?

H. pylori infection is present in 40 to 90 percent of patients with non-ulcer dyspepsia based on a wide range of published studies [3-6]. While it has been reported that the prevalence of infection is higher than in control groups, appropriate controls have often not been studied adjusting for factors such as age, socio-economic status, ethnic background and history of peptic ulcer disease, which all affect the prevalence of *H. pylori* infection. Thus, in a Dutch study that evaluated otherwise healthy volunteers, there was an association between *H. pylori* and dyspepsia, but this disappeared when those with a past history of ulcer disease were excluded [30]. A recent meta-analysis has suggested that there is indeed a two-fold increased risk of dyspepsia overall in infected cases, but this study could not take into account the quality of the data included [3]. Indeed, how many patients with reflux in fact were mislabelled as having dyspepsia

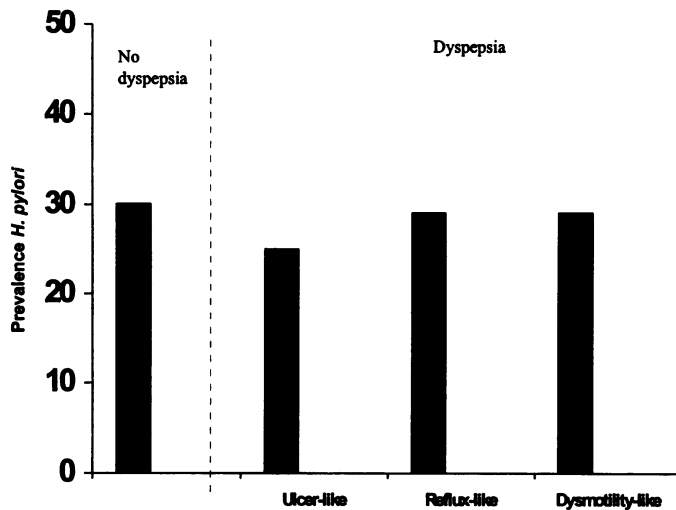


Figure 2. Prevalence of *H. pylori* (percent) among the dyspepsia subgroups in healthy blood donors. Note the similar prevalence in reflux-like dyspepsia compared with the other subgroups. From Reference [34] with permission.

remains an unknown quantity that may have variably affected the associations reported.

IS *H. PYLORI* A CAUSE OF SPECIFIC DYSPEPTIC SYMPTOMS?

A number of studies have investigated whether individual symptoms may be linked to *H. pylori* infection. No relationship between heartburn and *H. pylori* has been detected in most of the published studies [3-6]. However, Rosenstock et al. reported in a random sample of 3589 adult Danish subjects that heartburn was associated with *H. pylori* seropositivity [31]. Some studies have detected a link between other symptoms such as postprandial bloating [32], or epigastric pain or burning and *H. pylori* infection [33], but there is a total lack of consistency in the literature suggesting that many if not all of these associations are spurious [5].

Other studies have divided subjects with dyspepsia into symptom subgroups in order to try and detect whether there is a link between *H. pylori* and symptoms [34-36]. While these subgroups have been

variably defined, the studies have universally failed to detect an association between reflux-like dyspepsia and *H. pylori* [34-36]. Similarly, no association between ulcer-like or dysmotility-like dyspepsia and *H. pylori* has been identified (Figure 2) [34, 36].

DOES CURE OF *H. PYLORI* CURE NON-ULCER DYSPEPSIA?

This remains one of the key questions, which as yet does not have a clear answer. A number of studies have investigated the effects of bismuth in non-ulcer dyspepsia, but the results have been conflicting, symptom reduction was variable and only suppression of infection was achieved in most cases [37]. A number of more recent studies have tested the efficacy of cure of *H. pylori* infection [38]. Interpretation of the eradication trials is difficult as the results have been conflicting [39-45]. Unfortunately, relatively few studies have been randomized, double-blind placebo-controlled trials that have employed adequate follow-up (although how long follow-up needs to be in order to have complete cure of gastritis is as yet

Table 1. Randomized controlled trials of clinical efficacy of *H. pylori* eradication in patients with non-ulcer dyspepsia with more than six months follow up (1995-1997).

Author	Treatment	No.	Double-blind	Placebo group included	Time to follow-up (months)	Results
van Zanten et al. 1995, [39]	BSS + AMO + MTZ	53	Yes	Yes	6	NS*
Lazzaroni et al. 1996 [40]	CBS + MTZ vs. CBS + placebo	41	Yes	Yes	6	p <.05**
Schutze et al. 1996 [41]	CLR + RAN	54	No	No	12	NS**
Cucchiara et al. 1996 [42]	CBS + TIN + AMO 1 week vs. 4 weeks	64	No	No	6	NS**
Greenberg et al. 1996 [43]	CLR + OME	33	Yes	Yes	1,3,6,12	NS*
Sheu et al. 1996 [4]	CBS + AMO + MTZ vs. H ₂ blocker	41	No	No	6 and 12	p <.01***
Gilvarry et al. 1997 [45]	CBS + MTZ + TET vs. CBS + placebo	100	Uncertain	Yes	2, 6, 12	p <.01***

BSS, bismuth subsalicylate; MTA, metronidazole; CLR, clarithromycin; RAN, ranitidine; AMO, amoxycillin; CBS, colloidal bismuth subcitrate; TIN, tinidazole; OME, omeprazole; NS, not significant; *, comparison between patients with active treatment and placebo; **, comparison between patients with *H. pylori* eradicated and those with persistent infection or with persistent and current infections; ***, comparison between patients with *H. pylori* eradicated and those receiving other active therapy.

not well enough defined) (Table 1). It is also conceivable that a small minority of patients with non-ulcer dyspepsia may become worse because reflux symptoms are induced by *H. pylori* eradication. Thus, El-Omar et al. have reported among hypochlorhydric subjects with body-predominant *H. pylori* gastritis that gastric acid secretion increased in 12 of 15 after eradication therapy, and six of 15 developed heartburn [27]. A number of large well designed randomized controlled trials will be available in the near future, which hopefully will shed new light in this confusing area.

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