Systematic Review of the Epidemiological Evidence on Helicobacter pylori Infection and Nonulcer or Uninvestigated Dyspepsia

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Background: Previous studies have yielded conflicting results and substantial uncertainty about any independent association of Helicobacter pylori infection with dyspepsia, and about any benefits of antibiotic treatments for nonulcer or uninvestigated dyspepsia.

Objectives: To perform a systematic review of the literature to determine whether chronic infection with H pylori is relevant to nonulcer or uninvestigated dyspepsia.

Methods: Observational studies of associations between H pylori and dyspepsia published before April 1999 and randomized trials of the effects of H pylori eradication on dyspepsia published before January 2000 were identified by computer-assisted literature searches of relevant journals, reference lists, and discussions with authors. Relevant data were abstracted from the published reports by 2 investigators according to a fixed protocol.

Results: Thirty relevant observational studies were identified involving approximately 3392 patients with nonulcer dyspepsia, and 11 separate observational studies were identified, involving 6426 patients with uninvestigated dyspepsia. Reports of strong associations in small observational studies without appropriate adjustment for potential confounding factors were not generally confirmed by larger and better-designed studies. No studies have been reported, however, that can reliably confirm or exclude the existence of any weak associations. Twenty-two randomized trials of treatments against H pylori were found involving a total of 2340 patients with nonulcer dyspepsia, almost all with positive H pylori test results. Only a few of these trials involved effective antibacterial regimens with prolonged follow-up, and even these studies were too small to assess the possibility of moderate benefits.

Conclusion: The available evidence indicates that there is no strong association between H pylori and dyspepsia, but there is insufficient evidence to confirm or refute the existence of a modest association.

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 Dyspepsia refers to persistent or recurrent discomfort in the upper abdomen, possibly accompanied by other symptoms such as bloating and nausea. It can occur after use of certain drugs, such as nonsteroidal anti-inflammatory agents, and with various structural abnormalities of the upper digestive tract, including peptic ulceration, hiatus hernia, reflux esophagitis, and neoplasia. In the general population, however, dyspepsia occurs more commonly in the absence of such diagnoses. If upper gastrointestinal tract endoscopic (and other) investigations are normal, the symptoms are called “nonulcer dyspepsia”; in the absence of endoscopic and other test results, the symptoms are simply called “uninvestigated dyspepsia.” Estimates of the prevalence of dyspepsia in western adults generally range from 10% to 20%. During the past few decades, tens of millions of people with dyspepsia have been treated with courses of acid-lowering drugs (such as H2-receptor antagonists and proton pump inhibitors). These drugs, however, merely suppress symptoms and involve substantial long-term costs in contrast with brief courses of antibiotic treatment against Helicobacter pylori, which are usually curative of peptic ulceration. Different studies of H pylori and nonulcer or uninvestigated dyspepsia have, however, yielded conflicting results and substantial uncertainty. By 1999, groups of experts in Europe, North America, and elsewhere endorsed H pylori eradication strategies in patients with nonulcer dyspepsia—even though the available evidence was based mainly on small, nonrandomized studies with brief follow-up (or on meta-analyses of such studies). However, others deferred making treatment rec-
MATERIALS AND METHODS

SEARCH METHODS AND ELIGIBLE STUDIES

Observational studies published between January 1983 and April 1999 that reported on H pylori status in adult patients with dyspepsia and in control subjects without such disease were sought by MEDLINE searches; scanning of relevant reference lists; hand searching of gastroenterology, epidemiology, and other relevant journals; and discussion with authors of existing articles. Combinations of keywords were used relating to the infection (eg, *Helicobacter pylori* and *Campylobacter pylori*) and to the disease (eg, dyspepsia and nonulcer dyspepsia). Non–English-language articles were translated. All relevant identified epidemiological studies were included except 1 that selected only controls who were known to be infected with *H pylori*,2 that presented results for only one subtype of *H pylori* infection,17,18 and 2 that provided insufficient information.19,20 Similar searches were conducted for randomized trials reported before January 2000 of the treatment of nonulcer dyspepsia that compared *H pylori* eradication treatments with placebo tablets or short courses of other treatments not likely to affect *H pylori* status. All relevant identified studies were included except 4 that compared active anti-*H pylori* treatments with each other21-24 and 1 that involved an inappropriate crossover design rather than a parallel comparison.25

DATA ABSTRACTION

Data abstraction was done by 2 of us (J.D. and S.R.) according to a fixed protocol, and any discrepancies were resolved by further review and discussion. For observational epidemiological studies, the following information was sought from investigators or abstracted by us from published reports26-65: adjusted odds ratios (ORs) or risk ratios and 99% confidence intervals (CIs), numbers of patients and controls, study design (prospective or retrospective), case definition (uninvestigated or nonulcer dyspepsia), choice of controls (“internal controls” in prospective cohorts, “population controls” sampled from approximately the same source populations as the patients, and “other controls”; see the “Results” section), mean age of patients (or, for prospective studies, mean age at entry and mean follow-up duration), *H pylori* assay methods, location of study, and degree of adjustment for confounders (Figure 1 and Figure 2).

For randomized trials, the following information was sought from investigators or abstracted by us from published reports13-16,66-82: drug regimen and duration; mean duration of follow-up; numbers receiving active and control treatments, and corresponding numbers with symptomatic relapses at completion of follow-up; prevalence of *H pylori* in treatment arms after intervention; mean age; male-female ratio; location of study; endoscopic findings at baseline; and other design features relevant to trial quality (ie, double blinding, intention-to-treat analysis, randomization method, and allocation concealment83).

STATISTICAL ANALYSES

Odds ratios were plotted on logarithmic scales; because there were several dozen individual studies, 99% CIs were used for each study result to make some allowance for the increased scope for the play of chance in multiple comparisons. Calculation of summary estimates involved inverse variance weighted log ORs, and heterogeneity was assessed by standard χ² tests. For Figure 3, ORs were calculated by log (O − E)/V, where V is the variance of O − E (observed minus expected relapses), as described elsewhere.84

RESULTS

OBSERVATIONAL STUDIES

Since the first report in 1987, 41 observational epidemiological studies (31 peer-reviewed articles* and 10 abstracts26,27,41,43,50,56,62-64) from 19 different countries have reported on associations between *H pylori* and dyspepsia (Figures 1 and 2): 30 studies involved a total of 3392 patients with nonulcer dyspepsia (mean weighted age, 44 years; 56% males; Figure 1), in which individuals with any detectable upper gastrointestinal tract lesion should generally have been excluded after clinical examination and endoscopy, and the remaining 11 studies involved a total of 6426 patients with uninvestigated dyspepsia (weighted mean age, 45 years; 49% males; Figure 2), in which gastrointestinal symptoms had generally been assessed on the basis of postal or other questionnaires.

Nonulcer Dyspepsia

Several of these studies26,27,34,43,51 of nonulcer dyspepsia used laboratory-based enzyme-linked immunoassays to measure serum IgG antibodies to *H pylori*. These antibodies are fairly reliable indicators of chronic gastric infection with *H pylori*, and, in the absence of specific treatment, titers generally persist from early life, when the infection is typically acquired.85 A few were based on ¹³C- or ¹⁴C-urea breath tests,30,56,61 which are also generally highly accurate,86 or, in one study,49 on a combination
of noninvasive tests and gastric sampling. Most, however, performed only histological examination, culture, or a biopsy urease test after gastric sampling to detect \textit{H pylori}, which are all generally less sensitive than serologic or breath testing because of potential technical problems. Random measurement errors in such studies may therefore be substantial and would tend to weaken any real association. Systematic measurement errors could, by contrast, exaggerate the strength of any association, and only some studies based on gastric samples indicated that disease status was concealed from pathologists.

A problem in trying to find out whether a causal association exists between \textit{H pylori} and nonulcer dyspepsia is that certain potential confounding factors (such as age, cigarette smoking status, and indicators of socioeconomic status) seem to be associated with the infection and with the condition. Failure to make appropriate adjustment for potential confounders—because they were not recorded or because they were not measured accurately—could lead to spurious association of infection with dyspepsia or to inflated estimates of the strength of any real association (even in studies that made adjustments for several such confounders). Most studies of nonulcer dyspepsia in which controls were recruited opportunistically (“other controls” in Figure 1; for example, patients investigated for iron deficiency anemia) reported strong associations, but there was little adjustment for possible confounders in most of these studies, and only one adjusted for more than age and sex. Studies of nonulcer dyspepsia that tried to reduce the effects of selection biases by sampling controls from approximately the same population as their patients (“population controls” in Figure 1) and by adjusting for potential confounders tended to report much weaker associations. Figure 1 also shows that the 99% CIs in the published studies of nonulcer dyspepsia involve more than 2-fold uncertainty owing to the small numbers of patients: for example, only 2 studies involved more than 100 patients and 100 controls. But, although a previously published meta-analysis pooled the results of 19 published studies involving a total of 2700 patients with nonulcer or uninvestigated dyspepsia to report a combined OR of 2.3 (95% CI, 1.9-2.7) for \textit{H pylori} infection in dyspepsia, its conclusions are potentially misleading.

\begin{table}[h]
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\begin{tabular}{|l|c|c|}
\hline
Study Design & No. of Patients/ Controls & Degree of Adjustment \\
\hline
Population Controls & & \\
Holtmann et al\textsuperscript{26} 1995 & 39/455 & ++++
Olmos et al\textsuperscript{27} 1998 & 270/264 & +++
Katelaris et al\textsuperscript{28} 1992 & 111/80 & +
Bernsersen et al\textsuperscript{29} 1992 & 79/116 & +
Wilhelmson et al\textsuperscript{30} 1994 & 87/77 & --
\hline
Other Controls & & \\
Holtmann et al\textsuperscript{31} 1995 & 46/405 & ++++
Tucci et al\textsuperscript{32} 1992 & 45/15 & +
Holcombe et al\textsuperscript{33} 1991 & 40/40 & +
Holtmann et al\textsuperscript{34} 1996 & 16/16 & +
Dellewe et al\textsuperscript{35} 1989 & 625/31 & --
Gill et al\textsuperscript{36} 1993 & 526/82 & --
Ravns et al\textsuperscript{37} 1994 & 240/234 & --
Uyub et al\textsuperscript{38} 1994 & 159/1341 & --
Tsapa et al\textsuperscript{39} 1996 & 136/71 & --
Prasad et al\textsuperscript{40} 1994 & 119/30 & --
Pospel et al\textsuperscript{41} 1997 & 104/140 & --
Guerron et al\textsuperscript{42} 1998 & 96/26 & --
Xia et al\textsuperscript{43} 1998 & 88/77 & --
Trejci et al\textsuperscript{44} 1994 & 87/31 & --
Petros et al\textsuperscript{45} 1988 & 60/15 & --
Hobs et al\textsuperscript{46} 1996 & 56/147 & --
Rokkas et al\textsuperscript{47} 1987 & 55/15 & --
Mukhopadhyay et al\textsuperscript{48} 1992 & 50/10 & --
Strassu et al\textsuperscript{49} 1990 & 37/24 & --
Guanelli et al\textsuperscript{50} 1988 & 34/15 & --
Schiemper et al\textsuperscript{51} 1996 & 30/145 & --
Su et al\textsuperscript{52} 1995 & 28/10 & --
Inouye et al\textsuperscript{53} 1989 & 27/20 & --
Collins et al\textsuperscript{54} 1989 & 20/9 & --
\hline
\end{tabular}
\caption{Odds ratios in observational studies of Helicobacter pylori infection and nonulcer dyspepsia. Black squares indicate odds ratios, and their sizes are proportional to the number of patients, with horizontal lines representing 99% confidence intervals. Degree of adjustment for confounders is denoted as --, none reported; +, age and sex only; ++, age, sex, and smoking; ++++, age, sex, smoking, markers of socioeconomic status; and ++++, age, sex, smoking, markers of socioeconomic status, and information on diet or alcohol consumption. Question mark indicates that there was insufficient information.}
\end{table}
because the studies were not appropriately grouped by type of disease (nonulcer vs uninvestigated dyspepsia) or by study design features. Indeed, the present review of 30 published observational studies involving almost 3400 patients with nonulcer dyspepsia indicates that the substantial differences in study design and degree of adjustment for confounders makes formal combination of these data inappropriate.

Uninvestigated Dyspepsia

All 11 published observational studies of uninvestigated dyspepsia involved either serum antibody measurements for *H pylori* or urea breath tests and either “internal controls” from within large prospective cohorts, which should reduce selection biases, or “population controls.” All but 4 studies adjusted for at least age and sex (Figure 2). There was evidence of heterogeneity between the published findings of the separate studies (χ² 10 = 31.8; 2P < .001), and a combined analysis yielded an OR for dyspepsia of only 1.2 (95% CI, 1.0–1.4; 2P < .05). Despite the conventional significance of this combined OR, the causal relevance of *H pylori* to uninvestigated dyspepsia remains unclear. This weak association is compatible with chance effects, residual confounding, and/or the preferential publication of more extreme findings (ie, publication bias). Interpretation is further complicated by the lack of agreement on the definition of dyspepsia among studies and by the likely inclusion of some patients in these studies with structural abnormalities of the upper digestive tract, such as peptic ulceration and reflux esophagitis. Because these conditions can themselves be associated with the presence of *H pylori* and can vary in prevalence in different study populations, misclassification of disease could produce associations between *H pylori* and dyspepsia that either mimic or obscure any real association.

**RANDOMIZED TRIALS**

Since the first report in 1986, 22 randomized trials of *H pylori* eradication treatment (20 peer-reviewed articles)

and 2 abstracts involving 2340 patients with nonulcer dyspepsia (weighted mean age, 41 years; 47% male) from 26 different countries have been identified (Figure 3). All of these studies excluded patients with definite endoscopic lesions, and all but one included only patients with positive *H pylori* test results.

Only 7 trials involved treatment regimens that would be expected to achieve *H pylori* eradication rates of about 80%, and only 6 monitored patients for 12 months or longer. All but 4 trials reported the use of double blinding to conceal treatment allocation from patients and investigators, but only 4 trials specified the randomization method. Moreover, only 5 studies claimed to have made appropriate intention-to-treat analyses, but even these studies excluded about 5% of all randomized patients from the main comparisons. Most trials involved symptom scores as the major end point, but several numerical results could not be included in the present review because they were reported only for selected subgroups or as aggregated scores. Even if these results had been available, however, the evidence from those studies was too limited to affect this review’s overall interpretation of the available trials.

The generally weak associations observed in the observational studies suggest that only moderate effects, if any, can be realistically expected in *H pylori* eradication trials for dyspepsia. Consequently, attention in this review is restricted to trials that reported randomized treatment allocation since nonrandomized intervention studies can involve potential biases that may obscure or mimic any possible moderate effects. Figure 3 suggests that suboptimal *H pylori* regimens, such as brief courses of bismuth-based compounds alone that kill the infection in fewer than 20% of patients, may suppress dyspepsia for some weeks or a few months. There is no good evidence, however, that these treatments provide long-term benefit. The 4 largest published randomized trials each involved 12 months of follow-up and used regimens that achieve *H pylori* eradication in about 80% of patients. Results of a trial based in Glasgow suggested the possibility of substantial benefits, whereas results of

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3 multicenter trials13,15,16 were less promising. Each of these results, however, involved wide, overlapping CIs. In aggregate these 4 trials involved about 300 individuals relieved of dyspepsia 1 year after treatment (Figure 3) (crude odds ratios for dyspepsia were 1.3 (99% CI, 0.9-1.9). Even collectively, therefore, the results cannot reliably confirm or exclude a modest benefit.

**COMMENT**

The present systematic review of studies on *H pylori* and dyspepsia involves more than 3 times as many patients in observational studies (9818 vs 2764 patients) and almost 3 times as many in randomized trials of *H pylori* eradication (2340 vs 778 patients) as were in a 1999 update10,11 of previous reviews. Moreover, whereas these previous reviews inappropriately combined results from substantially different observational studies (eg, those involving different diseases and/or different study designs) and results from substantially different trials (eg, those with brief vs prolonged follow-up), the present review avoids such potential biases and the misleading claims that may arise from them.

In contrast to the 2- to 3-fold increased relative risks observed for peptic ulceration and for gastric cancer in people infected with *H pylori*,10,11 the available observational studies do not suggest the existence of such strong associations between *H pylori* and nonulcer or uninvestigated dyspepsia. Available epidemiological studies have generally been limited by inadequate sample sizes and potential biases and, hence, cannot reliably assess the existence of any moderate association that might still exist. Similarly, despite guidelines that advise antibiotic regimens for dyspepsia, previously reported randomized trials have not assessed reliably whether such treatment can provide long-term cure of dyspepsia owing to ineffective *H pylori* eradication regimens, inadequate sample sizes, and insufficient follow-up. Further studies are needed to resolve these uncertainties and to provide adequate evidence on which to base the management of dyspepsia.

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**REFERENCES**


