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Prevalence of Helicobacter pylori in patients with gastro-oesophageal reflux disease: systematic review

Anan Raghunath, A Pali S Hungin, David Wooff, Susan Childs

Abstract

**Objectives** To ascertain the prevalence of Helicobacter pylori in patients with gastro-oesophageal reflux disease and its association with the disease.

**Design** Systematic review of studies reporting the prevalence of *H pylori* in patients with and without gastro-oesophageal reflux disease.

**Data sources** Four electronic databases, searched to November 2001, experts, pharmaceutical companies, and journals.

**Main outcome measure** Odds ratio for prevalence of *H pylori* in patients with gastro-oesophageal reflux disease.

**Results** 20 studies were included. The pooled estimate of the odds ratio for prevalence of *H pylori* was 0.60 (95% confidence interval 0.47 to 0.78), indicating a lower prevalence in patients with gastro-oesophageal reflux disease. Substantial heterogeneity was observed between studies. Location seemed to be an important factor, with a much lower prevalence of *H pylori* in patients with gastro-oesophageal reflux disease in studies from the Far East, despite a higher overall prevalence of infection than western Europe and North America. Year of study was not a source of heterogeneity.

**Conclusion** The prevalence of *H pylori* infection was significantly lower in patients with than without gastro-oesophageal reflux, with geographical location being a strong contributor to the heterogeneity between studies. Patients from the Far East with reflux disease had a lower prevalence of *H pylori* infection than patients from western Europe and North America, despite a higher prevalence in the general population.

Introduction

Gastro-oesophageal reflux disease is a common condition affecting 25-40% of the population. It is managed mainly in primary care and is associated with the largest prescribing cost in the NHS. Although there is good evidence that infection with *H pylori* is the principal cause of peptic ulcer disease, there is uncertainty about the organism’s role in gastro-oesophageal reflux disease. Treating *H pylori* infection is effective in healing duodenal ulcers. The effect of eradication of the organism in patients with gastro-oesophageal reflux disease is less clear, with some reports suggesting that this might be counterproductive and that *H pylori* infection might protect against the disease. However, the recent Maastricht 2 guidelines on the management of patients with *H pylori* infection recommend eradication in those with gastro-oesophageal reflux disease who are likely to require long term proton pump inhibitor therapy. This is because profound acid suppression may accelerate the progression of *H pylori* induced atrophic gastritis, increasing the potential risk of cancer.

The evidence for an association between *H pylori* and gastro-oesophageal reflux disease remains mixed and largely uncertain. Studies evaluating the presence or absence of *H pylori* on gastro-oesophageal reflux disease have often had drawbacks in design and have given conflicting results. Fundamentally it is not certain whether there are differences in the prevalence of *H pylori* between patients with and without gastro-oesophageal reflux disease.

We conducted a systematic review to establish the overall prevalence of *H pylori* in patients with gastro-oesophageal reflux disease and to determine if this is significantly different from patients without the disease. This is important for determining if patients with the disease differ and to quantify the extent of infection. This topic is also of relevance because of the large numbers of patients in the community taking long term proton pump inhibitors, mostly for reflux. The determination of *H pylori* status in these patients has so far not been a clinical issue; gastro-oesophageal reflux disease is commonly diagnosed and treated in primary care on the basis of a clinical history alone.

Methods

We included studies to November 2001 fulfilling certain eligibility criteria (box) by searching Medline, Embase, Cinahl, and Cochrane, using subject terms and text words. Bibliographies of retrieved studies were reviewed, experts in six countries and pharmaceutical companies contacted (see bmj.com), and general medical and major gastroenterology journals searched over the previous year.

**Assessment of eligibility and trial quality**

Gastro-oesophageal reflux disease was defined according to published definitions. These comprised two categories, both in patients who had heartburn or reflux as the predominant symptoms. The first was the...
presence of endoscopically defined oesophagitis and the second, when endoscopy did not show oesophagitis, a positive result for pH monitoring with or without oesophagitis on histology.

Two investigators independently reviewed the papers according to the predefined criteria (see box). Abstracts were included only if they met the eligibility criteria. Disagreements were resolved by consensus with a third reviewer. Quality assessments focused on whether the methods for obtaining cases and controls, data collection, and H pylori testing were stated.

**Data extraction**

AR collated data from eligible studies on standardised forms, which were checked by SC. Data on the prevalence of H pylori in various grades of oesophagitis and the absence of visible reflux disease on endoscopy were recorded as reported, but for analysis the overall prevalence of H pylori in gastro-oesophageal reflux disease was used.

**Data synthesis**

Each of the 20 included studies was summarised according to its odds ratio, with an odds ratio of less than one indicating a higher prevalence of H pylori among controls than among patients with gastro-oesophageal reflux disease. Results were pooled with a fixed effect (Mantel-Haenszel) model, which was assessed with a test of homogeneity and a funnel plot. Odds ratios were pooled with a random effects model in cases of substantial heterogeneity. The statistical analysis was performed with the free package R, and the rmeta subpackage contributed by Thomas Lumley (University of Washington).

**Results**

Our initial search identified 654 articles, but only 45 evaluated the prevalence of H pylori in patients with gastro-oesophageal reflux disease. Thirty seven of these met the eligibility criteria; 16 were excluded after further scrutiny (see table A on bmj.com) and one was excluded because of overlap with a study by the same lead author (the proportions between the two studies were so close that there was virtually no difference in results; see table A on bmj.com). This left 20 studies for review, totalling 4134 patients, of whom 58.5% (n=2418) were in control groups (table).

**Prevalence of H pylori infection**

The average prevalence of H pylori infection in patients with gastro-oesophageal reflux disease was 38.2% (range 20.0-82.0%) compared with 49.5% (29.0-75.6%) in the comparator group. Four studies showed a higher prevalence of H pylori infection among patients with gastro-oesophageal reflux disease, but not significantly so (fig 1 and table B on bmj.com). The remaining studies showed a lower prevalence among patients with gastro-oesophageal reflux disease, significantly so in six studies. The pooled odds ratio was 0.58 (95% confidence interval 0.51 to 0.66), indicating a lower prevalence of H pylori infection among patients with gastro-oesophageal reflux disease (heterogeneity test: \( \chi^2 = 83.01, df=19, P < 0.001 \)).

We found no clear evidence of publication bias (fig 2); nor would any be expected in this context. Because of the presence of substantial heterogeneity, the studies were pooled with the DerSimonian-Laird random effects model (summary odds ratio 0.60, 0.47 to 0.78), which showed weaker but still strong evidence of a lower prevalence of H pylori infection among patients with gastro-oesophageal reflux disease.

Statistical heterogeneity was investigated by year of study (no effect) and by location. Five studies were of patients from the Far East, seven of patients from North America, and seven of patients from western Europe. One further study originated from Chile. Some similarities were found in results for studies from particular geographical locations (fig 1). When the three main groups were analysed separately, the results for western Europe gave an odds ratio of 0.76 (0.61 to 0.96) and a test for heterogeneity of \( \chi^2 = 14.01, df=6, P = 0.030 \). One study seemed to dominate the analysis, but repeating the analysis after excluding this study gave an odds ratio of...

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**Eligibility and quality criteria for inclusion in systematic review**

**Studies with a comparator, control, or reference group**

Patients with gastro-oesophageal reflux disease should have undergone gastroscopy.

- **Included:**
  - Patients with endoscopically proved oesophagitis
  - Patients with normal appearance of oesophagus on endoscopy and with confirmation of gastro-oesophageal reflux disease either by pH studies or histology
  - Patients known or discovered to have Barrett’s oesophagus
  - Patients with confirmed peptic ulcer disease
  - Patients who had received proton pump inhibitors within the previous two weeks or undergone eradication of H pylori

**Comparator group (one or more of the following)**

- Normal endoscopy result and absence of symptoms of gastro-oesophageal reflux disease
- Healthy asymptomatic volunteers
- Absence of pathological reflux on pH monitoring—that is, oesophageal pH is <4 for more than 3.5% of total recorded time, or as defined by the author of the study
- Normal endoscopy result and absence of oesophagitis on histology

**Quality criteria**

- Documentation of how cases were obtained
- Appropriateness of comparator
- Similar data collection for cases and comparator group
- Similar H pylori testing for cases and comparator group
- Basic data adequately described
- Statistical methods described and significance levels assessed
### Studies included in systematic review

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<td>Weimann and Loftf 1997&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Case-control, prospective</td>
<td>Consecutive patients undergoing endoscopy of upper gastrointestinal tract for upper abdominal symptoms or reflux symptoms. Cases (n=340, of which 116 patients with proved gastro-oesophageal reflux disease included). Rest with hiatus hernia and no reflux oesophagitis or with Barrett’s oesophagus excluded. Reference group (n=399), normal endoscopy and presumed absence of typical reflux symptoms</td>
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<td>We assumed from details that patients in reference group do not have reflux disease</td>
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<td>Kakei et al 1999&lt;sup&gt;42&lt;/sup&gt;</td>
<td>Case-control, prospective</td>
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<td>Cassades et al 1997&lt;sup&gt;35&lt;/sup&gt;</td>
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<td>Cases (n=140): patients with chronic gastro-oesophageal reflux disease (reflux oesophagitis, negative reflux disease on endoscopy) symptoms of at least three years duration. Controls (n=190): patients needing endoscopy, of whom had symptoms of gastro-oesophageal reflux disease</td>
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<td>This study looked at protective effect of corpus gastritis against reflux oesophagitis. We excluded Barrett’s oesophagus from our analysis</td>
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<td>Haruna et al 2000&lt;sup&gt;42&lt;/sup&gt;</td>
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<td>Liston et al 1995&lt;sup&gt;43&lt;/sup&gt;</td>
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<td>Although exclusion of patients with peptic ulcer disease had not been clearly stated, on reading the paper, we assumed this to be the case</td>
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<td>We excluded patients with Barrett’s oesophagus (as stated in our protocol) and also reflux disease negative on endoscopy (proved to have gastro-oesophageal reflux disease) from our analysis. Different methods of H pylori testing in cases and controls, no endoscopy in controls.</td>
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<td>Nihara et al 1998†</td>
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<td>Newton et al 1999†</td>
<td>Case-control, prospective, prevalence</td>
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<td>Perruzzi and Zanetti 2000†</td>
<td>Case-control, prospective, prevalence</td>
<td>Cases (122, of which 54 patients with proved gastro-oesophageal reflux disease included). 61 patients with negative reflux disease on endoscopy excluded because reflux not proved; consecutive patients referred for gastro-oesophageal reflux disease symptoms to endoscopy unit. Controls (n=49): patients who underwent endoscopy in same period as cases for reasons other than symptoms of gastro-oesophageal reflux disease. Barrett’s oesophagus, active or previous peptic ulcer disease, gastric or oesophageal neoplasms, or dyspepsia.</td>
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<td>Grade D (reflux disease negative on endoscopy, 68 patients) were not proved to have gastro-oesophageal reflux disease; hence we excluded them from our analysis.</td>
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<td>Schutzler and Schutt 1989†</td>
<td>Descriptive, prospective</td>
<td>All consenting patients referred for endoscopy between defined periods. Cases (n=170, of which 21 patients with proved gastro-oesophageal reflux disease included). Rest were classified into several diagnostic groups (duodenal ulcer, gastric ulcer, non-ulcer dyspepsia, gastritis, duodenitis) and therefore excluded. Control or comparator group (n=42): patients with absence of symptoms of gastro-oesophageal reflux disease and normal endoscopy result</td>
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<td>We assumed from details that patients in control group did not have symptoms of gastro-oesophageal reflux disease. Authors concluded that low prevalence of H pylori might result in milder grade of atrophic gastritis and consequently exacerbate reflux oesophagitis.</td>
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<td>Shirata et al 1999†</td>
<td>Descriptive, retrospective</td>
<td>Random selection of cases and controls from patients who underwent endoscopy of upper gastrointestinal tract between defined periods. Cases (n=170, of which 21 patients with proved gastro-oesophageal reflux disease included). Rest were classified into several diagnostic groups (duodenal ulcer, gastric ulcer, non-ulcer dyspepsia, gastritis, duodenitis) and therefore excluded. Control or comparator group (n=42): patients with absence of symptoms of gastro-oesophageal reflux disease and normal endoscopy result</td>
<td>Endoscopy of upper gastrointestinal tract. H pylori testing by histology, rapid urease test, and culture</td>
<td>H pylori prevalence in patients with gastro-oesophageal reflux disease (36%) and controls (61%). Pepsinogen 1 to pepsinogen 2 ratios determined to assess severity of atrophic gastritis.</td>
<td>We assumed from details that patients in control group did not have symptoms of gastro-oesophageal reflux disease. Authors concluded that low prevalence of H pylori might result in milder grade of atrophic gastritis and consequently exacerbate reflux oesophagitis.</td>
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<tr>
<td>Vaez et al 2000‡</td>
<td>Descriptive, prospective</td>
<td>Patients undergoing endoscopy of upper gastrointestinal tract. Based on questionnaire before endoscopy and endoscopy findings, patients were grouped into cases gastro-oesophageal reflux disease (n=108), short and long-segment Barrett’s oesophagus, and controls (n=65). Controls had normal endoscopy and no symptoms of gastro-oesophageal reflux disease</td>
<td>Endoscopy of upper gastrointestinal tract. H pylori testing by biopsy. H pylori testing by histology, rapid urease test, and culture</td>
<td>H pylori and CagA prevalence in cases gastro-oesophageal reflux disease (36%) and controls (42%).</td>
<td>Authors concluded that CagA positive H pylori strains might protect against Barrett’s oesophagus. We excluded patients with Barrett’s oesophagus from our analysis.</td>
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<tr>
<td>Varanasi et al 1998‡</td>
<td>Descriptive, retrospective</td>
<td>Review of records of all patients (n=185 years) who had endoscopy of upper gastrointestinal tract and rapid urease testing. Cases (n=54): gastro-oesophageal reflux disease (reflux oesophagitis or proved negative reflux disease on endoscopy, typical symptoms of gastro-oesophageal reflux disease, normal endoscopy, and histological oesophagitis) and Barrett’s oesophagus. Comparator (n=267): normal endoscopy and presumed absence of symptoms of gastro-oesophageal reflux disease</td>
<td>Endoscopy of upper gastrointestinal tract. H pylori testing by rapid urease test in all. Histopathology and serology in some</td>
<td>H pylori prevalence in patients with gastro-oesophageal reflux disease and normal endoscopy as well as stratifying for presence or absence of peptic ulcer disease in each group. H pylori prevalence in patients with gastro-oesophageal reflux disease (29%) and controls (34%).</td>
<td>We excluded patients with Barrett’s oesophagus and cases of reflux oesophagitis associated with peptic ulcer disease from our analysis. Authors found no variability of H pylori between different groups of patients with reflux oesophagitis.</td>
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<td>Venkatesh et al 1998†</td>
<td>Prospective, case-control</td>
<td>Cases: patients with classic symptoms of gastro-oesophageal reflux disease (53, of which 32 patients included) and 59 with Barrett’s oesophagus excluded, enrolled into study. Controls: patients undergoing endoscopy for reasons other than symptoms of gastro-oesophageal reflux disease. Barrett’s oesophagus, peptic ulcer disease, or dyspepsia</td>
<td>Endoscopy of upper gastrointestinal tract in cases and controls. H pylori testing by biopsy. H pylori testing by histology (haematoxylin and eosin and Giemsa stain) and serology</td>
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<td>Same patients with reflux disease negative on endoscopy but reflux not proved may have been included in our prevalence data. We excluded patients with Barrett’s oesophagus from our analysis.</td>
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0.97 (0.75 to 1.27) and a test for heterogeneity of $\chi^2=1.8, df=5, P=0.88$. The evidence for western Europe is therefore equivocal.

Consistent evidence was found for a lower prevalence of *H pylori* infection among both North American patients with gastro-oesophageal reflux disease (odds ratio 0.70, 0.55 to 0.9; test for heterogeneity, $\chi^2=0.92, df=5, P=0.99$) and patients from the Far East with gastro-oesophageal reflux disease (0.24, 0.19 to 0.32 and $\chi^2=2.36, df=4, P=0.670$). A single study from South America found a higher prevalence. Differences in location may explain much of the heterogeneity among the studies. Some of the remaining heterogeneity may be a product of clinical heterogeneity—for example, differences in methods of *H pylori* testing, pH measurements, and endoscopic classification of oesophagitis.

**Discussion**

Our systematic review found a significantly lower prevalence of *H pylori* infection among patients with gastro-oesophageal reflux disease than among those without the disease, geographical location being an important determinant. Although the results we found were based on studies with a comparator group, there were significant differences between study design (prospective or retrospective case-control, trial), study population, identification of cases and controls, inclusion and exclusion criteria, matching of cases and controls, and methods of testing for *H pylori*. Our results therefore need to be interpreted with caution.

Most of the participants underwent endoscopy for clinical reasons and thus did not constitute a population group as such, although we discovered three community based studies. Ascertaining the prevalence of *H pylori* thus depended on a proportion of patients who were being investigated for suspected lesions. This is unlikely to have substantially compromised our results because we excluded patients with symptoms of gastro-oesophageal reflux disease who had negative results for endoscopy or pH testing.

Given that there was substantial heterogeneity between the studies, we acknowledge issues about the appropriateness of reporting a pooled odds ratio. On further exploration we did find a possible difference between the Far East and North America or western Europe in prevalence of *H pylori* infection in patients with gastro-oesophageal reflux disease; a single study...
from South America gave a higher prevalence. This seems to indicate that the prevalence of *H pylori* in patients with gastro-oesophageal reflux disease is lower in countries where the prevalence of *H pylori* in the general population is high. Reasons are unclear and may be related to dietary or genetic factors. Four studies reported a higher prevalence among patients with gastro-oesophageal reflux disease, but in only one was the difference significant. Reasons are uncertain but may partly be related to factors such as study design, selection of cases and controls, and method of testing for *H pylori*. Again, presenting data as pooled estimates of odds ratios for geographical locations may give the impression of post hoc confirmatory analyses, but we strongly believe that there is a location effect evident in these data and that the prevalence has different patterns within locations.

We did not separately analyse the prevalence of *H pylori* infection in males and females. These data were not obtainable in many studies and, when available, there was no reported difference. We excluded patients with Barrett’s oesophagus because we thought that this condition merited a systematic review in its own right.

The clinical relevance of a lower prevalence of *H pylori* in patients with gastro-oesophageal reflux disease is unclear. Some studies have shown that *H pylori* may be protective against gastro-oesophageal reflux disease and that infected patients may have a less severe form of the disease.  

Evidence is also conflicting on the effect of *H pylori* infection on the efficacy of proton pump inhibitors. One study found that patients with gastro-oesophageal reflux disease and *H pylori* infection responded significantly better to proton pump inhibitors than those without the infection. Another trial found that patients not infected with *H pylori* did not need higher doses of acid suppression with proton pump inhibitors to stay in remission. Evidence shows that *H pylori* induces atrophic gastritis in the presence of long term acid suppression with proton pump inhibitors, and recent guidelines have advocated eradication of *H pylori* in patients receiving long term proton pump therapy.

We are unable to definitively comment on the benefit or possible detriment of *H pylori* eradication in patients with gastro-oesophageal reflux disease; a further review of this is in preparation. Our findings add insight into the complex relationship between *H pylori* infection and gastro-oesophageal reflux disease. Clearly, more, well designed, prospective, large scale, case-control studies and trials are required to determine the epidemiological relationship between *H pylori* and gastro-oesophageal reflux disease and the clinical implications of this association.

Contributors: AR developed the protocol, reviewed the literature, assessed eligibility of trials, checked eligibility assessments, performed data extraction, and wrote the manuscript. AP SH developed the protocol, checked eligibility assessments, and wrote and reviewed the manuscript. SC reviewed the literature, performed most of the eligibility assessments, and reviewed the manuscript. DW performed the statistical analyses and wrote and reviewed the manuscript. AP SH and AR will act as guarantors for the paper.

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