Cite this article as: BMJ, doi:10.1136/bmj.38082.626725.EE (published 4 May 2004)

Primary care

Randomised controlled trial of effects of *Helicobacter pylori* infection and its eradication on heartburn and gastro-oesophageal reflux: Bristol helicobacter project

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Abstract

Objectives To investigate the effects of *Helicobacter pylori* infection and its eradication on heartburn and gastro-oesophageal reflux.

Design Cross sectional study, followed by a randomised placebo controlled trial.

Setting Seven general practices in Bristol, England.

Participants 10 537 people, aged 20-59 years, with and without *H pylori* infection (determined by the ^{13}C-urea breath test).

Main outcome measures Prevalence of heartburn and gastro-oesophageal acid reflux at baseline and two years after treatment to eradicate *H pylori* infection.

Results At baseline, *H pylori* infection was associated with increased prevalence of heartburn (odds ratio 1.14, 95% confidence interval 1.05 to 1.23) but not reflux (1.05, 0.97 to 1.14). In participants with *H pylori* infection, active treatment had no effect on the overall prevalence of heartburn (0.99, 0.88 to 1.12) or reflux (1.04, 0.91 to 1.19) and did not improve pre-existing symptoms of heartburn or reflux.

Conclusions *H pylori* infection is associated with a slightly increased prevalence of heartburn but not reflux. Treatment to eradicate *H pylori* has no net benefit in patients with heartburn or gastro-oesophageal reflux.

Introduction

Infection with *Helicobacter pylori* usually causes antral gastritis, with increased acid secretion and risk of duodenal ulcer.[1 2] Pangastritis sometimes occurs, with a net suppression of acid secretion.[2] Eradication of the infection might therefore result in variable effects on acid related symptoms.

An increase in reflux oesophagitis after treatment to eradicate *H pylori* was first reported in 1991.[3] Later studies, with varying methods, have produced conflicting results; some showed an increase or unmasking of reflux oesophagitis,[4–6] others reported no effect,[7–9] and some even found a benefit.[10–13]

Randomised controlled trials generally provide more reliable information than observational studies. We carried out a large community based study of the effects of *H pylori* infection on heartburn and acid reflux.

Methods

This study was part of a large trial of the effects of *H pylori* infection and its eradication on the symptoms, treatment, and costs of dyspepsia in the community—the Bristol helicobacter project.[14] All people aged 20-59 years registered with seven general practices in northeast Bristol (total 26 203) were invited to participate. Of these, 10 537 (40.2%) gave informed consent to take part in the study and had a ^{13}C-urea breath test for active *H pylori* infection administered by using an orange juice and citric acid test meal.[14 15]

All participants completed a validated questionnaire describing the frequency and severity of any epigastric pain, heartburn, and gastro-oesophageal reflux. Details are described in the methods paper for the Bristol helicobacter project.[14] We compared the symptoms of all 1634 participants whose ^{13}C-urea breath test was positive for *H pylori* infection with those of twice that number (3268) of randomly selected *H pylori* negative controls (total 4902).

We randomised participants whose ^{13}C-urea breath test showed *H pylori* infection in equal numbers to receive 500 mg clarithromycin and 400 mg ranitidine bismuth citrate twice daily for two weeks or placebo. The ^{13}C-urea breath test was repeated six months later, but the results were not revealed until after the two year follow up. We recorded consultations with the general practitioner for dyspepsia after scrutiny of the participants' primary care notes.

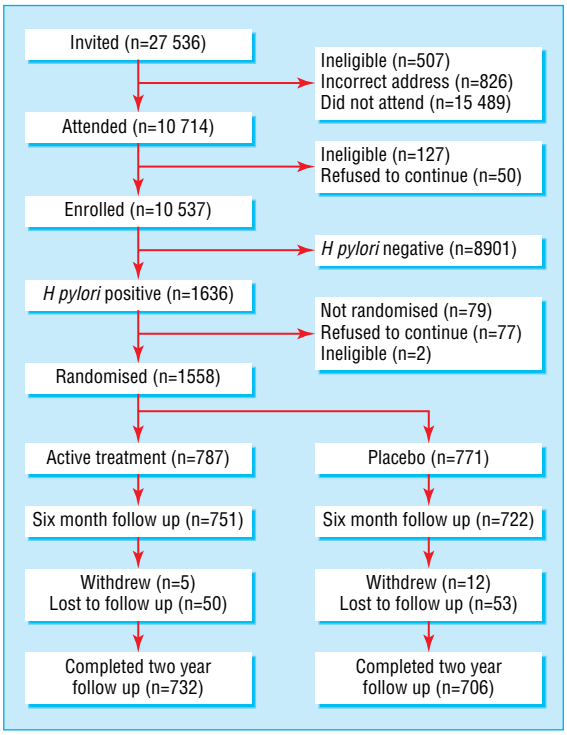
We used SPSS version 10 to do the statistical analysis. We analysed symptoms two years after treatment on an intention to treat basis.

Results

Of the 10 537 participants who had a ^{13}C-urea breath test, 1634 (15.5%) were positive for *H pylori* infection (figure). Of those with a positive test result, 1558 (95.3%) were randomised to receive either active treatment (787) or placebo (771). The characteristics of the two groups were similar (table 1).

Six months after treatment, the ^{13}C-urea breath test was negative in 659/727 (90.7%) of participants after active treatment (60 non-attenders) and in 99/706 (14.0%) of those given placebo (65 non-attenders). Two year follow up was complete in 1433/1558 (92.0%) participants. The unexpectedly high apparent loss of *H pylori* infection in the placebo group was mainly due to our use of δ3.5 rather than δ5.0 as a cut-off point to define infection in the ^{13}C-urea breath test. In 75 of the 99 instances of apparent eradication by placebo, the initial breath test reading was between δ3.5 and δ5.0. Such participants probably never had *H pylori* infection.

H pylori infection was associated with a small difference in the prevalence of heartburn ("any heartburn in the past month" 28.1% *v* 25.2%, $\chi^2 = 4.51$, $P = 0.034$) (table 2), but not



Trial profile

gastro-oesophageal reflux ("any reflux in the past month" 18.6% *v* 17.4%, $\chi^2 = 1.0$, P = 0.32) (table 3).

Heartburn was significantly associated with epigastric pain, acid reflux, obesity, regular consumption of non-steroidal anti-inflammatory drugs or proton pump inhibitors, smoking, and chest pain induced by exercise (table 4). Age, sex, alcohol intake, and socioeconomic status were not risk factors for heartburn.

H pylori eradication treatment had no significant effect on the prevalence of either heartburn (odds ratio 0.99, 95% confidence interval 0.88 to 1.12) or gastro-oesophageal reflux (1.04, 0.91 to 1.19) two years after treatment (table 5). Treatment had no impact on the development of heartburn (0.90, 0.78 to 1.04) or reflux (1.05, 0.90 to 1.21) in previously asymptomatic participants. In participants who had these symptoms at baseline, no significant improvement occurred in either heartburn (0.90, 0.71 to 1.14) or reflux (0.89, 0.62 to 1.29).

In those participants who had gastro-oesophageal reflux without heartburn before treatment (n = 248), *H pylori* eradication treatment had a protective effect against the development of heartburn over the two year period (0.56, 0.35 to 0.90). The number of general practice consultations for

Table 1 Baseline characteristics of two groups of participants with *Helicobacter pylori* infection who entered the prospective double blind study. Values are numbers (percentages)

Characteristic	Active treatment (n=787)	Placebo treatment (n=771)
Age (years):		
<40	120 (15.2)	110 (14.3)
41-54	452 (57.5)	451 (58.5)
≥55	215 (27.3)	210 (27.2)
Sex:		
Male	385 (48.9)	378 (49.0)
Female	402 (51.1)	393 (51.0)
Lifestyle:		
Smoking		
never	405/767 (52.8)	389/764 (50.9)
past	179/767 (23.3)	190/764 (24.9)
current	183/767 (23.9)	185/764 (24.2)
Alcohol consumption*	140 (17.8)	195 (25.3)
NSAIDs (any in past 3 months)	177/732 (24.2)	191/720 (26.5)
BMI >30 kg/m^2	221 (28.1)	195 (25.3)
Pretreatment symptoms†:		
Any epigastric pain	298/760 (39.2)	302/730 (41.4)
Monthly epigastric pain	185/760 (24.3)	194/730 (26.6)
Any heartburn	378/756 (50.0)	368/734 (50.1)
Monthly heartburn	213/756 (28.2)	202/734 (27.5)
Any acid reflux	301/760 (39.6)	298/732 (40.7)
Monthly acid reflux	144/760 (18.9)	133/732 (18.2)

NSAID=non-steroidal anti-inflammatory drug; BMI=body mass index.
*Current alcohol intake at least one unit per week.
†Any=any in past three months; monthly=at least once in past month.
The slight differences in the denominators are due to incomplete data for some participants.

Table 2 Effect of *Helicobacter pylori* infection on prevalence of heartburn. Values are numbers (percentages) unless stated otherwise

Frequency of heartburn	*H pylori* infection (n=1560)*	No infection (n=3164)*	Unadjusted odds ratio (95% CI) for *H pylori* positive participants
Any in past three months	781 (50.1)	1490 (47.1)	1.14 (1.05 to 1.23)
At least monthly	438 (28.1)	797 (25.2)	1.21 (1.11 to 1.32)

*Incomplete data for 178/4902 (3.6%) participants.

Table 3 Effect of *Helicobacter pylori* infection on prevalence of acid reflux. Values are numbers (percentages) unless stated otherwise

Frequency of reflux	*H pylori* infection (n=1566)*	No infection (n=3167)*	Unadjusted odds ratio (95% CI) for *H pylori* positive participants
Any in past three months	627 (40.0)	1184 (37.4)	1.05 (0.97 to 1.14)
At least monthly	291 (18.6)	551 (17.4)	1.05 (0.95 to 1.17)

*Incomplete data for 178/4902 (3.6%) participants.

Table 4 Factors associated with a significantly increased risk of heartburn. Values are numbers (percentages) unless stated otherwise

Factor	Heartburn		Unadjusted odds ratio (95% CI)
	No	Yes	
Epigastric pain*:			
No	3085 (88.2)	411 (37.2)	1.0
Yes	423 (11.8)	714 (62.8)	12.67 (10.54 to 15.28)
Acid reflux*:			
No	3201 (93.3)	623 (51.4)	1.0
Yes	231 (6.7)	590 (48.6)	7.25 (6.29 to 8.26)
Use of proton pump inhibitor:			
No	3443 (98.3)	984 (87.9)	1.0
Yes	59 (1.7)	136 (12.1)	8.07 (5.85 to 11.13)
Non-steroidal anti-inflammatory drugs:			
<1/month	2906 (84.2)	825 (76.7)	1.0
≥1/month	545 (15.8)	251 (23.3)	1.62 (1.37 to 1.92)
Obesity†:			
No	2902 (81.8)	644 (70.4)	1.0
Yes	817 (18.2)	343 (29.6)	1.89 (1.31 to 2.21)
Chest pain on exertion:			
No	3512 (98.9)	1115 (96.0)	1.0
Yes	41 (1.2)	47 (4.0)	3.61 (2.36 to 5.53)
Smoking:			
Never	1421 (48.3)	303 (32.5)	1.0
Ever	1521 (51.7)	629 (67.5)	1.94 (1.66 to 2.27)

Age over 50, sex, alcohol intake, and socioeconomic status were not risk factors for heartburn.
*At least monthly.
†Body mass index ≥30.0 kg/m^2.

Table 5 Effect of *Helicobacter pylori* eradication treatment on prevalence of heartburn and reflux at two years. Values are numbers (percentages) unless stated otherwise

Measure	Placebo (n=787)	Active treatment (n=771)	Unadjusted odds ratio (95% CI) for active treatment
Prevalence of heartburn* (n=1410)	170/702 (24.2)	169/708 (23.9)	0.99 (0.88 to 1.12)
Prevalence of reflux† (n=1419)	124/704 (17.6)	135/715 (18.9)	1.04 (0.91 to 1.19)

*Defined as heartburn at least once a month.
†Defined as reflux at least once a month.

heartburn or reflux over the two years after active treatment was not significantly greater than after placebo (1.63, 0.94 to 2.87).

Discussion

The most obvious mechanism by which *H pylori* infection might affect reflux oesophagitis is by affecting secretion of gastric acid. *H pylori* infection usually causes a predominantly antral gastritis, which results in a net increase in acid secretion.[16] In people with an incompetent antireflux mechanism, this would increase exposure of the lower oesophagus to acid, increasing the prevalence of heartburn.[4 5] Our findings that *H pylori* is associated with an increased prevalence of heartburn and that *H pylori* eradication treatment reduces the risk of patients with acid reflux developing heartburn support this hypothesis. Acid reflux depends more on the integrity of the lower oesophageal sphincter, hence the insignificant effect of *H pylori* infection on reflux. Patients with severe reflux oesophagitis are less likely to have *H pylori* infection,[17–26] possibly because corpus gastritis caused by helicobacter infection limits maximum acid output in these patients,[27–32] thus protecting them against the more severe forms of reflux oesophagitis. Such people might theoretically be at risk of increased exposure of the lower oesophagus to acid after eradication of *H pylori* infection.[29 31] However, our study suggests that no significant worsening of heartburn or reflux occurs after eradication of *H pylori* in patients in the community.

Our study has weaknesses. As it was community based, we had no direct information (from endoscopy, for example) as to the actual pathology underlying the symptoms of our participants. The randomised double blind design, the large numbers of participants, the high rate of *H pylori* eradication, the avoidance of prolonged acid suppression as part of the treatment, and the length and completeness of the two year period of follow up are compensating strengths.

We thank the participants in the Bristol helicobacter project and the general practitioners and health centre staff; the nursing team of Lynne Bradshaw, Julie Watson, Tina Critchley, Jo Lee, Carol Everson-Coombe, Penny Nettlefield, and Joanne Smith; Judy Millward, Helen Davies, Amy Hawkins, and Sarah Pike for secretarial support; and Erwin Brown, Paul Thomas, Nick Pope, and Phil Hedges of the microbiology department and Peter Spurr, Martin Bullock, and Fiona Greenwood of the pharmacy department, Frenchay Hospital, for help with the breath tests.

Contributors: RFH initiated the study, helped to plan the project, analysed the results, wrote the initial draft of the paper, and is the guarantor. JAL ran the Bristol helicobacter project from day to day and helped with analysis of the data and the final version of the paper. PN helped to set up the project. LJM, IMH, and JLD helped to plan the project, analyse the results, and produce the final version of the paper.

Funding: This study was funded jointly by the NHS South and West Regional Research and Development Directorate and GlaxoSmithKline UK. The Department of Social Medicine is the lead centre for the MRC Health Services Research Collaboration.

Competing interests: RFH and JAL were reimbursed by GlaxoSmithKline for attending the AGA symposium in 2000.

What is already known on this topic

Heartburn and gastro-oesophageal reflux are common symptoms in the population

Helicobacter pylori gastritis is also very common and might influence these symptoms by altering gastric acid secretion

Previous studies have reached differing conclusions about the effect of *H pylori* eradication on gastro-oesophageal reflux disease

What this study adds

In a general practice population, people with *Helicobacter pylori* infection had a slightly higher prevalence of heartburn (but not reflux) than other people

Helicobacter pylori eradication had no net effect on symptoms of gastro-oesophageal reflux disease

Ethical approval: The local research ethics committee approved the study.

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(Accepted 12 March 2004)

doi 10.1136/bmj.38082.626725.EE

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