

## 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 <sup>13</sup>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.<sup>1,2</sup> Pangastritis sometimes occurs, with a net suppression of acid secretion.<sup>2</sup> 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.<sup>3</sup> Later studies, with varying methods, have produced conflicting results; some showed an increase or unmasking of reflux oesophagitis,<sup>4-6</sup> others reported no effect,<sup>7-9</sup> and some even found a benefit.<sup>10-13</sup> 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.<sup>14</sup> 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 <sup>13</sup>C-urea breath test for active *H pylori* infection.<sup>14</sup>

All participants completed a validated questionnaire describing the frequency and severity of any epigastric pain, heartburn, and gastro-oesophageal reflux.<sup>14</sup> We compared the symptoms of all 1634 participants whose <sup>13</sup>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 <sup>13</sup>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 <sup>13</sup>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 analysed symptoms two years after treatment on an intention to treat basis.

### Results

Of the 10 537 participants who had a <sup>13</sup>C-urea breath test, 1634 (15.5%) were positive for *H pylori* infection. 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 <sup>13</sup>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

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**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 <sup>2</sup>	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.

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  $\delta 3.5$  rather than  $\delta 5.0$  as a cut-off point to define infection in the <sup>13</sup>C-urea breath test. In 75 of the 99 instances of apparent eradication by placebo, the initial breath test reading was between  $\delta 3.5$  and  $\delta 5.0$ . Such participants probably never had *H pylori* infection. *H pylori* infection was associated with a small increase in the prevalence of heartburn but not gastro-oesophageal reflux (see bmj.com).

*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 2). 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

**Table 2** 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.

### 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 *Helicobacter 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

against the development of heartburn over the two year period (0.56, 0.35 to 0.90). The number of general practice consultations for 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.<sup>15</sup> In people with an incompetent antireflux mechanism, this would increase exposure of the lower oesophagus to acid, increasing the prevalence of heartburn.<sup>4 5</sup> 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,<sup>16-19</sup> possibly because corpus gastritis caused by helicobacter infection limits maximum acid output in these patients,<sup>20-24</sup> 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.<sup>22 24</sup> 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.

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

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## A paediatric emergency

It was an ordinary evening surgery when a mother brought in her 2 week old baby, saying that he was "not himself, not feeding, sleepy ... perhaps, I'm being fussy ... fine until this morning," alternating between platitudes and anxiety. One glance was sufficient to realise that the baby required immediate attention. I had a sudden, automatic change to a clinical "hospitaloid" approach; no patient centred consultation, but an urgent demand to ascertain facts and assess the sick baby.

He was feverish, breathing satisfactory, awake, with no localising signs, no grunting, no rash or meningism, but probably septicaemic. As I explain to the parents that he will have to be admitted immediately I start to expedite the referral, simultaneously trying to contain their anxiety, shifting momentarily to being more patient centred. His father is dressing him when the child arches his back, rolls his eyes, and rapidly decompensates. I call for help instantly. Someone from reception gets the resuscitation kit and calls the other two doctors consulting that evening. We reassess the baby, set up oxygen, and administer antibiotic. One of us who has continued a weekly session in the local accident and emergency department has no hesitation in putting in an intravenous line despite the minuteness of the infant, and quickly calculates the volume of fluid to counter dehydration.

The response from the ambulance service is rapid, but what follows is a run of frustrating questioning as we try to understand each others' roles, which has rarely been more poignant. The baby responds and is carried into the ambulance. Parents and

child get "blue lighted" to accident and emergency. The outcome is good; he arrives at hospital in a better condition than when he entered the surgery—safely rehydrated, treatment ongoing, and the immediate crisis averted. Diagnosis: septicaemia secondary to a urinary tract infection. The hospital team comment favourably on the emergency care administered in our practice.

It's not often we save lives in the acute sense in general practice, but in this instance we did. However, we afterwards asked ourselves, "What if this had happened at a different time, with only one doctor in the surgery, a Saturday morning for example?" We reviewed this in our management meeting as a critical event, and were grateful for the programme of updating our resuscitation skills that was instigated by two partners, and for the readily accessible and user friendly resuscitation bag.

I have been a GP principal for 15 years, and this was the sickest baby I have ever seen in the community. As in every emergency, there is the uniqueness of the situation; in this case a new family, an unflustered mother, a quiet evening surgery. But there are many consistent features that we have worked hard to provide—easy access to medical attention, teamworking, essential lifesaving skills, a review of paediatric resuscitation skills that we have honed for just such a situation. Let's hope that it is at least another 15 years before they need deploying again. Meanwhile we must keep practising.

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