

Impact of *Helicobacter pylori* eradication on dyspepsia, health resource use, and quality of life in the Bristol helicobacter project: randomised controlled trial

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Abstract

Objective To determine the impact of a community based *Helicobacter pylori* screening and eradication programme on the incidence of dyspepsia, resource use, and quality of life, including a cost consequences analysis.

Design *H pylori* screening programme followed by randomised placebo controlled trial of eradication.

Setting Seven general practices in southwest England.

Participants 10 537 unselected people aged 20-59 years were screened for *H pylori* infection (¹³C urea breath test); 1558 of the 1636 participants who tested positive were randomised to *H pylori* eradication treatment or placebo, and 1539 (99%) were followed up for two years.

Intervention Ranitidine bismuth citrate 400 mg and clarithromycin 500 mg twice daily for two weeks or placebo.

Main outcome measures Primary care consultation rates for dyspepsia (defined as epigastric pain) two years after randomisation, with secondary outcomes of dyspepsia symptoms, resource use, NHS costs, and quality of life.

Results In the eradication group, 35% fewer participants consulted for dyspepsia over two years compared with the placebo group (55/787 v 78/771; odds ratio 0.65, 95% confidence interval 0.46 to 0.94; P=0.021; number needed to treat 30) and 29% fewer participants had regular symptoms (odds ratio 0.71, 0.56 to 0.90; P=0.05). NHS costs were £84.70 (£74.90 to £93.91) greater per participant in the eradication group over two years, of which £83.40 (\$146; €121) was the cost of eradication treatment. No difference in quality of life existed between the two groups.

Conclusions Community screening and eradication of *H pylori* is feasible in the general population and led to significant reductions in the number of people who consulted for dyspepsia and had symptoms two years after treatment. These benefits have to be balanced against the costs of eradication treatment, so a targeted eradication strategy in dyspeptic patients may be preferable.

Introduction

Dyspepsia affects up to 40% of the UK population and accounts for 4% of all consultations in primary care,^{1 2} with annual costs to the NHS of around £1.1 billion.³ Most dyspeptic patients are managed in primary care.

Two previous trials of community screening and *H pylori* eradication in Leeds and in Denmark showed modest reductions in self reported dyspepsia symptoms.^{4 5} However, the Danish study included many uninfected people, diluting the effects of eradication treatment, and the Leeds study included only people aged 40-49 years. A Cochrane review of management of dyspepsia in primary care concluded that *H pylori* eradication may benefit some dyspeptic patients,⁶ and the CADET-Hp trial of "test and treat" in uninvestigated dyspeptic patients in Canada showed clinical and economic benefits.⁷

The Bristol helicobacter project was established as a large community based randomised controlled trial to assess the impact of *H pylori* eradication on the outcomes of dyspepsia, quality of life, health resource use, and NHS costs over two years of follow-up among patients detected through screening.

Methods

Protocol

A community based screening study was followed by a randomised controlled trial of *H pylori* eradication. Briefly, unselected patients aged 20-59 years registered at seven general practices in southwest England were invited to attend screening for *H pylori* infection. Infected participants were randomised to *H pylori* eradication treatment or placebo.⁸

Assignment and masking

Participants were randomised to receive either ranitidine bismuth citrate (400 mg) and clarithromycin (500 mg) twice daily for 14 days or matching placebo. Both participants and researchers were blind to treatment allocation. Eradication was assessed by a

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urea breath test six months later, and the results were withheld from participants and staff conducting follow-up. General practitioners were requested not to prescribe *H pylori* eradication treatment during follow-up.

Outcomes and follow-up

The primary outcome was the consultation rate for dyspepsia (epigastric pain) in primary care over two years. Trained research nurses blinded to treatment allocation examined primary care records two years after randomisation. They recorded consultations related to dyspepsia or to heartburn, reflux, or dysmotility-type symptoms; prescribed dyspepsia treatments; and referrals to secondary care for dyspepsia. Secondary outcomes were the frequency and type of symptoms, impact on quality of life, resource use, and costs to the NHS two years after randomisation. We measured frequency of symptoms with self report

questionnaires.^{9 10} We used the SF-36 questionnaire to assess generic health status (quality of life).¹¹

We did the economic evaluation from the NHS viewpoint with a cost consequences analysis.¹² Resource use for each participant for the two years after randomisation came from the note reviews. We analysed dyspepsia related general practitioner consultations, secondary care referrals, and drugs.¹³ We applied costs at 2002 prices from UK sources.

Statistical analyses

We did intention to treat analyses with logistic regression, adjusted for sex and age, of all randomised participants with note review for the primary analysis, and all participants with completed follow-up questionnaires for the self reported secondary outcomes. The economic evaluation included all participants with complete resource use information. We assessed cost differences between treatment and placebo groups, with regression adjusted for sex and age.

Results

Study population flow, *H pylori* prevalence, and eradication

Of the 26 203 people who received an invitation letter, 10 714 (41%) attended. In all, 10 537 participants entered the study; 1636 (15.5%) participants were infected with *H pylori*, and 1558 (95%) of these agreed to be randomised. Eradication of *H pylori* was 91%. Recruitment took place between 1996 and 1999 and follow-up between 1998 and 2001. Follow-up was 99% (1539) for the primary outcome and 92% (1438) for the secondary outcomes.

Health resource use and costs of dyspepsia

The number of people consulting for dyspepsia in primary care was reduced by 35% (55 v 78) over two years in the eradication group compared with the placebo group (odds ratio 0.65, 95% confidence interval 0.46 to 0.94; P = 0.021). Thirty people with *H pylori* would have to be treated to prevent one person consulting their doctor for dyspepsia.

The total number of general practice consultations for dyspepsia over two years was also reduced in the eradication group, but all other resource use was similar (table 1). No significant differences existed between the two groups in the costs of general practice consultations, prescription drugs, or secondary care procedures (table 2). However, the cost of the *H pylori* eradication treatment (£83.40 (\$146; €121)) resulted in significantly greater NHS costs per participant in the eradication group (difference = £84.70, 95% confidence interval £74.90 to £93.91).

Cost consequences: dyspepsia symptoms and quality of life

Regular symptoms of dyspepsia were reported by 29% fewer participants two years after *H pylori* eradication treatment than after placebo (odds ratio 0.71, 0.56 to 0.90). No differences existed between the two groups in any of the quality of life dimensions at two years (table 3).

Table 1 Health resource use for dyspepsia over two years and unit costs

Resource use related to dyspepsia	Resource use events; mean (SD) per participant*		Unit cost or range (£) and source
	Eradication group (n=775)	Placebo group (n=750)	
General practitioner consultations	88; 0.11 (0.50)	120; 0.16 (0.52)	20†
General practitioner home visits	10; 0.001 (0.04)	10; 0.001 (0.04)	61†
Drug prescriptions	139; 0.18 (0.65)	127; 0.17 (0.56)	Variable‡
Endoscopies	25; 0.03 (0.20)	19; 0.03 (0.16)	65§
Secondary care procedures¶	21; 0.03 (0.20)	25; 0.03 (0.20)	65-226§

*Rounded to two decimal places.
†Netten and Curtis.¹⁸
‡BNF (gastrointestinal systems section 1.1-1.3).¹³
§North Bristol NHS Trust, Bristol.
¶Non-endoscopic secondary care procedures such as imaging combined as few occurred, and no inpatient stays occurred.

Table 2 Health service costs for dyspepsia over two years

Costs related to dyspepsia	Health service cost (£); mean (SD) per participant*		Difference† (95% CI) in mean adjusted costs (£)
	Eradication group (n=775)	Placebo group (n=750)	
General practitioner consultations	1 785; 2.30 (10.06)	2 417; 3.22 (10.47)	-0.93 (-1.87 to 0.18)
Drug prescriptions	14 363; 18.53 (82.63)	12 362; 16.48 (97.74)	2.16 (-7.08 to 10.52)
<i>Helicobacter pylori</i> eradication drugs	64 636; 83.40 (0)	0	83.40 (83.40 to 83.40)
Endoscopies	1 596; 2.06 (12.62)	1 204; 1.61 (9.97)	0.47 (-0.71 to 1.53)
Secondary care procedures‡	1 878; 2.42 (18.73)	2 119; 2.83 (16.95)	-0.40 (-2.11 to 1.43)
Total health care costs§	84 259; 108.72 (95.14)	18 101; 24.13 (101.39)	84.70 (74.90 to 93.91)

*Rounded to two decimal places.
†Eradication group minus placebo group, adjusted for the stratification variables.
‡Non-endoscopic secondary care procedures such as imaging combined, as few occurred and no inpatient stays occurred.
§Totals not exact due to rounding up by £0.01.

Table 3 Health related quality of life at two years. Values are mean (SD) scores unless stated otherwise

Dimension	Eradication group (n=787)	Placebo group (n=771)	P value*
Physical functioning	87 (19.8)	87 (19.5)	0.64
Social functioning	86 (18.4)	85 (19.0)	0.37
Role limitation—physical	85 (31.0)	83 (32.5)	0.20
Role limitation—emotional	86 (29.1)	86 (30.8)	0.95
Pain	76 (23.8)	75 (24.7)	0.34
Mental health	75 (16.7)	74 (17.7)	0.53
Vitality	67 (18.8)	67 (20.4)	0.72
General health perception	71 (20.6)	71 (20.5)	0.64

*Eradication group minus placebo group.

Discussion

Study validity and generalisability

The number of people who consulted for dyspepsia in primary care was reduced by about 30% two years after *H pylori* eradication. A large sample across a wide age range was recruited, with few exclusions, thus increasing generalisability. The high rates of *H pylori* eradication and follow-up, with blinded assessment of the primary outcome, enhanced internal validity of the study. Use of the breath test minimised misclassification biases and probably facilitated recruitment, as no blood test was necessary. The clinically important primary outcome of dyspepsia consultations in primary care contrasts with self reported dyspepsia symptoms used in the two other community based *H pylori* studies.^{4 5}

Forty one per cent of the target population participated in this study, which was more than in the other UK based *H pylori* eradication study (25%) but less than in the Danish study (63%).^{4 5} We were unable to access the primary care notes of non-responders to check if the population recruited was representative of the dyspepsia burden in primary care, but both previous trials found lower healthcare resource use for dyspepsia in non-responders.^{4 5} *H pylori* prevalence at 15% was comparable to the Danish study (17.5%) but lower than in the Leeds study (28%).

Comparison with other studies

Similar reductions in dyspepsia symptoms were observed in all three population based *H pylori* eradication trials.^{4 5} Results after one year showed a 4% absolute reduction in dyspepsia symptoms in the intervention arm of the Danish study, but this was not a placebo controlled trial. The Leeds study reported an overall reduction in dyspepsia symptoms of 5% in people aged 40-49 years, with a 74% *H pylori* eradication rate and 76% follow-up at two years. The lack of response to treatment in women observed in the Leeds study was not replicated in either our study or the Danish study.^{4 5}

Economic analyses

At £83.40 per participant, *H pylori* eradication treatment dominated costs in the economic evaluation. However, current treatment (Heliclear) costs £37.65, so halving the costs of screening and eradication to the NHS.¹³ The Leeds study reported non-significantly lower NHS costs (£11.42) over two years in the eradication group, but it is not clear if treatment costs were included.¹⁴ In contrast, a “test and treat” strategy in uninvestigated dyspeptic patients in Canada showed a cost effectiveness ratio of \$C387 (£188) in favour of *H pylori* eradication, showing that a targeted approach was more a cost effective policy.^{7 15}

A recent systematic review of the effects of *H pylori* eradication on quality of life in patients with functional dyspepsia noted that most evidence was drawn from secondary care patients.¹⁶ No major changes in quality of life were found after *H pylori* eradication in any of the three eradication trials based in the community.^{4 5} The scores for the individual dimensions of the quality of life obtained in our study were comparable to normative UK data.¹¹

What is already known on this topic

Dyspepsia is common and is usually managed in primary care

Helicobacter pylori infection is a major cause of peptic ulcer disease, but its role in dyspepsia is less certain

Dyspepsia symptoms were reduced after *H pylori* eradication in people aged 40-49 years in a community based trial

What this study adds

In the general practice population, the number of people who consulted for dyspepsia (epigastric pain) and who had symptoms decreased by 30% after *H pylori* screening and eradication

H pylori eradication in patients with dyspepsia offers long term relief from symptoms but with increased cost due to the eradication treatment

Policy implications and conclusions

The reduction in the numbers of people consulting for dyspepsia and reporting symptoms—alongside the potential future prevention of peptic ulcers and gastric cancer¹⁷—has to be balanced against the NHS costs. A targeted *H pylori* test and treat strategy focusing on uninvestigated dyspeptic patients was highly effective,⁸ and our study potentially supports that approach.

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Competing interests: JAL and RFH were funded by Glaxo-SmithKline to attend the AGA meeting in 2000.

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

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Compliance with QUOROM and quality of reporting of overlapping meta-analyses on the role of acetylcysteine in the prevention of contrast associated nephropathy: case study

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Abstract

Objective To appraise multiple systematic reviews on the same clinical topic, focusing on predictors and correlates of quality of reporting of meta-analysis (QUOROM) scores.

Design Case study.

Setting Reviews providing at least individual quantitative estimates on role of acetylcysteine in the prevention of contrast associated nephropathy.

Data sources PubMed, the database of abstracts of reviews of effects, and the Cochrane database of systematic reviews (updated March 2005).

Main outcome measures Funding, compliance with the QUOROM checklist, scores on the Oxman and Guyatt quality index, and authors’ recommendations.

Results 10 systematic reviews, published August 2003 to March 2005, were included. Nine pooled events despite heterogeneity and five recommended routine use of acetylcysteine, whereas the remaining studies called for further research. Compliance with the 18 items on the QUOROM checklist was relatively high (median 16, range 11 to 17), although shorter manuscripts had significantly lower scores ($R = 0.73$; $P = 0.016$). Reviewers who reported previous not for profit funding were more likely to score higher on the Oxman and Guyatt quality index. No association was found between QUOROM and Oxman and Guyatt scores ($R = -0.06$; $P = 0.86$), mainly because of greater emphasis of the Oxman and Guyatt scores on the appraisal of bias in selection and validity assessment (inadequate in five reviews).

Conclusions Multiple systematic reviews on the same clinical topic varied in quality of reporting and recommendations. Longer manuscripts and previous

not for profit funding were associated with higher quality.


Introduction


Since the mid-70s a large number of systematic reviews have been published, varying widely in quality and standards.¹⁻⁵ Anecdotal reports of multiple reviews focusing on the same clinical topic have differed in quality and methods used, leading to conflicting conclusions.^{4 6 7}

The quality of reporting of meta-analysis (QUOROM) statement was developed to improve and standardise the reporting of systematic reviews,⁸ not to avoid duplication of research. Yet the effect of the QUOROM guidelines on the design, conduct, and reporting of systematic reviews is unclear.

Several randomised controlled trials have investigated the role of acetylcysteine in the prevention of contrast associated nephropathy, but with conflicting results. A systematic review was therefore carried out to provide more comprehensive and robust conclusions.^{w1} Subsequent systematic reviews on the same topic were published, with different findings.

We appraised this cluster of duplicate systematic reviews, focusing on predictors and correlates of QUOROM quality scores. We explored the association between compliance with the QUOROM statement and characteristics of the manuscripts.

 Description of Oxman and Guyatt index and references w1-w10 are on *bmj.com*

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