Systematic review and economic evaluation of Helicobacter pylori eradication treatment for non-ulcer dyspepsia

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Helicobacter pylori eradication treatment in patients with non-ulcer dyspepsia infected with H pylori. The eligibility criteria required the intervention group to have received one of the following: proton pump inhibitor dual treatment (proton pump inhibitor plus either amoxicillin or clarithromycin for two weeks); new triple treatment (proton pump inhibitor H2 receptor antagonist, or ranitidine bismuth citrate with two out of three of amoxicillin, clarithromycin, and 5-nitroimidazole for at least one week); standard triple treatment (bismuth salt with two out of three tetracycline, amoxicillin, and metronidazole for at least one week); quadruple treatment (proton pump inhibitor plus standard triple treatment).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population was hypothetical patients with non-ulcer dyspepsia infected with H pylori. Patients with dyspepsia defined as “any upper gastrointestinal symptoms referable to the gastrointestinal tract,” which included dyspepsia defined according to the working group criteria (1989) and the Rome criteria (1991). Trials that included only patients with heartburn and acid reflux were excluded; peptic ulcer disease and oesophagitis were previously excluded in all participants by endoscopy or barium meal.

Setting
The setting was hospital. The economic analysis was carried out in the UK.

Dates to which data relate
The literature search procedure covered the period between January 1996 and May 2000. Effectiveness data were based on the studies which fulfilled the eligibility criteria, and which were published between 1996 and 2000. Resource use and cost data were based on sources published between 1998 and 1999. The price year was not specified.

Source of effectiveness data
The evidence for the final outcomes was based on a review of the literature.

Modelling
A Markov model was developed using TreeAge version 3.5 to compute the costs and effects associated with each adopted strategy over 1 year.
Outcomes assessed in the review
The outcomes obtained from the systematic review were the response rate at one year, the relative risk of dyspepsia with H pylori eradication treatment, and quality of life (which was measured by either the psychological general wellbeing index or SF-36).

Study designs and other criteria for inclusion in the review
Databases were searched for randomised controlled trials (between 1996 and 2000) comparing H pylori eradication with placebo or another drug treatment for non-ulcer dyspepsia. The eligibility criteria further required the studies to evaluate dyspeptic symptoms or quality of life assessed as an outcome with previously validated measures. Two investigators independently reviewed all identified papers according to the eligibility and quality criteria. Where disagreements occurred a third reviewer was involved and the majority view taken.

Sources searched to identify primary studies
Six electronic databases were searched. Experts in the field, pharmaceutical companies, and journals were contacted for information about any unpublished trials.

Criteria used to ensure the validity of primary studies
The quality criteria were as follows: true random allocation; concealment of allocation; patient reliably blinded to treatment allocation; analysis according to allocation, regardless of compliance (intention to treat); percentage of patients excluded from all analyses.

Methods used to judge relevance and validity, and for extracting data
"Investigator reliably blinded to treatment allocation" was used as a criterion to assess the validity of the primary studies. A single investigator extracted data from eligible trials on a standardised form, which was checked by a second investigator. Dyspepsia outcomes were regrouped into an a priori dichotomy of those with improved dyspepsia (mild symptoms) or resolved dyspepsia (no symptoms) versus those with the same or worse dyspepsia (moderate or severe symptoms). The effect of eradication in each trial was expressed as a relative risk.

Number of primary studies included
The initial search identified 5,146 articles, but after scanning titles and abstracts, the authors found only 47 trials that seemed to evaluate H pylori eradication treatment in non-ulcer dyspepsia. Twelve of these trials met the eligibility criteria and were included in the systematic review. Ten trials compared H pylori eradication treatment with placebo, or placebo plus a proton pump inhibitor, with follow up of 3-12 months. The other two trials compared H pylori eradication treatment with an alternative drug treatment and followed patients for only three months or less. Three trials presented data on quality of life at 12 months that were suitable for meta-analysis.

Methods of combining primary studies
Meta-analysis was the method of combination adopted. Relative risks were pooled using a fixed effect (Mantel-Haenszel) model, the appropriateness of which was assessed using a test of homogeneity and of funnel plot asymmetry. The impact of treatment on quality of life was estimated by combining standardised effect sizes because a mixture of instruments to measure quality of life had been used in the trials.

Investigation of differences between primary studies
Tests of homogeneity and of funnel plot asymmetry were performed. No significant heterogeneity was found between the trial results; there was also no evidence of funnel plot asymmetry.
**Results of the review**
The outcome values were as follows:

antacid response rate at one year, 28% (range: 21% - 58%) versus 36% (range: 21% - 58%) for the H pylori eradication treatment;

relative risk of dyspepsia with H pylori eradication treatment, 0.91 (95% CI: 0.86 - 0.96).

H pylori eradication treatment was significantly superior to placebo in treating non-ulcer dyspepsia (relative risk reduction, 9% (95% CI: 4% - 14%)), one case of dyspepsia being cured for every 15 people treated.

Overall, H pylori eradication treatment had no significant effect on quality of life compared with placebo (standardised mean difference, 0.01 (95% CI: -0.12 - 0.15).

**Measure of benefits used in the economic analysis**
The measure of benefit adopted was the number of dyspepsia-free months (the number of months of minimal or no dyspeptic symptoms during the year after treatment).

**Direct costs**
Costs were not discounted due to the short time frame of the cost analysis (one-year). Resource use quantities were reported separately from the costs. Cost items were reported separately. Cost analysis covered the costs of drugs and visits to general practitioners. The perspective adopted in the cost analysis was that of the National Health Service (NHS). Cost data were taken from the British National Formulary and other sources published between 1998 and 1999. The price year was not explicitly specified.

**Statistical analysis of costs**
A statistical analysis of costs was not carried out.

**Indirect Costs**
Indirect costs were not included.

**Currency**
UK pounds sterling ()

**Sensitivity analysis**
A series of one-way sensitivity analyses was performed on the main input parameters to evaluate the robustness of the cost-effectiveness results. The impact of individual trials on the overall results was investigated by performing sensitivity analysis using STATA (version 6.0). A probabilistic sensitivity analysis was performed using Monte Carlo simulation on relative risk reduction and costs of eradication regimens. An Excel 97 spreadsheet was used to construct a set of cost-effectiveness acceptability curves to reflect uncertainty in both effects and the maximum willingness to pay.

**Estimated benefits used in the economic analysis**
It was estimated that the patients receiving H pylori eradication treatment would benefit by an average of an extra 0.56 months free from dyspepsia than those given antacid.

**Cost results**
The average cost of antacid strategy per patient per year was 55.25 versus 87.01 for the H pylori eradication treatment.

**Synthesis of costs and benefits**
Incremental cost per dyspepsia-free month was estimated from the Markov model based on the estimated relative risk reduction, resulting in a value of 56 per extra month free from dyspepsia. This finding was robust to all one-way sensitivity analyses except for the size of relative risk reduction.

**Authors' conclusions**
H pylori eradication may be a cost-effective treatment for non-ulcer dyspepsia in infected patients but further evidence is needed on decision-makers' willingness to pay for relief of dyspepsia.

**CRD COMMENTARY - Selection of comparators**
The strategy of using antacid treatment was explicitly regarded as the comparator. It was assumed that antacid treatment acted as an inexpensive placebo and that patients whose symptoms continued despite treatment would be given advice on life style and reassurance by their general practitioner but no additional treatment beyond the first month. This allowed the active value of the eradication therapy to be evaluated. It was mentioned that the antacid strategy was used as the comparator because definitive evidence for the effectiveness of more expensive treatments such as antisecretory or prokinetic treatment was lacking.

**Validity of estimate of measure of effectiveness**
The internal validity of the effectiveness results is likely to be high due to the effectiveness data being based on randomised controlled trials (usually large) with no evidence of imbalance in baseline characteristics; outcomes being assessed with validated dyspepsia questionnaires; drop out rates being low; intention to treat analyses being reported for extended follow-up; and, more importantly, because a methodologically sound and systematic literature review and meta-analysis were performed.

**Validity of estimate of measure of benefit**
The Estimation of benefits was modelled. The instrument used to derive the measure of health benefit, the Markov model, was appropriate. It was noted that the model did not extend the effect of treatment beyond the length of the trials, although benefits should continue to accrue. The potential for increasing antimicrobial resistance rates was also not assessed, as the additional impact of treatment of non-ulcer dyspepsia on the present rate of antibiotic prescribing in the community is likely to be small.

**Validity of estimate of costs**
The following aspects of the cost analysis contributed to its validity: resource use quantities were reported separately from the costs; adequate details of methods of cost estimation were given; the perspective adopted in the cost analysis was specified; and the robustness of the cost results was investigated through sensitivity analysis. However, the effects of alternative procedures on indirect costs were not addressed, a statistical analysis of costs was not conducted, and the price year was not reported.

**Other issues**
The authors' conclusion appears to be justified given the thoroughness of the systematic review conducted and the extensive sensitivity analyses performed. Some comparisons were made with other studies. It was noted that the Markov model used in the study applies only to patients with non-ulcer dyspepsia diagnosed after endoscopy and should not be extrapolated directly to the management of undiagnosed dyspepsia.

**Implications of the study**
Treating the infection could be cost-effective provided a cost of 75 per month free from dyspepsia is acceptable. This cut off point is open to debate, and more research is needed into the willingness to pay for relief of dyspepsia symptoms.

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**Other publications of related interest**

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