Helicobacter pylori-associated ulcer bleeding: should we test for eradication after treatment

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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
The study examined testing for Helicobacter pylori (H. pylori) infection after completion of antibiotic therapy. The comparator was no testing.

Type of intervention
Screening.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of men and women aged 50 years with a first episode of a peptic ulcer haemorrhage and a positive H. pylori test, who underwent antibiotic eradication therapy.

Setting
The setting was primary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1993 and 2003. Resource use and prices were based on published cost data and Medicare reimbursements in 2002 and medication costs in 2003. The price year used was 2002/03.

Source of effectiveness data
The effectiveness data were derived from a review or synthesis of studies, and estimates of effectiveness based on opinion.

Modelling
A Markov decision analysis model was used to estimate the costs and benefits over the patients’ remaining lifetime. The model comprised six health states. These were treatment failure, no infection, undetected infection, lifelong proton-pump inhibitor (PPI), post-surgery and death. A 1-year cycle was used.

Outcomes assessed in the review
The outcomes assessed were:

the rate of H. pylori eradication with primary (triple) treatment or repeat (quadruple) treatment;
the rate of recurrent ulcer bleeding based on H. pylori status (negative, positive, positive with PPI therapy);
the rate of death from ulcer haemorrhage;
the rate of surgery for ulcer haemorrhage; and
the sensitivity and specificity of H. pylori testing.

**Study designs and other criteria for inclusion in the review**
Observational studies, clinical trials and a Cochrane Review were included in the review. No inclusion or exclusion criteria were reported.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
No criteria were used to ensure the validity of the primary studies.

**Methods used to judge relevance and validity, and for extracting data**
The method used to judge relevance and validity were not reported. Summary statistics were obtained from each study.

**Number of primary studies included**
Twenty-eight primary studies were included in the review.

**Methods of combining primary studies**
The studies were combined using a narrative method. Plausible ranges were derived for each outcome using data obtained from the primary studies. A base-case value was selected, based on either the mid-point of the range of primary studies or the point estimate in a single primary study.

**Investigation of differences between primary studies**
The authors reported that the success rate of initial H. pylori treatment with initial (triple) therapy was lower when considering the intention to treat analysis. No other investigation of differences between the primary studies was reported.

**Results of the review**
The probability of H. pylori eradication was 0.85 (range: 0.50 - 0.98) with initial (triple) therapy and 0.85 (range: 0.75 - 0.95) with repeat (quadruple) therapy.

The probability of recurrent bleeding was 0.01 (range: 0.005 - 0.02) for patients who were H. pylori negative, 0.10 (range: 0.01 - 0.30) for patients who were H. pylori positive, and 0.05 (range: 0.01 - 0.10) for patients who were H. pylori positive and on PPI therapy.

The probabilities of death or surgery due to ulcer haemorrhage were 0.07 (range: 0.04 - 0.10) and 0.08 (range: 0.03 - 0.14), respectively.

The H. pylori test was associated with a sensitivity of 0.90 (range: 0.85 - 0.99) and a specificity of 0.90 (range: 0.85 - 1.00).
Methods used to derive estimates of effectiveness
The authors also made assumptions to derive estimates of effectiveness.

Estimates of effectiveness and key assumptions
Patients with a second ulcer haemorrhage were assumed to receive lifelong PPI therapy. After suffering a recurrent ulcer haemorrhage and receiving medical or surgical treatment, patients were assumed to be H. pylori negative without being re-treated for H. pylori infection and suffered no further haemorrhage. The mortality rate from ulcer haemorrhage was assumed to include surgical mortality.

Measure of benefits used in the economic analysis
The measure of benefit used was the quality-adjusted life-years (QALYs) gained. The authors assumed a patient utility of one for all health states, given the lack of information on quality of life following surgery and on lifelong PPI therapy. Ulcer haemorrhage and surgery were assumed to be associated with tolls (zero utility) of 4 days and 1 week, based on a published cost-utility analysis. The health benefits were discounted at an annual rate of 3%.

Direct costs
The cost boundary adopted was costs to the health service from the perspective of a third-party payer. The resource quantities and the costs were analysed separately. A discount rate of 3% was applied to all costs. The direct costs were for the H. pylori test, H. pylori repeat treatment (14-day quadruple therapy), PPI treatment, and inpatient treatment for recurrent bleeding (medical treatment or surgery). The costs of the H. pylori test covered the C-urea breath test, stool antigen test and clo-test (the sensitivity analysis also included oesophagogastroduodenoscopy, histology and culture).

Estimates of the resource quantities were based on authors' assumptions, while estimates of the unit costs were derived from published data, Medicare reimbursements and the Red Book. The cost of PPI therapy was the average wholesale price for PPI medications. Inpatient treatment was based on Diagnosis-Related Group codes 174/175 (medical treatment) and 154/155 (surgical treatment). The price year used was 2002/03. The authors reported that the costs of treating side effects of antibiotic therapy were excluded, but would be covered by the cost variations in the sensitivity analysis.

Statistical analysis of costs
The quantities of resources used and costs were treated as point estimates.

Indirect Costs
The indirect costs were not included.

Currency
US dollars ($).

Sensitivity analysis
The variability in the data and the generalisation of the results were tested. One-way simple sensitivity analyses were performed. The parameters varied included the probabilities of H. pylori eradication with repeat treatment, recurrent bleeding and death from ulcer haemorrhage, and the costs of the H. pylori test and repeat treatment. Assumed minimum and maximum estimates, based on the results of the review, were used. A probabilistic sensitivity analysis (Monte Carlo simulation) was also performed. A sensitivity analysis was performed where the time horizon was restricted to 2 years. This was justified by a lack of information on the risk of rebleeding as a function of H. pylori status beyond 2 years.

Estimated benefits used in the economic analysis
Over a patient's lifetime, the testing strategy generated 0.07 additional QALYs compared with a strategy of no testing (18.57 QALYs versus 18.64 QALYs). The side effects of treatment were considered in the economic analysis as the disutility for surgery to treat recurrent bleeding. In the Monte Carlo analysis, testing generated 0.12 additional QALYs gained compared with no testing (18.68 QALYs versus 18.56 QALYs). All QALYs were discounted at an annual rate of 3%.

Cost results
The total costs were not reported in the text. From the figures provided, the total costs were approximately $4,700 (no testing) and $3,900 (testing) per patient lifetime.

The incremental cost was $836 per patient lifetime with testing.

The costs of adverse effects were not included.

In the Monte Carlo analysis, the mean total costs were $3,927 with testing and $4,866 with no testing (i.e. $939 saved with testing).

All the costs were discounted at an annual rate of 3%.

Synthesis of costs and benefits
The costs and benefits were combined as the incremental cost per QALY gained, discounted at an annual rate of 3%. However, in the base-case analysis, testing was cost-saving and generated more QALYs. Therefore, the testing strategy was dominant and an incremental cost per QALY gained was not established.

In the probabilistic sensitivity analysis, testing dominated in 86% of simulations and the incremental cost per QALY gained was less than $50,000 in 7% of simulations. Testing dominated in all one-way sensitivity analyses, except for the variation in the cost of H. pylori testing. Testing increased the total costs if the cost of initial testing and retreatment exceeded $765. The cost per QALY gained was $11,500 in the 2-year model.

Authors' conclusions
It was cost-effective (more effective and cost-saving) to test, rather than not to test, for Helicobacter pylori (H. pylori) infection after the initial antibiotic treatment of an H. pylori-associated ulcer haemorrhage.

CRD COMMENTARY - Selection of comparators
A justification was given for the comparator of no testing: since recurrent bleeding is rare and eradication of H. pylori is successful in 80 to 95% of patients, providers might not consider that it is worthwhile to test.

Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature had been undertaken. The effectiveness estimates were combined using narrative methods. The authors reported the ranges obtained from the review of the literature. However, it was unclear how the base-case values or limits for the sensitivity analysis were selected from these ranges. The authors do not appear to have weighted the results according to the study sample sizes or quality. The only consideration of differences between studies on the impact of effectiveness was to acknowledge that the success rate of H. pylori treatment was lower in the intention to treat analysis. Estimates based on the authors' assumptions were neither justified nor investigated in a sensitivity analysis.

Validity of estimate of measure of benefit
The estimation of benefits was modelled. QALYs gained over a patient's lifetime from the time of testing (50 years of age) were estimated using a Markov model. This was appropriate given the impacts on mortality and morbidity of
recurrent bleeding episodes and associated treatments. The utility values were derived from the literature, but the authors did not report the methodological approach used to derive such utility weights. The authors explored a range of utility values in the sensitivity analysis. The benefits were discounted.

**Validity of estimate of costs**
All the categories of cost relevant to the perspective adopted were included in the analysis. The costs of treating potential side effects from antibiotic therapy were not included in the model. However, the authors stated that variation in other costs examined in the sensitivity analysis would be likely to account for these costs. The cost estimates were reported separately from other model parameters. A sensitivity analysis of the cost of the H. pylori test was performed. The lower limit (stool antigen test only) and upper limit (all likely tests) would appear to be reasonable. A sensitivity analysis of H. pylori repeat treatment cost was also performed, but it was unclear whether the resource quantities or prices were varied. Elsewhere, a sensitivity analysis of the prices was not conducted. The costs and benefits were discounted at a rate that was appropriate given the time horizon of the analysis. The cost data were reported for specified price years (2002/03).

**Other issues**
The authors did not make appropriate comparisons of their findings with those from other studies. They did not present their results selectively. Since the issue of generalisability to other settings such as the National Health Service was not addressed, the authors’ conclusions can only be applied to the US health care system. The study assessed the cost-effectiveness for persons aged 50 years, but the authors generalised their conclusions to all persons with a first ulcer haemorrhage and positive H. pylori test who underwent antibiotic eradication therapy. The authors reported a number of further limitations to their study. Specifically, the model did not consider:

- the cost and effectiveness of more extensive testing and treatment following two failed antibiotic treatment courses;
- any decreased risks of non-bleeding complications (e.g. gastric cancer) following H. pylori eradication;
- variation in the annual risk of ulcer bleeding over time;
- any long-term reduction in quality of life following surgery; and
- a second repeat bleeding episode in the base-case model.

**Implications of the study**
The authors suggested that all patients with an H. pylori-associated ulcer haemorrhage should be tested for successful eradication after antibiotic therapy. This approach should become the standard practice of care because it decreases patient morbidity, mortality and health care costs. Further studies to examine current practice patterns regarding testing for H. pylori eradication after ulcer haemorrhage are warranted.

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