Antibiotic prophylaxis prior to endoscopic retrograde cholangiopancreatography in patients with obstructive jaundice: is it worth the cost?

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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 health intervention considered in the study was antibiotic prophylaxis performed prior to endoscopic retrograde cholangiopancreatography (ERCP) in patients with obstructive jaundice.

Type of intervention
Antibiotic prophylaxis.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients older than 15 years of age, with obstructive jaundice, defined as total bilirubin greater or equal to 2.5 ml/dL or, in the absence of documented bilirubin, having frank jaundice documented by physical examination at the time of ERCP. Patients were excluded if they had received antibiotics other than single-dose prophylaxis during the 7 days prior to ERCP or had received antimicrobial drugs during or following ERCP based on ERCP findings or for a febrile illness other than biliary sepsis or cholangitis.

Setting
The setting was a university hospital. The economic study was conducted at the Division of Gastroenterology and Hepatology of the University of Alabama at Birmingham, Alabama, USA.

Dates to which data relate
Data on effectiveness were derived from a sample of patients enrolled from August 1998 to July 2000 and from studies published between 1976 and 2001. No dates for resource use were reported. The price year was 2000.

Source of effectiveness data
Effectiveness data were derived from a review of the literature and a single study based on authors' experience. An assumption was also made in the effectiveness analysis.

Link between effectiveness and cost data
The costing was conducted retrospectively on a sample of patients different from that used in the effectiveness study.

Study sample
Power calculations were not performed. Of an initial sample of 243 patients undergoing ERCP for obstructive jaundice at the study institution, 148 subjects were excluded from the initial study sample because they were not eligible and a
A group of 95 patients was included in the final group under examination: 90 patients (mean age: 61.2 +/- 18.3 years; 54% men; 19% inpatient) had not received antibiotic prophylaxis before ERCP and 5 patients (mean age: 39.2 +/- 18.1 years; 60% men; 60% inpatient) had received it.

**Study design**
This was a retrospective case-control study, carried out in a single centre. The length of follow-up was seven days and only patients whose follow-up data were available were selected and included in the analysis, thus no loss to follow-up was reported.

**Analysis of effectiveness**
All patients included in the initial sample were taken into account in the effectiveness study. The primary outcomes estimated in the analysis were endoscopic endpoints, such as biliary structure, choledocholithiasis, primary sclerosis cholangitis, other results, no obstruction, unsuccessful cannulation of common bile duct (CBD), successful drainage, stone extraction, sphincterotomy, and placement of endoprosthesis. Comparability of study groups was not reported, but baseline characteristics appear to have been quite different between the two groups in terms of age and inpatient status.

**Effectiveness results**
The effectiveness results were as follows:

- Biliary structure occurred in 62% of patients in the no antibiotic prophylaxis group and 20% of patients in the antibiotic prophylaxis group.
- Choledocholithiasis occurred in 16% of patients in the no antibiotic prophylaxis group and 60% of patients in the antibiotic prophylaxis group.
- Primary sclerosis cholangitis occurred in 7% of patients in the no antibiotic prophylaxis group and 20% of patients in the antibiotic prophylaxis group.
- Other results occurred in 3% of patients in the no antibiotic prophylaxis group and 0 of patients in the antibiotic prophylaxis group.
- No obstruction occurred in 7% of patients in the no antibiotic prophylaxis group and 0 patients in the antibiotic prophylaxis group.
- Unsuccessful cannulation of CBD occurred in 5% of patients in the no antibiotic prophylaxis group and 0 patients in the antibiotic prophylaxis group.
- Successful drainage rate was 90% of patients in the no antibiotic prophylaxis group and 100% of patients in the antibiotic prophylaxis group.
- Stone extraction occurred in 13% of patients in the no antibiotic prophylaxis group and 60% of patients in the antibiotic prophylaxis group.
- Sphincterotomy was performed in 26% of patients in the no antibiotic prophylaxis group and 40% of patients in the antibiotic prophylaxis group; and
- Placement of endoprosthesis occurred in 62% of patients in the no antibiotic prophylaxis group and 40% of patients in the antibiotic prophylaxis group.

**Clinical conclusions**
The effectiveness analysis, which was intended to provide probability values of events considered in the decision model, showed that none of the patients in the group receiving antibiotic prophylaxis developed cholangitis, while a few
patients who did not receive antibiotic prophylaxis developed cholangitis.

Modelling
A decision tree model was constructed to model clinical outcomes and costs of ERCP performed with or without antibiotic prophylaxis. A hypothetical cohort of 100 patients with obstructive jaundice either received or did not receive antibiotic prophylaxis prior to ERCP and then developed cholangitis or other complications. The probabilities used in the decision model were derived from the literature and from the single study.

Outcomes assessed in the review
The primary health outcomes (model inputs) were the probabilities of the following events: cholangitis with prophylaxis, cholangitis without prophylaxis, complications from ERCP and percutaneous transhepatic cholangiography (PTC), death from cholangitis, and death from complications from ERCP and PTC.

Study designs and other criteria for inclusion in the review
Three of the primary studies included in the review were randomised controlled trials.

Sources searched to identify primary studies
The MEDLINE database was searched to identify relevant primary studies using the terms "ERCP", "biliary obstruction", "cholangitis", "antibiotic", "prophylaxis", and "antibiotic prophylaxis". The references found via MEDLINE were then used to identify further studies.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
Six primary studies were used as the source of effectiveness.

Methods of combining primary studies
Primary studies were combined using narrative methods.

Investigation of differences between primary studies
Not carried out.

Results of the review
The probability values were 0.0549 for cholangitis with prophylaxis, 0.0661 for cholangitis without prophylaxis, 0.05 for complications from ERCP and 0.18 for complications from PTC, 0.1 for death from cholangitis, and 0.025 for death from complications from ERCP and 0.051 for death from complications from PTC.

Methods used to derive estimates of effectiveness
The authors made an assumption used in the decision model.
Estimates of effectiveness and key assumptions
The authors assumed that the probability of serious drug reaction was 0.01.

Measure of benefits used in the economic analysis
The model outcomes estimated from the decision model were the episodes of cholangitis and deaths due to cholangitis expected in the hypothetical sample of 100 patients. These outcomes were obtained by populating the model with data from either the literature or the single study based on authors’ experience.

Direct costs
Discounting was not performed, as the time horizon of the study was short. Unit costs were not reported separately from quantities of resources used. The health service costs included in the analysis were antibiotics, cholangitis, management of complications of ERCP, ERCP, PTC, and management of antibiotic side effects. The cost/resource boundary adopted was that of the third party payer. The estimation of costs was based on actual data, derived from average wholesale prices for drugs, and average Medicare reimbursement rates at the authors’ institution for the remaining items. The cost of management of antibiotic side effects was based on authors’ assumptions. Total costs were obtained using modelling. Neither source nor dates for resource use were reported. The price year was 2000.

Statistical analysis of costs
Costs were treated deterministically.

Indirect Costs
Indirect costs were not included in the analysis.

Currency
US dollars ($).

Sensitivity analysis
One-way and two-way sensitivity analyses were conducted to assess the robustness of the estimated costs to variations in the following model inputs: probability of cholangitis with antibiotic prophylaxis, probability of cholangitis without antibiotic prophylaxis, probability of severe antibiotic reaction, cost of antibiotic and cost of cholangitis.

Estimated benefits used in the economic analysis
When data from the literature were used, the expected episodes of cholangitis per 100 patients were 5 in the group of those receiving antibiotic prophylaxis and 6 among those who did not receive antibiotic prophylaxis, and the expected number of deaths due to cholangitis was 0.5 when antibiotic prophylaxis was performed prior to ERCP and 0.6 in patients who did not receive antibiotic prophylaxis.

When data from the single study were used, the expected episodes of cholangitis per 100 patients were 0 in the group of those receiving antibiotic prophylaxis and 3 among those who did not receive antibiotic prophylaxis, while the expected number of deaths due to cholangitis was 0 when antibiotic prophylaxis was performed prior to ERCP and 0.3 in patients who did not receive antibiotic prophylaxis.

Cost results
When data from the literature were used, the expected costs per patient were $1,925 in the group of those receiving antibiotic prophylaxis and $2,005 for those patients who did not receive antibiotic prophylaxis.

When data from the single study were used, the expected costs per patient were $1,419 in the group of those receiving
antibiotic prophylaxis and $1,649 among those who did not receive antibiotic prophylaxis.

The sensitivity analyses showed that antibiotic prophylaxis remained cost-saving in comparison with no antibiotic prophylaxis under several conditions. In particular, at a value of relative risk reduction of cholangitis greater than 4.5%, antibiotic prophylaxis was cheaper than no antibiotic prophylaxis.

**Synthesis of costs and benefits**
Costs and benefits were not combined and it appears that a cost-consequences analysis was conducted.

**Authors’ conclusions**
The authors concluded that single-dose antibiotic prophylaxis was effective and cost-saving in patients undergoing ERCP.

**CRD COMMENTARY - Selection of comparators**
The rationale for the choice of the comparator was clear. ERCP without antibiotic prophylaxis was selected as the aim of the study was to assess the active value of antibiotic prophylaxis before ERCP. You, as a user of this database, should decide whether it represents a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**
The analysis of effectiveness was intended to provide data required to populate the decision model and two sources of data were used: the single study and the review of the literature. As regards the single study, the analysis of effectiveness was based on a case-control study, which was appropriate for the study question; but the authors acknowledged that study groups were not comparable and not well balanced, although strict follow-up was performed. In addition, the study was conducted retrospectively and the method of patient allocation to study groups was not randomised. These issues may have limited the internal validity of the analysis. As regards the review of the literature, limited details of the review were reported and it was not clear whether the authors took into consideration the differences across primary studies when estimating the effectiveness. Further, the authors reported that data from the primary trials were skewed and most of the patients were enrolled in one large single study. Finally, an assumption was made, although this was then investigated in the sensitivity analyses. As a result, caution should be exercised when using such effectiveness estimates in the decision model as each source of data used in the analysis may present some limitations.

**Validity of estimate of measure of benefit**
No summary benefit measure was used in the economic analysis. The analysis was therefore categorised as a cost-consequences study (see validity of effectiveness comments above).

**Validity of estimate of costs**
The perspective adopted in the study was reported and it appears that all relevant categories of costs were included in the analysis. Unit costs were not reported separately from quantities of resources and costs were treated deterministically. However, sensitivity analyses were conducted on cost estimates. The price year was reported, thus making reflation exercises in other settings easier. The source of cost data was appropriately reported, but dates and sources of resource use data were not reported. The authors noted that the costs of antibiotic therapy referred to cephalosporins and piperacillin, which were used in most of the trials from which data were derived, but the use of other antibiotics should not affect the conclusions of the analysis as the uncertainty on the cost of antibiotics was investigated in sensitivity analyses.

**Other issues**
The authors did not compare their findings with those from other studies and did not address the issue of the
generalisability of the study results to other settings, although some sensitivity analyses were performed to evaluate the robustness of the estimated costs. The study referred to a sample of patients with obstructive jaundice and this was reflected in the conclusions of the analysis. The authors commented on some of the limitations of their analysis, and these have been reported above.

**Implications of the study**
The authors' highlight the fact that their findings strongly support the recommendation to adhere to guidelines regarding antibiotic prophylaxis in patients suspected of presumed biliary obstruction, as previously suggested by the American Society for Gastrointestinal Endoscopy and the British Society of Gastroenterology.

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