Endoscopic screening for esophageal varices in cirrhosis: is it ever cost effective

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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
Six strategies for the primary prophylaxis of oesophageal varices in patients with cirrhosis were examined.

Strategy 1 was universal screening endoscopy (EGD) followed by beta-blocker (BB) therapy (EGD-BB) if varices are present. Patients who develop intolerance to BB therapy are offered endoscopic band ligation (EBL).

Strategy 2 was EGD followed by EBL (EGD-EBL) if varices are present.

Strategy 3 was selective screening endoscopy (sEGD) in high-risk patients followed by BB therapy if varices are present (sEGD-BB). High-risk patients are those with a platelet count of less than 88,000/mL, a prothrombin time activity of less than 70%, a portal vein diameter of greater than 13 mm, or splenomegaly. Patients who develop intolerance to BB therapy are offered EBL.

Strategy 4 was sEGD followed by EBL (sEGD-EBL) if varices are present.

Strategy 5 was empiric BB therapy in all patients. Patients who develop intolerance to BB therapy are referred for upper endoscopy and are then offered EBL if moderate or large oesophageal varices are identified.

Strategy 6 was no prophylactic therapy (i.e. "do nothing").

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients with compensated (Child's Class A or B) cirrhosis in whom the presence of underlying oesophageal varices was not known, and that had not undergone prior evaluation for varices (e.g. upper endoscopy, barium swallow, or computed tomography of the chest or abdomen). Patients with contraindications to BB therapy, such as advanced obstructive lung disease, baseline hypotension, bradycardia or heart block, were excluded.

Setting
The setting was a hospital and secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data and some resource use data were derived from studies published between 1981 and 2002. The price year could have been 2001.
Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies and authors' assumptions.

Modelling
A Markov model was constructed to examine the clinical and economic outcomes associated with the six prophylactic strategies in a hypothetical 50-year-old patient with newly diagnosed Child's class A or B cirrhosis. The time horizon of the model was 3 years and the cycle length was 1 month. Patients entered the model in one of three initial health states, that is, alive with no underlying varices, alive with small underlying varices, or alive with moderate or large underlying varices. During each cycle, individual patients either remained in their assigned health state or progressed to a new health state. Patients without varices could progress to form small varices. Moderate or large varices could bleed, which may or may not lead to death. Each patient progressed through the health states until either the 36-month time horizon was reached or the patient died from a variceal bleed.

Outcomes assessed in the review
The outcomes estimated from the literature were:

- the probability of underlying varices in cirrhotic patients;
- the odds ratio (OR) of underlying varices in high-risk patients versus low-risk patients;
- the proportion of patients with one or more risk factors for underlying varices (high-risk proportion);
- the 3-year rate of variceal haemorrhage once varices have formed in patients on no prophylactic therapy;
- the OR of variceal haemorrhage once varices have formed in patients on BB therapy versus no prophylactic therapy;
- the OR of variceal haemorrhage once varices have formed in patients receiving prophylactic EBL versus no prophylactic therapy;
- the probability of non-compliance with medical therapy in patients receiving empiric BB therapy;
- the probability of non-compliance with medical therapy in patients receiving BB after confirming varices by screening endoscopy;
- the proportion of patients receiving prophylactic EBL who do not complete a full course of therapy;
- the average number of sessions required to obliterate varices with prophylactic EBL;
- the probability of severe complications requiring hospitalisation and surgery from screening endoscopy;
- the probability of severe endoscopic complications requiring hospitalisation and surgery from prophylactic band ligation;
- the annual rates of developing new oesophageal varices and small oesophageal varices progressing to moderate or large varices;
- the probability of dying from an initial variceal haemorrhage;
- the average length of hospital stay for an initial variceal haemorrhage;
- the probability of underlying varices among high- and low-risk patients; and
- the risk of bleeding in patients on BB therapy and in patients receiving prophylactic EBL.
Study designs and other criteria for inclusion in the review
A systematic review of the literature was undertaken to identify relevant sources of data. Most of the primary studies were clinical trials. Some published systematic reviews of clinical trials were also used.

Sources searched to identify primary studies
MEDLINE and HealthSTAR were searched for relevant English language publications from January 1985 to January 2002.

Criteria used to ensure the validity of primary studies
Specific criteria were not used to ensure the validity of the primary studies. However, most of the studies were randomised clinical trials, which usually have a high internal validity.

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

Number of primary studies included
Forty-one primary studies provided the clinical data.

Methods of combining primary studies
The methods used to combine the primary studies were not explicitly reported, but the authors stated that when there was a range of data available, the estimates that favoured the EGD-BB strategy were chosen (the model was biased against the other five strategies).

Investigation of differences between primary studies
Not stated.

Results of the review
The probability of underlying varices in cirrhotic patients was 40%.

The OR of underlying varices in high-risk patients versus low-risk patients was 2.9.

The proportion of patients at high risk was 70%.

The 3-year rate of variceal haemorrhage once varices have formed in patients on no prophylactic therapy was 33%.

The OR of variceal haemorrhage once varices have formed in patients on BB therapy versus no prophylactic therapy was 0.5.

The OR of variceal haemorrhage once varices have formed in patients receiving prophylactic EBL versus no prophylactic therapy was 0.36.

The probability of non-compliance with medical therapy in patients receiving empiric BB therapy was 35% (10% was the dropout rate, 15% was the reported non-compliance probability).

The proportion of patients receiving prophylactic EBL who do not complete a full course of therapy was 20%.

The average number of sessions required to obliterate varices with prophylactic EBL was 3.3.

The probability of severe complications requiring hospitalisation and surgery was 0.02% from screening endoscopy.
The annual rate of developing new oesophageal varices was 7%.

The annual rate of developing small oesophageal varices progressing to moderate or large varices was 10%.

The probability of dying from an initial variceal haemorrhage was 33%.

The average length of hospital stay for an initial variceal haemorrhage was 4 days.

The probability of underlying varices was 49% among high-risk patients and 17% in low-risk patients.

The risk of bleeding was 16.5% in patients on BB therapy and 11.9% in patients receiving prophylactic EBL.

**Methods used to derive estimates of effectiveness**
The authors made some assumptions that were used to derive clinical inputs not available from the literature.

**Estimates of effectiveness and key assumptions**
Small varices were assumed not to bleed but may progress to form moderate or large varices. Death from nonvariceal causes was equal between health states. The unreported non-compliance probability with medical therapy in patients receiving BB was 10%. The probability of non-compliance with medical therapy in patients receiving BB after confirming varices by screening endoscopy was 30%. The probability of severe complications requiring hospitalisation and surgery was 0.02% from prophylactic band ligation.

**Measure of benefits used in the economic analysis**
The summary benefit measure was the proportion of patients avoiding a variceal haemorrhage. This was derived from the decision model.

**Direct costs**
The authors stated that discounting was not relevant because of the relatively short time horizon and the even distribution of costly events. The unit costs were presented, but resource use data were not provided for all items. The health services included in the economic evaluation were endoscopy, EBL, BB therapy, inpatient admission for variceal haemorrhage, treatment of complicated ulcer haemorrhage, emergency room, gastroenterologist and endoscopist visits, admission for severe complications, management of bowel perforation, surgeon and anaesthetist visits. The cost/resource boundary of the third-party payer was adopted. The costs were estimated from the American Medical Association Current Procedural Terminology, the Medicare Fee Schedule, and the Red Book of average wholesale prices. The resource use data came from published studies and authors' assumptions. The costs appear to have been estimated using 2001 values.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not included in the economic evaluation.

**Currency**
US dollars ($).

**Sensitivity analysis**
Univariate sensitivity analyses were carried out on all model inputs to examine the robustness of the estimated incremental cost-effectiveness ratios (ICER) to variations in base-case assumptions. The ranges were derived from authors' opinions, which were based on published evidence. Threshold analyses were also performed.

**Estimated benefits used in the economic analysis**

The proportion of patients avoiding a variceal haemorrhage was not reported for each strategy. It was only stated that the option of "do nothing" was the least effective, with 87% of patients avoiding a variceal haemorrhage.

**Cost results**

Similarly, the estimated costs were not reported for each strategy. It was only stated that the option of "do nothing" was the least expensive, with an average cost per patient treated of $2,401.

**Synthesis of costs and benefits**

An ICER (i.e. the incremental cost per additional variceal haemorrhage avoided) was calculated to combine the costs and benefits of the alternative prophylactic strategies. The ICER of the empiric BB strategy over "do nothing" was $12,408. In turn, the ICER of the EGB-BB over the empiric BB strategy was $175,833. The ICER of the EGD-EBL strategy over EGD-BB was $178,400. The incremental analysis revealed that both selective screening endoscopy strategies were dominated.

The relative order of the six strategies was not altered in the sensitivity analysis. However, significant variations in the values of the ICER were observed. For example, the ICER between the EGD-EBL strategy and the empiric BB strategy fell below the threshold of $50,000 with a 66% reduction in the 3-year rate of variceal haemorrhage with EBL, or when 80% of the cohort was non-compliant with BB therapy. When the 3-year probability of variceal haemorrhage was increased to 73%, the ICER between "do nothing" and the empiric BB strategy was $0. The ICER between EGD-BB and empiric BB therapy fell to $50,000 when the cost of screening endoscopy fell by two thirds, or when the cost of generic propranolol increased 7-fold.

**Authors' conclusions**

Current guidelines for the prevention of oesophageal varices that recommend the use of universal screening endoscopy followed by beta-blocker therapy (EGD-BB) in patients with cirrhosis were not cost-effective in comparison with alternative prophylactic strategies. In particular, a strategy of empiric BB therapy in all patients provided the lowest incremental cost-effectiveness ratio (ICER) over a strategy of "do nothing". The analysis revealed also that selective screening strategies were not cost-effective.

**CRD COMMENTARY - Selection of comparators**

The authors provided a justification for their choice of the comparators, which were appropriately selected. In particular, the authors noted that the strategy of EGD-BB represented current US guidelines for the prevention of oesophageal varices in patients with cirrhosis. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**

The effectiveness evidence came from a systematic review of the literature. Limited details on the methods and conduct of the review were reported. The authors provided only search methods, without reporting inclusion and exclusion criteria. Information on the design of the primary studies was unclear, although the authors stated that some data were derived from clinical trials. The methods used to extract and combine the data were not described, although the authors appear to have made conservative assumptions. Further, key model inputs were varied in the sensitivity analysis, which addressed the issue of uncertainty in some estimates.
Validity of estimate of measure of benefit
The summary benefit measure was specific to the disease considered in the study, thus limiting the possibility of making comparisons with the benefits of other health care interventions. The authors stated that death was not modelled as the main outcome because mortality had not been shown to be significantly different between the prophylactic interventions.

Validity of estimate of costs
The authors stated explicitly the perspective adopted in the study. As such, it appears that all the relevant categories of costs have been included in the analysis. The source of the costs was provided and the unit costs were reported. The information on resource consumption was less clear and was based on both authors' assumptions and published evidence. The costs were varied in the sensitivity analysis, which addressed the issue of variability in the data. The authors did no discount the estimated costs. However, since the model was run for a 3-year period, discounting would have been relevant, as generally recommended in economic evaluation guidelines. The price year was not explicitly stated, but it appears to have been 2001.

Other issues
The authors did not compare their findings with those from other published studies. They also did not address the issue of the generalisability of the study results to other settings. Sensitivity analyses were carried out, which enhances the external validity of the study. The authors noted that the robustness of their model relied on the validity of the primary sources. Despite the attempt to identify the most valid sources of data, some estimates came from studies of varying design, patient population, follow-up and quality.

Implications of the study
The study results supported the use of empiric BB therapy for the prevention of oesophageal varices in patients with cirrhosis, with EBL reserved for patients with contraindications to, or intolerance of medical management. The authors suggested that endorsement of the current clinical guidelines should be reappraised with a prospective trial comparing the accrued cost and effectiveness of the competing management strategies.

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Other publications of related interest


Park BJ, Shehab TM, Inadomi M. Primary prevention of variceal hemorrhage in high-risk patients: a cost-effectiveness
analysis incorporating patient compliance. Gastroenterology 2001;120:A1924.

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