The evaluation of rectal bleeding in adults: a cost-effectiveness analysis comparing four diagnostic strategies

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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
Four diagnostic strategies for the evaluation of rectal bleeding in adults were examined. The strategies were watchful waiting (WW), flexible sigmoidoscopy (FS), flexible sigmoidoscopy followed by air contrast barium enema (FS+ACBE), and colonoscopy (COL).

Type of intervention
Diagnosis.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients over the age of 40 years with otherwise asymptomatic rectal bleeding. This was defined as blood on toilet paper, in toilet bowl, mixed in stool, or on stool. Patients with melena were not included. The patients were asymptomatic with no family or personal history of colon cancer or polyps, and had not been screened within the last 10 years.

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

Dates to which data relate
The effectiveness data were, in part, derived from studies published from 1975 to 2003. The costs and resource use data were estimated from studies published between 1995 and 2001. The price year was 2001.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and some assumptions.

Modelling
A decision model was constructed. A Markov model was then used to simulate the natural history of patients with rectal bleeding and the impact of the four diagnostic strategies on the costs and benefits. The model was carried out in a hypothetical 55-year-old patient presenting with one or more episodes of rectal bleeding. The time horizon of the model was the patient's lifetime. Annual cycles appear to have been used. The model assumed that patients in the WW arm would only be worked up with COL if they had recurrent bleeding after 1 year. Patients in both the FS and FS+ACBE arms proceeded to COL if they had positive findings on FS, ACBE, or an incomplete examination. For FS, an incomplete examination was defined as the visualisation of less than 45 cm of the colon. For ACBE, it was defined as the inability of the patient to tolerate the examination, or films of sufficiently poor quality as to preclude interpretation.
The discovery of adenomatous polyps, colorectal cancer, or inflammatory bowel disease (IBD) constituted a positive examination. In the FS+ACBE arm, a negative FS was followed by an ACBE. A graphical representation of the Markov model was provided.

Outcomes assessed in the review
The outcomes estimated from the literature were the prevalence of serious disease in patients with rectal bleeding and the accuracy of the diagnostic tests. Mortality rates due to diseases associated with rectal bleeding or due to other causes, utility values, and procedure-associated complication and completion rates were also estimated.

Study designs and other criteria for inclusion in the review
A systematic review of the literature was carried out to identify all relevant studies providing clinical data for the decision model.

The inclusion criteria for articles on cause of rectal bleeding were prospective design, diagnosis confirmed by COL, FS+ACBE or more than 5 years’ clinical follow-up, and community-based population including adults older than 40 years.

The inclusion criteria for accuracy of diagnostic tests were prospective design, comparison of at least one diagnostic modality with another, reference standard of COL or FS+ACBE plus clinical follow-up, and sufficient data to calculate the sensitivity and specificity.

Quality of life values were mainly derived from patients who had already undergone a resection of a colorectal polyp. Other utility values came from patients who had colorectal cancer, as well as from a review study assessing quality of life in various disease states. Mortality due to other causes was estimated from life tables, while data from a cancer registry were used for other estimates.

Sources searched to identify primary studies
MEDLINE was searched for studies published in English from 1980 to 2000. The keywords were "rectal bleeding" and "rectal hemorrhage", and the MeSH terms were "gastrointestinal hemorrhage", "hemorrhage", "rectal diseases" and "rectum". In addition, reference lists from review articles and the Cochrane Database of Clinical Trials were also searched.

Criteria used to ensure the validity of primary studies
The authors stated that the validity of the included articles was assessed according to the presence of selection bias, verification bias and reference standard bias.

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

Number of primary studies included
Eighty-five primary studies provided the clinical inputs used in the decision model.

Methods of combining primary studies
Data obtained from studies on the causes of rectal bleeding were pooled using a random-effects model to achieve a weighted mean. In cases where pooling was not possible, point estimates for the base-case scenario were based on data from an expert panel review.
Investigation of differences between primary studies

Not stated.

Results of the review
The causes of rectal bleeding were:

- Polyp 16% (range: 0.7 - 25.2), large polyp (≥1 cm) 30% (range: 20 - 50), small polyp (<1 cm) 70% (range: 59 - 80);
- Colorectal cancer 7% (range: 0 - 11.5), Dukes A 47% (range: 8 - 47), Dukes B 20% (range: 20 - 46), Dukes C 26% (range: 26 - 50), Dukes D 7% (range: 0 - 15), IBD 8% (range: 3 - 16).

The locations of lesions were as follows:

- Cancers in left colon, 72% (range: 66 - 82);
- Polyps in left colon, 78% (range: 66 - 86);
- Right-sided lesions with associated left-sided lesions, 48% (range: 30 - 80).

The 5-year colorectal cancer mortality was 11.12% for Dukes A, 24.25% for Dukes B, 42.69% for Dukes C, and 93.69% for Dukes D.

The sensitivity of FS was 95% (range: 85 - 100) for rectosigmoid cancer, 85% (range: 75 - 98) for rectosigmoid polyp, and 67% (range: 50 - 100) for IBD.

The specificity of FS was 96% (range: 92 - 100).

The sensitivity of ACBE was 83% (range: 60 - 100) for cancer, 58% (range: 27 - 93) for polyp, and 33% (range: 23 - 43) for IBD.

The specificity of ACBE was 93% (range: 78 - 100).

The sensitivity of COL was 95% (range: 90 - 100) for cancer, 96% (range: 75 - 100) for polyp, and 83% (range: 83 - 93) for IBD.

The procedural complication rates were:

- For haemorrhage due to COL, 0.007 (range: 0.0024 - 0.046);
- For perforation due to COL, 0.004 (range: 0.00001 - 0.0214);
- For mortality due to COL, 0.0001 (range: 0.00005 - 0.0003);
- For perforation due to FS, 0.001 (range: 0.0001 - 0.05);
- For mortality due to FS, 0.00000006 (range: 0 - 0.00005);
- For perforation due to ACBE, 0.0001 (range: 0.00004 - 0.0002);
- For mortality due to ACBE, 0.00002 (range: 0.000004 - 0.00002).

The procedural completion rates were 75% (range: 65 - 85) for FS, 85% (range: 75 - 95) for ACBE, and 90% (range: 80 - 100) for COL.

The quality of life utilities were as follows:
Dukes A, 0.74 (range: 0.7 - 0.9);
Dukes B, 0.74 (range: 0.59 - 0.9);
Dukes C, 0.63 (range: 0.59 - 0.84);
Dukes D, 0.27 (range: 0.24 - 0.84);
terminal stage, 0.27 (range: 0.24 - 0.65);
IBD, 0.85 (range: 0.55 - 0.9); and
undiagnosed IBD, 0.65 (range: 0.55 - 0.75).

Other literature-based assumptions were also made.

Methods used to derive estimates of effectiveness
The authors made some assumptions to derive some clinical estimates. Experts' opinions were also used.

Estimates of effectiveness and key assumptions
The annual probability of recurrent rectal bleeding was 5% (range: 1 - 30).

It was assumed that patients diagnosed with small adenomatous polyps (polyps <1 cm without villous or high-grade dysplastic features) had a surveillance COL every 5 years, while those with large adenomatous polyps (>1 cm or with villous or high-grade dysplastic features) had a surveillance COL every 3 years. Surveillance continued life long.

Patients with missed cancers, polyps or IBD would ultimately become symptomatic, prompting further diagnostic evaluation by COL. Ninety per cent of polyps would be diagnosed within 7 years, and 90% of Dukes A, B, C and D cancers by 2, 2, 1 and 1 year, respectively. It was estimated that 90% of patients with IBD would be diagnosed within 2 years.

Measure of benefits used in the economic analysis
The summary benefit measure was the quality-adjusted life-years (QALYs). These were estimated using a Markov model in which survival and quality of life data derived from the literature were combined. An annual discount rate of 3% was applied.

Direct costs
An annual discount rate of 3% was used as the lifetime costs were estimated. The unit costs were not presented separately from the quantities of resources used for all items. The economic evaluation considered the costs of the diagnostic procedures examined in the study, the costs of cancer care, and the costs of IBD. A breakdown of the cost categories was not provided. The cost/resource boundary of the study was unclear. The costs and resource use data were derived from studies and other published sources. In particular, the costs of the diagnostic procedures came from Medicare reimbursement rates, while those for cancer care came from studies published between 1995 and 2001. All the costs were inflated to 2001 values using the Medical Care Consumer Price Index.

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
All individual model inputs were varied in a univariate sensitivity analysis using ranges obtained from the literature, or plausible ranges set by the authors. Two-way sensitivity analyses were carried out by simultaneously varying age and prevalence of polyps or cost of FS and cost of COL. Four alternative scenarios were considered:

- adjusting serious disease prevalence to that seen in patients aged 40 to 49;
- using procedure charges from the community setting;
- adjusting treatment costs to those seen in managed care;
- adjusting quality of life estimates to those seen in colorectal cancer survivors.

Estimated benefits used in the economic analysis
The estimated QALYs were 14.876 with FS, 14.890 with COL, 14.885 with FS+ACBE, and 14.665 with WW. COL was thus associated with the highest QALYs gained.

Cost results
The estimated costs were $17,100 with FS, $17,200 with COL, $17,300 with FS+ACBE, and $17,500 with WW. FS was thus the least costly strategy in the base-case.

Synthesis of costs and benefits
An incremental cost-utility ratio was calculated to combine the costs and QALYs of the alternative diagnostic strategies.

In the base-case, the incremental cost per QALY saved was $5,480 with COL over FS, and $25,107 with FS+ACBE over FS. COL dominated both WW and FS+ACBE, which were less effective and more expensive.

The univariate sensitivity analysis showed that the cost-utility ratio of COL increased with high prevalence of IBD, prolonged time to diagnosis of this disease, high sensitivity of FS for polyps, a low sensitivity of FS for IBD, and maximal rates of perforation and haemorrhage during COL. However, in all cases, the incremental cost per QALY of COL compared with FS was relatively low and was never over $16,000.

COL was not the preferred strategy in the following cases:

- age at entry higher than 80 years (cost per QALY: $987 with FS and $35,532 with COL compared with WW);
- prevalence of polyps lower than 7% (cost per QALY: $1,876 with FS and $15,168 with COL compared with WW); and
- cost per COL higher than $2,200 (cost per QALY: $33,955 with COL compared with FS).

The multivariate sensitivity analysis suggested that the greatest predictor of cost-effectiveness was age. As age increased, the cost per QALY of all strategies increased. Except for the youngest cohort, FS was always more cost-effective than COL. In the youngest cohort, the cost-effectiveness of COL and FS were almost identical and were always better than WW. The scenario analysis showed that when using disease prevalence data from patients aged 40 to 49, the incremental cost per QALY for COL compared with FS fell to $1,686. In the other scenarios, COL always remained the most effective strategy with a relatively low incremental cost-effectiveness ratio versus the other strategies.
Authors’ conclusions
Flexible sigmoidoscopy (FS) was the cheapest test for the evaluation of rectal bleeding, while colonoscopy (COL) was the most cost-effective initial test. FS followed by air contrast barium enema (ACBE) was both more expensive and less effective than COL, while watchful waiting (WW) was the most expensive and least effective diagnostic option, except in elderly patients with very low prevalence of polyps.

CRD COMMENTARY - Selection of comparators
The selection of the comparators was appropriate as the most commonly used diagnostic approaches for the evaluation of rectal bleeding were considered in the analysis. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from published evidence as well as from a series of assumptions. A systematic review of the literature was carried out to identify relevant studies. Extensive details of the methods and conduct of the review were reported. The methods used to combine the primary studies and to ensure their validity were provided in the technical appendix. Other clinical inputs were estimated from published studies that were identified selectively. In terms of the assumptions made, some of them were made by the authors to reflect treatment patterns used to construct the model. Other assumptions were based on experts’ opinions. The authors stated that some assumptions biased the analysis against COL. Owing to uncertainty in the estimates used in the model, all inputs were varied in the sensitivity analysis. Key variables were investigated further in multivariate analyses, which enhanced the robustness of the effectiveness evidence.

Validity of estimate of measure of benefit
The use of QALYs as the summary benefit measure was appropriate as they incorporate the two most relevant dimensions of health (quality of life and survival). The utility values were derived from the literature and information on the source of these data was provided. Discounting was performed, as recommended by US guidelines. QALYs are comparable with the benefits of other health care interventions.

Validity of estimate of costs
The authors stated that a modified societal perspective was adopted and the indirect costs were not included. In effect, only direct medical costs were considered. Most of the costs were presented as macro-categories and a detailed breakdown of single items was not provided. No information on resource consumption was provided, which limits the possibility of replicating the study in other settings. The source of the data was reported. The costs were treated deterministically, but key cost estimates were varied in the sensitivity analysis. The price year was reported, which aids reflation exercises in other settings. Alternative scenarios for the economic data were considered.

Other issues
The authors compared their findings with those from a published study and found overall consistent results, albeit with some discrepancies. The issue of the generalisability of the study results to other settings was not explicitly addressed, although extensive sensitivity analyses were carried out. This makes the results of the analysis transferable to other settings and enhances the external validity of the analysis. The results of the analysis were clearly presented. The authors noted some limitations of the analysis. For example, the fact that evidence on some clinical inputs (i.e. natural history of rectal bleeding and re-bleeding rates) was not reliable because of the lack of robust published data. Further, the exclusion of the indirect costs was conservative since their inclusion would have further favoured the COL option. The clinical management of patients presenting to primary care physicians was unclear since the decision to proceed to invasive work-up would be based on historical, physical and anoscopy findings. Thus, assumptions were made to represent diagnostic patterns.

Implications of the study
The study results supported the use of COL for the evaluation of rectal bleeding and suggested also that COL could be recommended in patients aged 40 to 49 years. The authors stressed that in situations where COL was not readily available, FS followed by ACBE provided very similar prolongation of life expectancy at a slightly higher cost.

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