Cost-effectiveness analysis evaluating fidaxomicin versus oral vancomycin for the treatment of Clostridium difficile infection in the United States

Stranges PM, Hutton DW, Collins CD

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.

CRD summary
The objective was to assess the cost-effectiveness of fidaxomicin, compared with oral vancomycin, for the treatment of Clostridium difficile, in patients aged 59.9 years. The authors concluded that, under most scenarios, fidaxomicin was cost-effective. The study reporting was generally good. A key flaw in the analysis was the validity of the patient utilities, but the authors’ conclusions seem appropriate for a $100,000 willingness-to-pay threshold.

Type of economic evaluation
Cost-utility analysis

Study objective
The objective was to assess the cost-effectiveness of fidaxomicin, compared with oral vancomycin, for the treatment of Clostridium difficile, in in-patients and out-patients, aged 59.9 years.

Interventions
Patients received a 10-day course of either fidaxomicin or oral vancomycin, for their first infections of Clostridium difficile. If this failed, patients received another three days of therapy, followed by oral vancomycin 500mg every six hours for 10 days, followed by four weeks of oral vancomycin taper. Patients with more than one recurrence received oral vancomycin for 10 days, followed by an oral vancomycin taper. Patients who failed to respond to these treatments progressed to surgery or ongoing treatment with vancomycin and intravenous metronidazole.

Location/setting
USA/secondary care.

Methods
Analytical approach:
Published decision models were adapted to assess the cost-effectiveness of fidaxomicin, over 23 years. Up to three episodes of infection were modelled. The authors stated that the a third-party payer perspective was adopted.

Effectiveness data:
The two key effectiveness estimates were the comparative clinical cure rate, and the recurrence rate (defined as the reappearance of Clostridium difficile within four weeks of successful treatment), for in-patients and out-patients. These values were from a randomised, open label, multicentre trial, conducted in the USA and Canada. Other clinical inputs were from published retrospective reports, systematic reviews, or other published literature.

Monetary benefit and utility valuations:
Quality-of-life estimates, for infected patients, were estimated from the utility measures for grade three to four diarrhoea, associated with chemotherapy. Patients who underwent total colectomy were assigned a utility weight the same as that for patients with an ileostomy.

Measure of benefit:
The health benefit was measured by quality-adjusted life-years (QALYs). Future QALYs were discounted at an annual rate of 3%.
Cost data:
The cost categories included drug acquisition, hospitalisation, computed tomography, and colectomy. Drug acquisition costs were from a publication of dose-specific costs. Total hospitalisation costs were from the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project on *Clostridium difficile*. The costs were reported in 2011 $, and updated, where necessary, using the Medical Care Services section of the Consumer Price Index. Future costs were discounted at an annual rate of 3%.

Analysis of uncertainty:
Univariate sensitivity analysis and probabilistic sensitivity analysis were conducted to assess the impact of model uncertainty on the results. A cost-effectiveness acceptability curve was constructed to show the probability that the intervention was cost-effective over a range of willingness-to-pay thresholds.

Secondary analyses were conducted to investigate the impact of changes in the medication acquisition costs, patient hospitalisation status before initial medication selection, the clinical cure and recurrence rates, disease severity, and the utilities. The clinical cure rates were varied to match the pooled results of two prospective double-blind, randomised studies. The alternative utilities were based on those for patients with active inflammatory bowel syndrome.

In an alternative analysis, fidaxomicin was compared with metronidazole, assuming that metronidazole had a similar efficacy to oral vancomycin.

Results
The incremental effect of fidaxomicin, over oral vancomycin, was 0.017 QALYs, with an incremental cost of $1,117. The incremental cost-effectiveness ratio for fidaxomicin, compared with oral vancomycin, was $67,576 per QALY gained.

At a willingness-to-pay threshold of $100,000 per QALY gained, the results were sensitive to variations in the clinical cure and recurrence rates, the rate of hospitalisation, and the probability of death from *Clostridium difficile*. The cost-effectiveness acceptability curve indicated that fidaxomicin was cost-effective in 80.2% of simulations at a threshold of $100,000, and 25.9% of simulations at a threshold of $50,000 per QALY gained.

Secondary analyses revealed that fidaxomicin was cost-effective in patients receiving concomitant antimicrobials, in patients with mild-to-moderate infections, and compared with oral metronidazole in patients with mild-to-moderate disease. Fidaxomicin was dominated by oral vancomycin if the infection was caused by the NAP1/Bl/027 strain, and it was dominant in institutions that did not compound oral vancomycin from its intravenous form (making it cheaper).

Authors' conclusions
The authors concluded that, under most scenarios, fidaxomicin was cost-effective, compared with oral vancomycin.

CRD commentary
Interventions:
The intervention and comparator were clearly stated, but their assumed dosages, at each stage of treatment, were not. Oral vancomycin and metronidazole were described as the usual treatments. Metronidazole was assessed in a secondary analysis, but its efficacy was assumed to be equal to that of vancomycin. It is unclear if this assumption was justified, and so whether the results of that analysis are valid. The main results, for oral vancomycin, should apply only to settings where the standard care is oral vancomycin. The authors highlighted the fact that treatment guidelines could vary significantly between settings.

Effectiveness/benefits:
The effectiveness data were clearly reported. The main estimates were from a randomised trial, which should minimise the risk of selection bias. The trial was not described in detail, but it appears to have been appropriate for the study population. The authors did not justify their selection of this trial. Given the sensitivity of the results to these values, and the fact that the authors stated that a wide range of values was reported in the literature, these estimates may not have been appropriate. Potential side-effects and mortality associated with treatment were not included in the model, due to a lack of reliable evidence. It was argued that this biased the model against fidaxomicin, since early evidence indicated that fidaxomicin had lower risks than the alternatives. Limited details were reported on the measurement and
valuation of the utilities, so it is not possible to properly assess their validity. It appears that the utilities were primarily assigned based on whether patients had *Clostridium difficile* or not, which offers only a crude measure of utility.

**Costs:**
The costs were clearly reported and were appropriate for the perspective. Their sources were stated, but not discussed in detail, so it is unclear whether they were appropriate for the population and setting. The authors argued that it was likely that the model was biased against fidaxomicin, as the wholesale acquisition cost of fidaxomicin was likely to have overestimated its actual cost. The price year was clearly stated and costs were appropriately adjusted. Future costs were appropriately discounted.

**Analysis and results:**
The model was clearly described and a diagram was provided. An intention-to-treat, incremental analysis was conducted, which was the most appropriate form of analysis. The results were clearly reported. Appropriate sensitivity analyses were conducted. The authors pointed out that fidaxomicin was cost-effective at a $100,000 threshold, but the appropriate threshold was contentious, and might vary between decision makers. At a lower threshold, the results were less robust to parameter changes in the sensitivity and scenario analyses, and the authors' conclusion of cost-effectiveness might be inappropriate.

**Concluding remarks:**
The study reporting was generally good. A key flaw in the analysis was the validity of the patient utilities, but the authors' conclusions seem appropriate for a $100,000 willingness-to-pay threshold.

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