The cost-effectiveness of cefepime plus metronidazole versus imipenem/cilastatin in the treatment of complicated intra-abdominal infection

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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 use of cefepime plus metronidazole, compared with imipenem/cilastatin, for the treatment of complicated intra-abdominal infections.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised hospitalised patients (>= 18 years of age) who had a preoperative diagnosis of complicated intra-abdominal infection, or a postoperative diagnosis of abscess or peritonitis (the "intend-to-treat" population, n=323). Patients were excluded from the original study if any of the following conditions applied:

- renal insufficiency (creatinine clearance <11 mL/minute);
- total leukocyte count less than 2,000/mm3;
- probable need for more than 14 days of antibacterial therapy;
- an Acute Physiology and Chronic Health Evaluation (APACHE) II score greater than 30;
- gynaecologic infection;
- non-perforated appendicitis;
- traumatic hollow viscus perforation of less than 12 hours' duration;
- perforated gastroduodenal ulcer of less than 24 hours' duration;
- history of seizures; or
- hypersensitivity to penicillins or cephalosporins.

The cost-effectiveness analyses were performed for three populations. More specifically, the total population, patients having an APACHE II score of more than 15, and those having an APACHE II score of 15 or less.

Setting
The setting was tertiary care. The economic study was carried out in university-affiliated hospitals in the USA and
Dates to which data relate
The data on clinical effectiveness and use of health resources were collected during the conduct of a randomised, double-blind, multi-centre clinical trial, which was published in 1996. The price year was 1996.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the effectiveness analysis.

Study sample
The effectiveness data for the study were taken from a "parent" study (Barie et al. 1997, see 'Other Publications of Related Interest' below for bibliographic details). The authors did not report whether power calculations were carried out to estimate the impact of chance on the results. Three hundred and twenty-three hospitalised patients (aged 18 years or older) who had a preoperative diagnosis of complicated intra-abdominal infection, or a postoperative diagnosis of abscess or peritonitis, were enrolled in the study. Of the 323 intent-to-treat patients enrolled, 164 were given cefepime (2 g intravenously every 12 hours) plus metronidazole (500 mg intravenously every 6 hours), and 159 were given imipenem/cilastatin (500 mg intravenously every 6 hours) plus placebo.

Study design
The study was a randomised, double-blind, multi-centre, clinical trial. The reader should consult the parent study for further details (Barie et al. 1997).

Analysis of effectiveness
The analysis of the clinical study was conducted on an intention to treat basis. The primary health outcomes were measured by the differences in the length of hospitalisation, the number of surgical procedures after treatment and the cure rates. The chi-squared test and Fisher's exact test were used to evaluate the comparability of the treatment groups for categorical variables. A two-way analysis of variance was performed on rank-transformed data to evaluate the clinical data for continuous variables. The treatment groups were comparable in terms of age, gender, surgical diagnosis, site of infection, vital signs at study entry, pretreatment haematology and serum chemistry values, and type of surgery.

Effectiveness results
Comparing cefepime plus metronidazole versus imipenem/cilastatin (results presented as mean +/- standard deviation):

- the patients’ postoperative hospital stay was 16.4 (+/- 18.5) days versus 18.6 (+/- 21.1) days, (p=0.09);
- the days from initial surgery to the start of the 10-day antibiotic-free period were 10.5 (+/- 7.7) versus 12.5 (+/- 9.8), (p=0.10);
- the days spent in a regular medical or surgical unit were 7.5 (+/- 6.7) versus 8.3 (+/- 7.5), (p=0.44);
- the days spent in an intensive care unit (ICU) were 3.0 (+/- 6.1) versus 4.2 (+/- 8.6), (p=0.18);
- the days given the study antibiotic were 7.7 (+/- 4.0) versus 8.7 (+/- 4.5), (p=0.04); and
- post-treatment surgical procedure was 7.9% versus 15.7%, (p=0.03).
Sixteen surgical procedures in the cefepime group and 39 in the imipenem group were required post-treatment.

**Clinical conclusions**
Clinically, cefepime plus metronidazole was as effective as imipenem/cilastatin, with similar clinical cure rates (82% versus 76%) in the treatment of complicated intra-abdominal infections, (p=0.36).

**Modelling**
A decision tree model was used to estimate the expected costs of treatment based on the probability of the various patient outcomes and associated costs.

**Measure of benefits used in the economic analysis**
The measure of health benefits used was the cure rate.

**Direct costs**
The direct costs included the treatment costs associated with each treatment strategy. These were the length of hospital stay stratified by the total number of days in the ICU and ward, the number, type and cost of post-treatment surgical procedures, the cost of study drugs and the cost of non-study antibiotics.

The quantities and the costs were analysed separately, with both being estimated from actual data. The average wholesale price for the antibiotics was obtained from the 1996 Red Book. The costs used for a day in an ICU or a ward were based on written communication with Millard Fillmore Health Systems in Buffalo, New York, for 1996. The costs for post-treatment surgical procedures performed in an operating room or a procedure room were from the New York-Presbyterian Hospital - Weill Cornell Medical Centre. Professional fees for surgeons or radiologists were not considered. The costs were not discounted because of the short duration of the treatment.

**Statistical analysis of costs**
A two-way analysis of variance was performed to evaluate the cost data.

**Indirect Costs**
The indirect costs were not included.

**Currency**
US dollars ($).

**Sensitivity analysis**
Sensitivity analyses were carried out to test the robustness of the results over a range of plausible values for the specified resource costs and the outcome probabilities included in the decision tree. Specifically, sensitivity analyses were used to determine decision thresholds (i.e. the values at which the treatment alternatives produced equal cost-effectiveness ratios). One-way sensitivity analyses were performed on the cost of study antibiotics, the ICU bed cost, the ward bed cost, the infection cure rate, the percentage of patients requiring post-treatment surgical procedures, and the percentage of patients having an APACHE II score greater than 15.

**Estimated benefits used in the economic analysis**
For the total population, the cure rate was 0.817 in the cefepime group and 0.761 in the imipenem group.

For severely ill patients (APACHE II score >15), the cure rate was 0.846 in the cefepime group and 0.360 in the
imipenem group.

For less severely ill patients (APACHE II score <=15), the cure rate was 0.815 in the cefepime group and 0.836 in the imipenem group.

**Cost results**
Comparing cefepime plus metronidazole with imipenem/cilastatin, the expected cost of patient care was $8,218 (cefapime-metronidazole) versus $10,414 (imipenem/cilastatin). For severely ill patients (APACHE II score >15), the expected cost was $12,962 versus $23,153. For less severely ill patients (APACHE II score <=15), the expected cost was $7,810 versus $8,038.

**Synthesis of costs and benefits**
Cost-effectiveness ratios were calculated in order to combine the costs and benefits of the treatment strategies.

Comparing cefepime plus metronidazole with imipenem/cilastatin, the cost-effectiveness ratio per cure was $10,059 (cefepime-metronidazole) versus $13,685 (imipenem/cilastatin). For severely ill patients (APACHE II score >15), the cost-effectiveness ratio per cure was $15,321 versus $64,313. For less severely ill patients (APACHE II score <=15), the cost-effectiveness ratio per cure was $9,853 versus $9,615.

An incremental analysis was performed in less severely ill patients.

The incremental cost-effectiveness ratio of cefepime plus metronidazole over imipenem/cilastatin was $10,875/cure. An incremental cost-effectiveness ratio was not calculated in the total population and in severely ill patients, because in both populations the cost profile was lower and the effectiveness profile was higher in the cefepime plus metronidazole treatment arm than in the imipenem/cilastatin treatment arm, as determined from the decision analysis model.

The sensitivity analyses performed on data for patients having an APACHE II score greater than 15 showed that the cost-effectiveness results were robust across a wide range of values. The sensitivity analyses performed on data for patients having an APACHE II score of 15 or less showed that, with the exception of re-operation rates, nominal changes in the initial values used in the decision tree would change the cost-effectiveness ratios for the two regimens.

**Authors’ conclusions**
Cefepime plus metronidazole was more cost-effective than imipenem/cilastatin in the treatment of complicated intra-abdominal infections, primarily because of it involved fewer post-treatment surgical procedures and shorter hospital stays. The primary advantage accrued to severely ill patients who had an APACHE II score greater than 15.

**CRD COMMENTARY - Selection of comparators**
It was unclear why the comparators used were chosen, and the authors did not provide a justification for their choice. You should decide if this is a widely used health technology in your own setting.

**Validity of estimate of measure of effectiveness**
The estimates of the measure of effectiveness are likely to be valid because the analysis was based on a randomised controlled trial that was carried out in multiple centres. This was appropriate for the study question. The study sample included all patients who met the inclusion criteria. The patient groups were shown to be comparable at analysis. Appropriate statistical analyses were undertaken to account for potential biases and confounding factors.

**Validity of estimate of measure of benefit**
The estimates of measure of benefit were taken directly from the effectiveness analysis.
Validity of estimate of costs
The cost perspective adopted in the study was not reported. Only the direct costs associated with treatment were included; professional fees for surgeons or radiologists were not considered. The indirect costs were not included. The costs and the quantities were reported separately. Discounting was unnecessary because of the short period of treatment.

Other issues
The authors made some comparisons of their findings with those from other studies. In addition, the issue of generalisability to other settings was addressed. The authors reported several limitations of their retrospective pharmacoeconomic analysis. First, only the period of hospitalisation was estimated, rather than the full economic and health consequences of treatment to the patient. Second, the consumption of resources was determined by the protocol, rather than what might occur in regular practice. Finally, the research setting (academic tertiary care institutions) possibly differs from "real-world" practice. The authors suggested that, in interpreting and extrapolating the results of this analysis, it must be recognised that treatment patterns at one specific hospital may differ from those observed in actual medical practice.

Implications of the study
This study implied that cefepime plus metronidazole is an attractive regimen for the treatment of complicated intra-abdominal infections, particularly in critically ill patients. The authors suggested that institutions should collect data on patient outcomes and outcomes specific to their organisation, and then incorporate these data into the cost-effectiveness analysis so that system-wide costs associated with treating infectious diseases can be considered.

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Other publications of related interest


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