Cost-effectiveness of cefepime plus netilmicin or ceftazidime plus amikacin or meropenem monotherapy in febrile neutropenic children with malignancy in Turkey

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 three therapies for the treatment of infections in febrile neutropenic children with malignancy:

- cefepime (100 mg/kg per day intravenous (i.v.) in 3 doses) plus netilmicin (5 mg/kg per day i.v. in 2 to 3 doses), (CEF/NET);
- ceftazidime (100 mg/kg per day i.v. in 3 doses) plus amikacin (15 mg/kg per day i.v. in 2 doses), (CEFT/AMI); and
- meropenem alone (60 mg/kg per day i.v. in 3 doses), (MER).

All patients were on prophylactic treatment with ketoconazole and trimethoprim-sulfamethoxazole.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised children with fever (axillary at least 38.5 degrees C on one occasion, or at least 38 degrees C on two occasions within 12 hours), neutropenia (absolute neutrophil count less than 1x10^9/L) and a presumed infection (i.e. fever unlikely to be due to a non-infectious cause such as drug or blood product transfusion). Patients were excluded if they had received any i.v. antibiotic during the neutropenic episode or during the preceding 96 hours, had a known allergy to any of the protocol antibiotics, or had a renal or hepatic failure.

Setting
The setting was a hospital. The economic study was carried out in Turkey.

Dates to which data relate
The effectiveness and resource use data were gathered between January 1998 and January 1999. No price year was reported. In subsequent correspondence with the authors we have been informed that the price year was in fact 1998.

Source of effectiveness data
The effectiveness evidence came from a single study.

Link between effectiveness and cost data
The costing appears to have been conducted prospectively on the same patient sample as that used in the effectiveness study.

**Study sample**
Power calculations to determine the sample size were not performed. In addition, the authors failed to provide evidence that the initial sample size was appropriate for the study question and the method of sample selection was not reported. The overall sample included 82 patients experiencing 87 febrile neutropenia episodes. There were 27 children (median age: 9 years) and 28 febrile episodes in the CEF/NET group, 28 children (median age: 7 years) and 29 febrile episodes in the CEFT/AMI group, and 27 patients (median age: 6 years) and 30 febrile episodes in the MER group.

**Study design**
This was a randomised controlled trial, which was carried out in a single centre. The method of randomisation was not reported and the outcome assessment was not blinded. The patients were followed throughout the treatment, but the length of follow-up was not stated. No loss to follow-up was reported. However, in subsequent correspondence with the authors they have stated that the length of follow-up varied by patient according to the program for malignancy and additionally, there was no loss to follow-up during antibiotic therapy.

**Analysis of effectiveness**
The basis for the analysis of the clinical study was intention to treat. The primary health outcomes used in the effectiveness analysis were microbiologically documented infections with or without bacteremia, clinically documented infections, fever of unknown origin (FUO), and response rate. The response was defined as a success if fever and clinical signs of infection resolved and the infecting organisms were eradicated without change of the antibacterial therapy. Adverse effects were also reported. The authors stated that the groups were similar in terms of their demographics and clinical characteristics at baseline, and that they were also well balanced for the stratification of underlying diseases.

**Effectiveness results**
There were 10 (35%) microbiologically documented infections in the CEF/NET group, 10 (34.5%) in the CEFT/AMI group, and 6 (20%) in the MER group;

there was 1 (3.6%) clinically documented infection in the CEF/NET group, 4 (13.8%) in the CEFT/AMI group, and 3 (10%) in the MER group;

there were 17 (60.7%) FUO cases in the CEF/NET group, 15 (51.7%) in the CEFT/AMI group, and 21 (70%) in the MER group;

the success rate was 22 (78.5%) in the CEF/NET group, 23 (79.3%) in the CEFT/AMI group, and 22 (73.3%) in the MER group.

None of the differences in any of the outcome measures achieved statistical significance. Adverse effects (vomiting) were only observed in three patients in the MER group.

**Clinical conclusions**
The effectiveness analysis showed that the three therapies were similar in terms of all outcome measures used in the study.

**Measure of benefits used in the economic analysis**
The effectiveness study showed that the three therapies were similarly effective. Thus, it appears that a cost-minimisation analysis was conducted.
Direct costs
Discounting was irrelevant since the costs were incurred over a short time period. The daily drug use was the unique cost item used in the economic evaluation, but the unit drug acquisition costs were not reported separately from the quantities of resources. The cost/resource boundary adopted was not reported. Resource use was likely to have been estimated alongside the clinical trial, although it was not explicitly stated. The source of the cost data was not reported and no price year was given.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not included in the analysis.

Currency
US dollars ($).

Sensitivity analysis
No sensitivity analyses were performed.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The total daily drug costs ($ per 30 kg patient per day) were $53.8 in the CEF/NET group, $46.2 in the CEFT/AMI group, and $121.4 in the MER group.

Synthesis of costs and benefits
Not relevant as a cost-minimisation analysis was conducted.

Authors’ conclusions
The ceftazidime plus amikacin (CEFT/AMI), and meropenem alone (MER) therapies produced similar success rate and comparable outcome measures for febrile neutropenic children with malignancy. However, monotherapy MER was far more expensive than CEF/NET and CEFT/AMI.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators was clear. The three therapies represented the most innovative interventions for the treatment of infections in febrile neutropenic children with malignancy. You should decide whether they are widely used in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness used a randomised controlled trial, which seems to have been appropriate given the study question. However, limited details of the study design were reported. The study groups were shown to be comparable at baseline and the analysis of the clinical study was conducted on an intention to treat basis. The authors reported the number of centres in which the study took place, but not the method of sample selection, the length of follow-up and
the randomisation process. The major threat to the internal validity of the analysis was the small sample size and the fact that power calculations were not performed to determine the appropriate size of the sample. Only limited details on the assessment method were reported. The study sample appears to have been representative of the study population.

Validity of estimate of measure of benefit
No summary benefit measure was used in the economic analysis and no statistically significant differences were found in any of the clinical outcomes used in the effectiveness study. The analysis was therefore categorised as a cost-minimisation study.

Validity of estimate of costs
The perspective adopted in the study was not stated, and only the drug costs were included in the economic evaluation. The authors did not explain why other categories of costs were excluded. Again, overall, only limited details were provided. The costs were treated deterministically and no sensitivity analyses were performed. The unit costs and the quantities of resources used were not reported separately. In addition, the price year was not given. The costing was presumably conducted on the same patient sample as that used in the effectiveness study, although it was not explicitly stated.

Other issues
The authors made some comparisons of their effectiveness findings with those from other studies. However, they did not address the issue of the generalisability of the study results to other settings. The external validity of the analysis was fairly low, as no sensitivity analyses were performed.

Implications of the study
The main implication of the study is that the use of MER monotherapy for febrile neutropenic children with malignancy is as effective as combined therapies such as CEF/NET and CEFT/AMI. Its use, however, should be limited in developing countries with scarce resources, such as Turkey. The authors stated that a further analysis was planned to assess the impact of CEFT/AMI as first-line therapy for patients with an absolute neutrophil count of 500 to 1,000/mm3. For patients with severe neutropenia (absolute neutrophil count of less than 500/mm3), the comparison will be between carbapenem plus aminoglycoside and CEFT/AMI, to prevent emerging resistance to monotherapy.

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