Empiric carbapenem monotherapy in pediatric bone marrow transplant recipients

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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 imipenem/cilastatin or meropenem in pre-engrafted paediatric bone marrow (BMT) patients was investigated. Imipenem/cilastatin (20 mg/kg) was infused over 1 to 2 hours, every 6 hours, while meropenem (20 mg/kg) was infused over 30 minutes, every 8 hours.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised children who had undergone BMT and were currently in the pre-engraftment stage of recovery.

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

Dates to which data relate
Some effectiveness and resource data were gathered after July 1998 (prospective analysis). The remaining effectiveness and resource data were gathered during the prior 2 years (retrospective analysis). The price year was not stated.

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

Link between effectiveness and cost data
The costing (both prospective and retrospective) was undertaken on the same patient sample as that used in the effectiveness analysis.

Study sample
No power calculations were reported. The method of sample selection was not reported for the prospective study of meropenem, whereas in the retrospective analysis of imipenem/cilastatin, the patients were selected from an institutional database of past BMT patients. Thirty-two patients were included in the study, 16 in each group. The patients in the imipenem/cilastatin group were matched on patient characteristics. The patients had a mean age of 9.7 (+/- 1.4) years in the meropenem group and 9.6 (+/- 1.4) years in the imipenem/cilastatin group, and the body weights were 34.5 (+/- 5) kg and 33.4 (+/- 4) kg, respectively.
Study design
This was a single-centre matched cohort design with both prospective and retrospective analyses being undertaken. The person selecting patients for the retrospective group was blinded to information on the patient's clinical course and outcome, but not to type of BMT, emetogenic potential of the preparative regimen, primary disease status, age, weight and gender. The mean follow-up period was 20 days. The loss to follow-up for the prospective group was not reported. The retrospective group of patients was studied in terms of their treatment over 2 years prior to the study.

Analysis of effectiveness
The primary outcomes used in the analysis related to the effectiveness and tolerability of the antibiotic regimens. The effectiveness of antibiotic regimens was assessed by documenting possible bacterial infection (positive bacterial cultures, fever >/- 38.5 degrees C, or other clinical signs requiring additional concurrent antibiotics). The tolerability was assessed by the incidence of vomiting episodes. The secondary health outcomes were the use of serotonin antagonists and the duration of concurrent total parenteral nutrition (TPN). All 32 patients were included in the analysis. The groups were deemed comparable in age, weight, gender, primary disease and type of BMT.

Effectiveness results
The only statistically significant difference between the groups on any health outcome was in the incidence of vomiting.

The mean number of vomiting episodes per course of therapy was 30.38 (+/- 5.08) for the imipenem/cilastatin patients and 9.75 (+/- 3.53) for the meropenem patients, (p=0.0021).

There were no documented positive bacterial cultures for patients in either group.

The duration of empiric antibiotic courses was similar for the groups.

There was a trend toward reduced duration of TPN support in meropenem-treated patients (13.9 +/- 2.4 days versus 19.2 +/- 2.9 days; p=0.1662).

Clinical conclusions
The authors concluded that meropenem-treated patients experienced significantly fewer vomiting episodes than did children who received imipenem/cilastatin. There were no statistically significant differences in the other therapeutic outcomes.

Measure of benefits used in the economic analysis
No summary measure of benefit was used in the economic evaluation. The authors demonstrated effectiveness equivalence of the treatment regimens and only analysed costs in the economic analysis.

Direct costs
The hospital costs included the costs of drug acquisition and the cost of TPN. The resource use data for the imipenem/cilastatin patients were obtained from an institutional database, whereas those for the meropenem group were derived from actual data. The costs and the resource use were presented separately for both treatment regimens. Although no price year was reported, 1998 prices seem to have been used. It appears that the costs have been taken from a single institutional setting. Discounting was not carried out as the costs were incurred during less than 2 years.

Statistical analysis of costs
Mean values were given for both the resource use and cost data.
Indirect Costs
In line with the perspective chosen, the indirect costs were not included.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analysis was not conducted.

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

Cost results
The average total costs for the two treatment regimens showed a statistically significant difference in favour of meropenem as a less expensive drug.

The daily cost of the antibiotic was $125.82 (+/- 11.31) for imipenem/cilastatin and $78.35 (+/- 7.19) for meropenem, (p=0.0013).

The daily cost of antibiotic plus antiemetics was $167.34 (+/- 19.83) with imipenem/cilastatin and $94.28 (+/- 11.88) with meropenem, (p=0.0036).

The total cost of antibiotic plus antiemetics was $3,077.11 (+/- 482.41) with imipenem/cilastatin and $1,863.40 (+/- 227.28) with meropenem, (p=0.0302).

The total cost of antibiotic plus antiemetics plus TPN was $4,995.86 (+/- 740.06) with imipenem/cilastatin and $3,213.59 (+/- 398.10) with meropenem, (p=0.0423).

The inclusion of antiemetics reflected the costs of adverse effects of the treatments.

Synthesis of costs and benefits
The costs and benefits were not combined.

Authors' conclusions
Whilst there was no difference in effectiveness between the two drug treatments under investigation, the tolerance in meropenem-treated patients (in terms of reduced incidence of vomiting) was significantly higher than in patients treated with imipenem/cilastatin. Meropenem was also significantly less expensive (with a reduction in adverse effects and associated therapies considered in the analysis) than the use of imipenem/cilastatin in paediatric bone marrow transplant (BMT) patients.

CRD COMMENTARY - Selection of comparators
The comparators were chosen on the basis that imipenem/cilastatin represented the established treatment, while meropenem had become a subsequent drug of choice on the basis of its associated lower cost, increased patient tolerance and convenience of administration. You should decide if these represent widely used technologies in your own setting.

Validity of estimate of measure of effectiveness
The analysis was based on a matched cohort design, using both prospective and retrospective data. The authors claimed that a prospective comparative trial was not feasible. The research design was not ideal for the study question, as the comparability of the groups at baseline could not be determined and confounding factors (potentially impacting on the results) could not be taken into consideration. Thus, the internal validity of the study was considered to be poor. The lack of power calculation and the subsequent small sample size meant that it was unclear whether the study sample was sufficiently large to prove the statistically significant difference in health outcomes.

**Validity of estimate of measure of benefit**
No summary measure of benefit was derived. Therapeutic equivalence of the treatments was demonstrated, although the strength of the results is potentially hindered by the small sample size (as mentioned already). A cost-minimisation analysis was subsequently conducted.

**Validity of estimate of costs**
It appears that the categories of direct costs included were relevant to the hospital perspective. The authors referred to other indirect costs (relating to adverse effects), but these were classed as direct costs for the purposes of this abstract. The costs and the quantities were reported separately, thus enhancing the reproducibility of the study in other settings. The resource use and cost data were taken from the authors’ setting. The lack of any statistical or sensitivity analyses on both parameters potentially limits the interpretation of the findings. The failure to report the price year also limits any future reflation exercise.

**Other issues**
The authors compared their clinical results with those from other studies. However, they did not compare the economic results with other studies, so it is not possible to say whether these were comparable with other published results. The authors did not directly address the issue of the generalisability of the effectiveness results to other settings, although they acknowledged that the costs might vary across different institutions. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis. Indeed, (in their assessment of study limitations), the authors emphasised that this is a particularly complex patient population and that multiple clinical issues can potentially affect treatment outcomes. This is an issue for consideration when adopting any recommendations.

**Implications of the study**
The authors concluded that (in their institution) meropenem is verified as the recommended treatment option in febrile, neutropenic, paediatric BMT patients. However, concerns raised about the validity of this economic evaluation should be borne in mind when considering this recommendation.

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