Monotherapy with piperacillin/tazobactam versus cefepime as empirical therapy for febrile neutropenia in pediatric cancer patients: a randomized comparison

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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 study examined two antibiotic treatments for febrile neutropenia in paediatric patients with cancer. One treatment was piperacillin-tazobactam (PIP-TAZO), 80 mg/kg PIP and 10 mg/kg TAZO every 6 hours (maximum 4.5 g/dose). The other treatment was cefepime, 50 mg/kg every 8 hours (maximum 2 g/dose). Treatment could be stopped only after fever had subsided and a neutrophil count of at least 500 cells/mm3 had been reached, or after eradication of microbiological or clinical infection. If patients still had fever after 4 full days of empirical therapy, the addition of teicoplanin (10 mg/kg per dose, 12 hourly first 3 doses, continued with the same dose 24 hourly) was allowed in the absence of positive cultures, while the choice of the antibiotic was based on in vitro sensitivity for documented infections.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised febrile neutropenic children and adolescents (aged 18 years or younger) who had been treated for primary, refractory, or relapsed solid tumours and haematological malignancies. Fever was defined as a single axillary temperature 38.5 degrees C or 38.0 degrees C for more than 1 hour. Neutropenia was defined as an absolute neutrophil count of less than 500 cells/mm3, or a count of less than 1,000 cells/mm3 with a predicted decrease to less than 500 cells/mm3 within 24 to 48 hours. The exclusion criteria included fever attributed to malignancy or transfused blood products or other medication, and the administration of any systemic antibiotic within 3 days prior to study drug administration. Further exclusion criteria were a history of hypersensitivity reaction to cephalosporin or penicillins, and hepatic or renal insufficiency.

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 from March 2004 to March 2005. The price year was not stated.

Source of effectiveness data
The effectiveness evidence was 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**
A sample of 58 consecutive episodes of fever and neutropenia was documented in 28 eligible children during the study period. Patients could be included more than once if they had a distinct episode and antibiotic treatment had been completed 2 weeks earlier. However, 8 episodes were ineligible because of an inclusion criteria violation or fever related to malignancy. Therefore, the final study sample comprised 50 episodes (25 in each group) in 27 patients (11 boys and 16 girls). The mean number of episodes per patient was 1.8 (+/- 1.0). The median age was 8.4 (+/- 5.2) years (range: 0.7 to 18). Power calculations were not reported.

**Study design**
This was a prospective, randomised clinical trial that was carried out in a single centre, the Pediatric Oncology and Hematology Divisions of the Kocaeli University in Izmit-Kocaeli. The authors stated that randomisation was consecutive. The patients were followed until hospital discharge. No patient was lost to the follow-up assessment. Blinding was not performed.

**Analysis of effectiveness**
Only patients with evaluable data were included in the analysis. The primary outcome measures were:

- the rate of success without treatment modification,
- the rate of persistent fever after 72 hours,
- treatment modification day,
- the total number of modifications,
- the median duration of fever,
- the mean duration of treatment,
- the mean duration of neutropenia, and
- the frequency of adverse events.

Treatment modification was defined as all changes in the empirical antimicrobial therapy after the first 96 hours. Success without modification was defined as disappearance of fever, clinical improvement, eradication of any of the infecting organisms, and maintenance of response for at least 7 days after discontinuation of treatment. The study groups were comparable at baseline in terms of their demographic and clinical characteristics (e.g. age, gender, body weight, microbiological factors, bacteraemia, and the focus of infection). A multivariate analysis was carried out to identify the relationship of the following parameters with response to therapy (duration of fever and hospitalisation): disease status, underlying cancer, duration of neutropenia, severity of neutropenia, presence of bacteraemia, and presence of therapy modification.

**Effectiveness results**
The rate of success without modification was 56% in the PIP-TAZO group and 48% in the cefepime group.

The rate of persistent fever was 48% in the PIP-TAZO group and 40% in the cefepime group.

The modification day was 4.8 (+/- 0.8) (range: 4 to 7) in the PIP-TAZO group and 5.3 (+/- 1.3) (range: 4 to 10) in the cefepime group.
The total number of modifications was 36% in both groups.

The median duration of fever was 3 days (range: 1 to 20) in the PIP-TAZO group and 2 days (range: 2 to 28) in the cefepime group.

The mean duration of treatment was 10.8 (+/- 4.9) days (range: 5 to 25) in the PIP-TAZO group and 11.8 (+/- 7.7) days (range: 4 to 40) in the cefepime group.

The mean duration of neutropenia was 7.5 (+/- 4.0) days (range: 5 to 25) in the PIP-TAZO group and 8.1 (+/- 4.5) days (range: 3 to 24) in the cefepime group.

No infection-related mortality was observed. Adverse events were not severe and were comparable between the groups.

All outcome measures were comparable between the groups and none of the differences reached statistical significance.

The multivariate analysis showed that the most important parameter determining the duration of fever and hospitalisation was duration of neutropenia, (p<0.001). Other factors of importance were severity of neutropenia, (p=0.026), presence of bacteraemia, (p=0.003), and presence of modification, (p=0.002).

**Clinical conclusions**
The effectiveness analysis showed that the two treatments were equally effective and safe.

**Measure of benefits used in the economic analysis**
No summary benefit measure was used in the economic analysis since the two treatments were equally effective. A cost-minimisation analysis was therefore carried out.

**Direct costs**
The perspective of the study was not explicitly stated. The analysis considered the costs of antimicrobial therapy, hospitalisation and supportive care (haematopoietic growth factors and transfusion of blood products). The unit costs were not presented separately from the resource quantities. The estimation of resource consumption was based on the sample of patients included in the clinical trial and took place from March 2004 to March 2005. Storage duration of diluted blood products (for transfusion) was also calculated. The sources of the costs were not explicitly stated. Discounting was not relevant since the costs per patient were incurred during a short timeframe. The price year was not reported.

**Statistical analysis of costs**
Statistical analyses were performed to test the statistical significance of cost-differences between the groups. As in the analysis of effectiveness, a multivariate analysis was carried out to identify the relation of the following parameters with cost of therapy: disease status, underlying cancer, duration of neutropenia, severity of neutropenia, presence of bacteraemia, and presence of therapy modification.

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

**Currency**
US dollars ($).

**Sensitivity analysis**
Sensitivity analyses were not carried out.
Estimated benefits used in the economic analysis  
See the 'Effectiveness Results' section.

Cost results  
The total costs per episode were $1,266 in the PIP-TAZO group and $1,235 in the cefepime group, (p=0.742). Differences in the individual cost categories were not statistically significant.  
The statistical analysis revealed that the duration of neutropenia and presence of modification were the most important factors determining the cost of treatment.

Synthesis of costs and benefits  
A synthesis of the costs and benefits was not relevant as a cost-minimisation analysis was carried out.

Authors' conclusions  
Piperacillin-tazobactam (PIP-TAZO) monotherapy was as effective, safe and costly as cefepime monotherapy, which had already been proven to be effective for febrile neutropenic episodes in cancer patients.

CRD COMMENTARY - Selection of comparators  
The authors justified the choice of the comparators, which were accurately described. Dosages and drug switches were reported. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness  
The effectiveness evidence was obtained from a clinical trial, which was appropriate for the study question. The use of a randomised design should have reduced the impact of selection bias. The method of randomisation was not described, but extensive information on the approach used to select the sample of patients was reported. Further, inclusion and/or exclusion criteria were clearly stated. The study groups were well balanced at baseline, which strengthens the robustness of the comparison. However, the main limitation of the study was the small sample size. Power calculations were not performed and no justification for the size of the sample was provided. Moreover, the trial was open-label, thus assessment bias might have affected the results of the study. The patients were enrolled at a single institution, which might reduce the representativeness of the patient population. The length of follow-up was appropriate although short. These issues might limit the internal validity of the analysis.

Validity of estimate of measure of benefit  
No summary benefit measure was used because a cost-minimisation analysis was conducted. Please refer to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

Validity of estimate of costs  
The perspective of the study was unclear, although it appears to have been that of the authors' institution. The unit costs and the quantities of resources used were not presented, which will limit the possibility of replicating the study in other settings. The sources of the costs were not reported. The cost estimates were specific to the study setting. The impact of using alternative cost estimates was not investigated. Appropriate statistical tests were carried out to assess the significance of the cost comparison, and to determine the factors with the greatest impact on the total costs. The price year was not reported, which will make reflation exercises in other time periods difficult.

Other issues  
The authors reported the results from other studies assessing the effectiveness of PIP-TAZO. The current findings
appear to corroborate those observed in other series of patients. However, none of these studies compared PIP-TAZO with cefepime, and the authors stated that this was the first study to make this comparison in children. The issue of the generalisability of the study results to other settings was not addressed and sensitivity analyses were not carried out. Therefore, the external validity of the analysis was low. The study referred to paediatric cancer patients with an episode of febrile neutropenia and this was reflected in the authors’ conclusions.

Implications of the study
The study results suggest that PIP-TAZO may represent a good alternative to cefepime for the treatment of febrile neutropenia in paediatric cancer patients. However, the limitations of the analysis should be taken into consideration.

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Bibliographic details
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Other publications of related interest


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