Single-daily ceftriaxone plus amikacin versus thrice-daily ceftazidime plus amikacin as empirical treatment of febrile neutropenia in children with cancer

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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 health interventions examined in the study were two empirical antibiotic therapies for the treatment of fever and neutropenia in children with cancer: thrice-daily ceftazidime (33 mg/kg/dose, maximum 1g/dose) and amikacin (5 mg/kg/dose) (CAZ-AMK) versus once-daily ceftriaxone (80 mg/kg/dose, maximum 2 g, once daily) in combination with amikacin (15 mg/kg/dose, maximum 250 mg, once daily) (CRO-AMK). Ceftazidime and amikacin were administered as slow boluses while ceftriaxone was infused over 30 minutes.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised febrile, neutropenic children aged up to 14 years suffering from cancer or aplastic anaemia. Fever was defined as an oral temperature 38 degrees C or higher sustained for more than 2 hours or a single reading of 38.5 degrees C or higher. Neutropenia was defined as an absolute peripheral blood neutrophil count of less than 1 x 10^9/L. The authors also reported some exclusion criteria: treatment with more than 1 dose of another antibiotic for presumed infection within 48 hours prior to enrolment in the study or treatment with study antibiotics in the previous 14 days, concomitant amphotericin B therapy or colony-stimulating factor use. The use of cotrimoxazole for Pneumocystis carinii prophylaxis was not considered as an exclusion criterion.

Setting
The setting was a hospital oncology unit. The economic study was carried out in Kuala Lumpur, Malaysia.

Dates to which data relate
Data on effectiveness and resource use were gathered from 1 October 1997 to 31 December 1998. No price year was reported.

Source of effectiveness data
A single study was used as the source of effectiveness evidence.

Link between effectiveness and cost data
The costing was carried out prospectively on the same patient sample as that used in the effectiveness analysis.
Study sample
Power calculations were not performed. A sample of 191 consecutive patient-episodes was enrolled in the study, but 15 cases were excluded, mainly due to protocol violations. As a result, a final sample of 176 evaluable cases was included in the analysis: 90 cases (mean age: 5.90 years; 55 boys) in the CRO-AMK group and 86 cases (mean age: 6.23 years; 55 boys) in the CAZ-AMK group.

Study design
This was an open, randomised, controlled trial, carried out in a single centre (the Department of Paediatrics of the University of Malaya Medical Centre in Kuala Lumpur, Malaysia). Patients were allocated to study groups by drawing consecutive lots from a sealed container. Patients could be entered into the study more than once during successive neutropenic episodes, but their subsequent assignments were independently randomised and it was assumed that data from different neutropenic episodes in the same patient were observations of independent variables. No stratification by age or diagnosis was performed. Patients were evaluated daily. The maximum length of follow-up was 14 days (for bacteraemic patients). No loss to follow-up was reported.

Analysis of effectiveness
All patients included in the initial study were accounted for in the effectiveness analysis, implying intention to treat. The primary health outcomes used in the analysis were the number of positive blood cultures, the success rate (resolution of fever and any clinical signs of infection and eradication of isolated bacteria without change of the all coated antibacterial therapy), time to defervescence, infection-related deaths and incidence of adverse effects (nephrotoxicity, ototoxicity, hepatotoxicity, and hypokalaemia). Study groups were shown to be comparable at baseline in terms of demographics and clinical conditions.

Effectiveness results
There were 50 positive blood cultures: 12 were Gram-positive bacteria, 33 were Gram-negative bacteria and 5 were fungi.

The overall success rate was 55.5% in the CRO-AMK group and 51.2% in the CAZ-AMK group, (p=0.56).

Median time to defervescence was 4.2 days in the CRO-AMK group and 4.3 days in the CAZ-AMK group, (p=0.83).

Response rate in 45 bacteraemic patients was 40% in the CRO-AMK group and 24% in the CAZ-AMK group, (p=0.25).

There were 5 (5.5%) infection-related deaths in the CRO-AMK group and 4 (4.6%) infection-related deaths in the CAZ-AMK group.

The incidence of adverse events was low in both study groups.

Clinical conclusions
The effectiveness analysis showed that there was no statistically significant difference across the two treatment groups.

Measure of benefits used in the economic analysis
There was no summary measure of benefit: this study was a cost-consequences analysis.

Direct costs
Discounting was not relevant as costs were incurred over a period of less than two years. Unit costs and quantities of resources were reported separately only for hospital stay. The health service costs included in the analysis were drug acquisition costs and delivery costs (pharmacy equipment, drug administration equipment, nursing time and laboratory
The cost/resource boundary adopted was that of the hospital. The source of cost data for drug administration was a previously published study. All unit costs were based on hospital charges. The estimation of quantities of resources was based on actual data derived from the trial. No price year was reported.

**Statistical analysis of costs**
No statistical analysis of costs was performed.

**Indirect Costs**
Indirect costs were not included in the analysis.

**Currency**
Malaysian ringgit (RM). Costs were also reported in US dollars ($), but the exchange rate and date was not reported.

**Sensitivity analysis**
Sensitivity analyses were not conducted.

**Estimated benefits used in the economic analysis**
Please refer to the effectiveness results reported earlier.

**Cost results**
The total daily cost was RM 197.38 ($52) in the CRO-AMK group and RM 239.63 ($63) in the CAZ-AMK group. Total treatment costs were $511.16 in the CRO-AMK group and $635.67 in the CAZ-AMK group.

**Synthesis of costs and benefits**
This was not relevant because a cost-consequences analysis was conducted.

**Authors’ conclusions**
The authors concluded that the single-day therapy with ceftriaxone-amikacin for the treatment of febrile neutropenia in children with cancer was as effective as the standard three-day intervention based on ceftazidime-amikacin. It was also associated with lower overall treatment costs.

**CRD COMMENTARY - Selection of comparators**
The authors justified the choice of the comparators: thrice-daily ceftazidime and amikacin represented the standard care for febrile neutropenia in children with cancer at the study institution, while ceftriaxone in combination with amikacin represented a recently available therapy. You, as a user of this database, should decide whether they represent widely used treatments in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness estimates were based on a randomised controlled trial, which appears to have been appropriate for the study question. The method of randomisation was reported and study groups were comparable at baseline. All patients were accounted for in the effectiveness analysis. The authors allowed patients to re-enter the study when successive neutropenic episodes occurred, but their subsequent assignments were independently randomised. However, power calculations were not performed and the authors acknowledged that the sample size may not have been large enough to detect statistically significant differences between the study groups, which could be an important flaw given the general lack of statistical significance.
Validity of estimate of measure of benefit
No summary benefit measure was used in the economic analysis as health outcomes were similar in the two study groups. Thus a cost-consequences analysis was performed. Please refer to the above paragraph for comments.

Validity of estimate of costs
The analysis of costs was carried out from the perspective of the hospital. It appears that all relevant categories of costs were included in the analysis. However, unit costs and quantities of resources were reported separately only for hospital stays, limiting transparency and generalisability, and no statistical analysis of costs or quantities was performed. Estimated costs were based on charges, which may not reflect the true costs of the interventions, again, reducing generalisability. A previously published study was used to derive the cost estimates, which were quite specific to the study setting. Conversions into US dollars were reported, but the exchange rate was not provided. No price year was given, thus making reflation exercises to other settings difficult. All these factors reduce generalisability.

Other issues
The authors made some comparisons of their findings with those from other studies. The issue of the generalisability of the study results to other settings was not addressed and sensitivity analyses were not performed, thus limiting the external validity of the analysis. A sample of children with cancer and suffering from febrile neutropenia was selected and this was reflected in the conclusions of the study. The authors noted that the sample size might have been inadequate for the objective of the effectiveness analysis.

Implications of the study
The authors suggested that the single-daily regimen for the treatment of febrile neutropenia in children with cancer should be recommended especially in developing countries with limited health resources, due to the lower costs of the intervention in comparison with three-day therapy. The authors also stated that “this empirical regime should be used with caution during outbreaks of ESBL-producing organisms or in centres with a high rate of ESBL-producing isolates”. These recommendations should be viewed in the light of the caveats discussed above.

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MeSH
Adolescent; Amikacin /administration & dosage /adverse effects /economics; Anti-Bacterial Agents /administration & dosage /adverse effects /economics; Bacteremia /drug therapy /etiology; Ceftazidime /administration & dosage /adverse effects /economics; Ceftriaxone /administration & dosage /adverse effects /economics; Child; Child, Preschool; Cost-Benefit Analysis; Drug Therapy, Combination; Female; Humans; Logistic Models; Male; Multivariate Analysis; Neoplasms /complications; Neutropenia /drug therapy /etiology; Prospective Studies; Statistics, Nonparametric

AccessionNumber