Pharmacoeconomic analysis of empirical therapy with ceftazidime alone or combination antibiotics for febrile neutropenia in cancer patients
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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
A single-agent broad spectrum antibacterial (ceftazidime) compared with two combination antibiotic regimens (tobramycin plus piperacillin with cefazolin (CAP), and tobramycin plus piperacillin without cefazolin (AP)) in cancer patients with febrile neutropenia.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Cancer patients with fever (>38C) and neutropenia (<1 x 10⁹ neutrophils

Setting
Hospitals.

Dates to which data relate
Effectiveness data was taken from studies published between 1966 to 1993. 1993 prices were used.

Source of effectiveness data
Effectiveness data were based on a synthesis of previously completed studies.

Modelling
A decision-based analytical model of cost-effectiveness analysis was used.

Outcomes assessed in the review
The clinical outcome of therapy was evaluated between 3 and 5 days after starting treatment. Outcome was classified as either response or failure: clinical response was defined as recovery from fever associated with neutropenia after 3 to 5 days of unmodified empirical treatment, whilst failure was measured in 2 ways:

1) death or inability to eradicate the microorganism after 3 to 5 days of unmodified empirical therapy; or

2) persistent fever necessitating modification of the empirical regimen after 3 to 5 days, regardless of eventual outcome.
Study designs and other criteria for inclusion in the review
Only human studies comparing any of the 3 regimens with a randomised comparative design were included in the review. Studies reported only as correspondence, reviews or summary articles were excluded. Studies primarily involving children were excluded.

Sources searched to identify primary studies
MEDLINE and CancerLit were searched between 1966 and 1993.

Criteria used to ensure the validity of primary studies
Randomised comparative designs were selected.

Methods used to judge relevance and validity, and for extracting data
Agreement by 2 evaluators who were blinded to author, title and journal. Disagreements were resolved through discussion with the principal investigator until a consensus was reached. Individual data was extracted from the primary studies.

Number of primary studies included
Seven studies were included in the review.

Methods of combining primary studies
Meta-analysis.

Investigation of differences between primary studies
The authors investigated the differences between the primary studies, such as that the studies included data from patients with both solid organ tumours and leukemia, and that there may have been differences in the preparation time of the antibiotics. Sensitivity analysis was used to try to overcome some of the potential biases of the former problem and the difference in the preparation cost between piperacillin and tobramycin was expected to balance the overall cost of preparation.

Results of the review
The pooled data resulted in a response rate of 63.5% (+/- 9.5%) for ceftazidime monotherapy. The response rate for CAP was 75.3% (+/- 15.1%) and the response rate for AP was 58.8% (+/- 8.9%). The summary odds ratio for ceftazidime relative to CAP and AP was 1.03 (95% CI: 0.61 to 1.75); the odds ratio for CAP relative to ceftazidime and AP was 1.58 (95% CI: 0.94 to 2.66); the odds ratio for AP relative to ceftazidime and CAP was 1.22 (95% CI: 0.88 to 1.68). The most important adverse drug reaction was nephrotoxicity and its incidence was reported to be: ceftazidime, nil, CAP, 6.6%, and AP, 5.8%.

Measure of benefits used in the economic analysis
The measure of benefits was successfully treated patients; response to or failure of treatment as defined above. A decision-tree analysis was used. All costs and benefits associated with therapy were calculated from a hospital perspective. The outcome of therapy at day 4 was used in the economic analysis.

Direct costs
Discounting was not applied in this study because of the short time periods involved. Health service costs were included in the analysis and a decision-tree model was used to estimate the expected quantity/costs of the alternatives. The costs
of dose preparation and hospital administration (including personnel and supplies) were obtained from pharmacy
ordering catalogues and pharmacy and nursing workload measurement statistics. The cost of daily hospitalisation was as
reported by the Ontario Hospital Association. Laboratory test costs were obtained from local departments of
biochemistry and microbiology. Patient care costs were obtained from hospital pricing statistics. Adverse drug reaction
management costs were calculated according to standard hospital protocols for treating routine adverse effects. Four
days' therapy was costed in all cases and, if a successful response resulted, a further 7 days of the same therapy was
continued.

Failure at 4 days was followed by a change of treatment.

Case 1, vancomycin was added and therapy continued for 10 more days;

Case 2, ceftazidime was added to AP, tobramycin added to ceftazidime monotherapy and treatment continued for 10
more days;

Case 3, therapy was continued for 7 days then the patient was reassessed for possible fungal infection.

Within each treatment group the total cost for the treatment option was the total cost of treatment success multiplied by
the probability response plus the total cost of treatment failure multiplied by 1-the probability of response.

Currency
Canadian dollars (Can$).

Sensitivity analysis
A sensitivity analysis was conducted to test the robustness of the findings. The parameters tested were:

(1) the response rates for ceftazidime, CAP and AP in febrile neutropenia in patients with solid organ tumours and
haematological malignancies;

(2) a reduction in the dosage of ceftazidime;

(3) using the early response rates to unmodified therapy reported by the first study that compared CAP with
ceftazidime;

(4) the response rates and cost-effectiveness ratios with/without one particular study which had a high drop-out rate.

Estimated benefits used in the economic analysis
The pooled data resulted in a response rate of 63.5% (+/- 9.5%) for ceftazidime monotherapy. Response rates for CAP
and AP were 75.3% (+/- 15.1%) and 58.8% (+/- 8.9%) respectively.

Cost results
In the case of ceftazidime the total cost of a successful treatment was Can$4,939.73, the cost for a failure under case 1
was Can$3,953.94, under case 2 was Can$3,754.29 and under case 3, was Can$2,839.37. Using CAP the total cost of
treatment response was Can$6,308.96, cost of treatment failure under case 1 was Can$2,777.16, under case 2 was
Can$2,590.77 and under case 3 was Can$2,069.47. Using AP the total cost of treatment response was Can$4,711.92,
cost of treatment failure under case 1 was Can$4,567.73, under case 2 was Can$4,308.42 and under case 3 was
Can$3,301.55.

Synthesis of costs and benefits
In case 1, CAP therapy was approximately 16% more cost-effective than ceftazidime and 31% more cost-effective than
AP. In case 2, CAP was 16% more cost-effective than ceftazidime and 30% more cost-effective than AP. In case 3,
CAP was approximately 10% more cost-effective than ceftazidime and 22% more than AP. Cost effectiveness ratios were calculated by adding the cost of response to the cost of failure and dividing the result by the probability of response at day 4.

The ratios per successful outcome are as follows:

Case 1, ceftazidime Can$14,005.78, CAP Can$12,066.56 and AP Can$15,781.72;
Case 2, ceftazidime Can$13,691.37, CAP Can$11,819.03 and AP Can$15,340.71;
Case 3, ceftazidime Can$12,250.55, CAP Can$11,126.73 and AP Can$13,628.35.

Authors' conclusions
CAP was the most cost-effective therapy from a hospital perspective even though ceftazidime would have been cheapest had all treatments been equally effective.

CRD COMMENTARY - Selection of comparators
The reason for the choice of comparators is clear.

Validity of estimate of measure of benefit
The measure of benefits is likely to be internally valid and the reason why response at 4 days was chosen was explained.

Validity of estimate of costs
Costs and prices were not reported separately and greater detail of prices could have been given.

Other issues
The authors' conclusions appear to be justified but generalisability to other countries with other price structures was not addressed.

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