Randomized placebo-controlled trial of oral antibiotics in pediatric oncology patients at low-risk with fever and neutropenia

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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 oral antibiotics upon discharge for the treatment of fever and neutropenia in children with cancer. The antibiotic treatment consisted of cloxacillin syrup or capsules (75 to 100 mg/kg per day, four times daily) plus cefixime syrup (8 mg/kg per day).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised paediatric oncology patients whose neutropenia persisted at the time of discharge from hospital, and who were considered to be "low-risk". Low-risk was defined as having no fever for the last 24 hours, negative blood cultures and an absence of clinical sepsis.

Setting
The setting was a hospital. The economic study was carried out at the Hospital for Sick Children in Toronto, Canada. This hospital is described as a quaternary centre that provides primary paediatric oncology care to the local population. The economic study was also carried out in Toronto, Canada.

Dates to which data relate
The effectiveness and resource use data related to 1996 to 1998 inclusive. The price year was 1998.

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

Link between effectiveness and cost data
The costing was undertaken on the same patient sample as that used in the effectiveness study. It was unclear whether the resource use data were collected prospectively or retrospectively.

Study sample
All 225 patients admitted between 1 August 1996 and 30 April 1998 with 431 episodes of fever and neutropenia were assessed for the study. Of these, 117 episodes were eligible. The other 73% were excluded because the absolute neutrophil count (ANC) had recovered to the threshold level (26%), there was localised bacterial infection (13%), the
blood cultures were positive (10%), bone marrow disease was not in remission (9%), prolonged fever (7%),
comorbidity (6%) and for other reasons (3%). This initial sample was appropriate for the study question. Forty-four of
these 117 episodes were not enrolled, 19 due to their refusal to participate and 25 for other reasons. A total of 73
episodes occurred in the 54 patients enrolled in the study (37 episodes in the antibiotics arm, 36 in the placebo arm).

A power calculation was performed. This calculated that a sample size of 34 episodes per group was required to detect a
three-fold difference in the fever relapse rate with 80% power and a one-sided significance level of 5%.

Study design
This was a randomised, double-blind, placebo-controlled trial carried out in a single centre. Computer-generated block
randomisation was used and the patients were stratified according to a threshold ANC level. Both the patients and
doctors were blinded. All episodes were followed-up until ANC recovery, which occurred, on average, 9 days after
admission.

Analysis of effectiveness
The data were analysed on an intention to treat basis. Student t-tests and Pearson chi-squared tests were conducted.
These detected no statistically significant differences between the two treatment arms at baseline. The primary health
outcome was the recurrence of fever or newly documented bacterial infection before neutrophil recovery.

Effectiveness results
Five episodes (14%, 95% confidence interval: 2 - 25) in the antibiotic arm and two placebo episodes (6%, 95%
confidence interval: 0 - 13) were readmitted with recurrent fever while still neutropenic, (p=0.43).

Side effects, mostly gastrointestinal, tended to be more frequently reported among antibiotic episodes (31% versus
11%, p=0.095).

The compliance rates were high (84 to 94%), with no significant differences reported between the two treatment arms.

Clinical conclusions
"Oral antibiotics administered at the time of discharge did not prevent readmission to hospital."

Measure of benefits used in the economic analysis
No summary benefit measure was used. This was therefore categorised as a cost-consequences analysis.

Direct costs
The costs included in the analysis were mainly hospital costs, and related to blood transfusions, laboratory tests,
radiographic tests, inpatient days, pharmaceuticals and physician services. The quantities of these resources were
recorded for each patient for the duration of the study period, but they were not reported separately. The unit costs
were derived from hospital charges and the Ontario Schedule of Benefits (for physician services). No charge-to-cost
conversion was reported. Discounting was irrelevant because the study period covered less than one year. The resource
use data related to the period from 1996 to 1998. The costs were reported in 1998 dollars.

Statistical analysis of costs
The authors stated that a Pearson chi-squared test was used to compare the costs between the two groups. However, no
test statistics or significance levels were reported. The authors did not show that the study was powered to detect a
difference in the costs. The observed difference in the average costs was small and a sensitivity analysis was carried out.
**Indirect Costs**
The indirect costs were not included in this analysis.

**Currency**
Canadian dollars (Can$).

**Sensitivity analysis**
A one-way sensitivity analysis was carried out to assess the robustness of the cost results to changes in the unit cost of hospital days, which accounted for 44% of the overall costs. Also, with the aim of enhancing the generalisability of the results, the cost results were recalculated using a unit cost that was 50, 150 and 200% of the baseline cost.

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

**Cost results**
Using baseline unit costs, the antibiotic treatment cost an average of $1,887 per episode compared with $1,753 for the placebo treatment. Thus, the incremental cost of the antibiotic treatment was $13,409 per 100 episodes of fever and neutropenia. This figure ranged from $9,962 to $20,300 in the sensitivity analysis.

**Synthesis of costs and benefits**
Not relevant.

**Authors' conclusions**
This study showed that the use of antibiotics did not prevent readmissions, nor did it result in cost-savings. The use of oral antibiotics upon discharge should be discontinued in this population in order to prevent side effects and superinfection.

**CRD COMMENTARY - Selection of comparators**
This was a placebo-controlled trial. The use of the placebo was justified as the authors wished to test whether the use of antibiotics could be safely discontinued in this patient population.

**Validity of estimate of measure of effectiveness**
This was a randomised, double-blind placebo-controlled study, which was appropriate for the study question. As already mentioned, 44 of the 117 episodes eligible for the study were not enrolled. The enrolled patients were younger and more likely to have acute lymphoblastic leukaemia than non-enrolled patients. The authors discussed the possibility of selection bias, but concluded that it was unlikely to have affected the results because the enrolled and non-enrolled patients had similar readmission rates. Among the enrolled patients, statistical tests found the two treatment arms to be comparable at baseline. Appropriate statistical analyses were carried out on the trial data.

The authors cited, as the study's main limitation, the possibility that it was underpowered. However, they concluded that a larger study would probably have reached the same clinical conclusion, because the upper 95% confidence limit of a 13% readmission rate in the placebo group was still less than the observed rate in the antibiotics group (14%). In addition, it was comparable to published results on this population.

**Validity of estimate of measure of benefit**
No summary benefit measure was used since this was a cost-consequences study.
Validity of estimate of costs
All the relevant costs were included in the analysis. The resource use quantities were not reported separately. However, the costs were subjected to a sensitivity analysis, which may enhance the generalisability of the results. The authors stated that hospital charges were used to proxy the admission, overhead and laboratory costs. These charges are likely to be a reasonable estimate of the costs since the hospital is a non-profit agency.

Other issues
The authors made appropriate comparisons of their findings with those of three other studies. Their conclusion that placebo dominated the use of antibiotics (cheaper and at least as effective) is justified given the high-quality study design.

Implications of the study
The authors recommend further study to ascertain whether bone marrow recovery should be a factor in determining whether or not a patient is “low-risk”.

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The antibiotics and placebos were supplied by Rhone-Poulenc Rorer Canada Inc and Apotex Inc.

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