Early hospital discharge followed by outpatient management versus continued hospitalization of children with cancer, fever, and neutropenia at low risk for invasive bacterial infection


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
Early discharge followed by outpatient treatment was compared with continued hospitalisation among children with febrile neutropenia (FN) who were at low risk for invasive bacterial infection (IBI). Children with FN classified as at low risk of contracting IBI were given 24 to 36 hours of hospital treatment. This was followed by ambulatory treatment in which the patients were monitored until the episode was over. They had to return to the oncology clinic every day for visits lasting 90 to 120 minutes. The comparator treatment was for the patients to be kept in hospital throughout the episode. The antimicrobial treatment given to both groups was intravenous (IV) ceftriaxone (Acantex; Roche, Basel), 100 mg/kg/day every 24 hours, and IV teicoplanin (Targocid; Aventis Pharma, Bridgewater), 20 mg/kg per day every 12 hours for the first day followed by 10 mg/kg per day every 24 hours. After a minimum of 3 days of IV therapy, the switch to oral cefuroxime axetil (Curocef; GlaxoSmithKline Biologicals, Research Triangle Park), 50 mg/kg per day every 12 hours, was made on the basis of predefined criteria describing the course of the episode.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised children 18 years old or younger with cancer, fever and severe neutropenia, who were classified by a study physician as at low risk for IBI. The classification of low risk was made on the basis of a validated risk prediction model, details of which were given elsewhere (Santolaya et al. 2001 and 2002, see ‘Other Publications of Related Interest’ below for bibliographic details).

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

Dates to which data relate
The effectiveness and resource evidence referred to 2000 to 2003. The price year was 2003.

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

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**
The sample size was calculated on the basis that the frequency of an unfavourable outcome was the same in both groups, in this case 10%. Using this value, a maximum acceptable difference between the groups of 15%, a Type I error of 0.05 and a power of 0.90, it was decided that 69 patients were needed in both groups. A total of 390 episodes of FN occurred in 313 children. Of these, 168 episodes were initially classified as low risk for IBI. After hospitalisation for 24 to 36 hours, 7 episodes were reclassified as high risk and were excluded from the study. Of the 161 episodes definitively classified as low risk for IBI, 12 were excluded because of lack of informed consent, rural origin, lack of notification, or medical reasons. In the end, 149 low-risk febrile episodes occurring in 107 patients were randomly allocated to either the ambulatory group (n=78) or the hospital-based group (n=71). The mean age was 55 years (95% confidence interval, CI: 45 - 66) in the ambulatory group and 66 years (95% CI: 57 - 74) in the hospital-based group. There were 43% males in the ambulatory group and 49% in the hospital-based group.

**Study design**
This was a multi-centre randomised controlled trial (RCT). Children from six hospitals were randomly assigned to either ambulatory or hospital-based treatment. The method of randomisation was not reported and the study was unblinded. The patients were followed up until the fever resolved and the absolute neutrophil count reached 500/microL

**Analysis of effectiveness**
The analysis was conducted on an intention to treat basis. The primary health outcome used was the proportion of favourable outcomes (i.e. no indication of IBI was present and the child completed follow-up without requiring antimicrobial adjustments or readmission). An unfavourable outcome was defined as one or more of the following:

- haemodynamic instability not attributable to volume loss;
- axillary temperature more than 38 degrees C after day 4;
- increase in temperature for at least 24 hours after a 48-hour afebrile period;
- an ascending serum C-reactive protein (CRP) curve or a non descending curve over normal limits after day 3 persisting for at least 2 consecutive days;
- isolation of a bacterial pathogen from a significant sample on day 3; or
- death resulting from a febrile episode, attributable to infection.

The groups were shown to be comparable at baseline.

**Effectiveness results**
Seventy-four (95%) of the ambulatory group and 67 (94%) of the hospital-based group had a favourable outcome. The difference was described as not statistically significant but the p-value was not given.

There were 11 unfavourable outcomes in 8 patients (4 in each treatment group). Seven of these patients eventually recovered after their therapy was changed, but a 1-year old child (with a Stage III neuroblastoma) who had initially been allocated to the hospital-based group died.

**Clinical conclusions**
When children with FN were classified as low risk of IBI, the chance of a favourable outcome was no different whether they were treated in a hospital setting or given ambulatory treatment.
Measure of benefits used in the economic analysis
No summary measure of benefits was produced. Therefore, the authors carried out a cost-consequences analysis.

Direct costs
No discounting was carried out as the costs were incurred during less than 1 year. The quantities of the following resources used were given, but were not individually priced: hospital bed days, transitory bed days, number of medical visits, number of IV lines, litres of IV fluids, gloves, masks, syringes, haematology tests, serum biochemistry tests, microbiology tests, imaging studies, IV antibiotics, oral antibiotics and transportation costs. The costs of medical care, medical supplies, laboratory tests, antibiotics, and transport costs incurred by the family were given. The costs were estimated from actual data. For all items, apart from transport costs, the prices used were obtained from the Chilean National Health Fund and the quantities were obtained by a study nurse. The price year was 2003.

Statistical analysis of costs
The costs were compared using Student's t-test and the Mann-Whitney U-test.

Indirect Costs
No indirect costs were estimated.

Currency
US dollars ($). The 2003 official exchange rate was used.

Sensitivity analysis
No sensitivity analysis was carried out.

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

Cost results
The mean cost was $638 (95% CI: 572 - 703) for ambulatory treatment and $903 (95% CI: 781 - 1,025) for hospital-based treatment, (p=0.003).

The costs of adverse effects appear to have been taken into consideration.

Synthesis of costs and benefits
The costs and benefits were not combined as the study was a cost-consequences analysis.

Authors' conclusions
Ambulatory treatment was as effective and safe as hospital-based treatment, and also significantly cost-saving in comparison with hospital-based treatment, for children with febrile neutropenia (FN) at low risk for invasive bacterial infection (IBI).

CRD COMMENTARY - Selection of comparators
The choice of the comparator (hospital-based treatment) was justified by it having been current practice in the past in the authors' setting. You should decide if the comparator represents current practice in your own setting.
Validity of estimate of measure of effectiveness
The effectiveness data were derived from a single study. The study design, an RCT, was appropriate for the study question. The study sample included all patients attending six hospitals who met the inclusion criteria. Therefore, the study sample should have been representative of the study population as there was no sample selection. According to the power calculations performed, an appropriate sample size was used. The patient groups were shown to be comparable at analysis. Appropriate statistical analyses were performed to test for statistically significant differences between the three groups. All these facts suggested that the internal validity of the study is likely to be high. The main weaknesses of the study were the lack of methods of randomisation and blinding of the outcome assessment. There were no other sources of effectiveness data.

Validity of estimate of measure of benefit
The authors did not derive a summary measure of health benefit. The health benefits are therefore those associated with the effectiveness outcomes.

Validity of estimate of costs
From the cost perspective adopted (i.e. the health care system), all the relevant direct costs were included. No major cost components appear to have been omitted from the analysis. The inclusion of indirect costs associated with the families bringing the children to the clinic would have permitted the adoption of a societal perspective. In addition, it would have reduced the cost-advantage of ambulatory treatment. Although some quantities were reported individually, the costs were not broken down into prices and quantities and this will limit the generalisability of the authors' results. The resource use quantities were taken from a single study, while the prices were taken from the authors' setting and a published source. No other sources of resource quantities were used. A statistical analysis of the quantities was performed. The prices used were not the real economic cost to the country as they were subsidised by the government. The authors converted the costs at the 2003 exchange rate with the dollar, but they did not report the exchange rate used. Since all the costs were incurred during less than one year, they were appropriately not discounted.

Other issues
The authors made appropriate comparisons of their effectiveness results with the findings from other studies. The issue of generalisability to other settings was addressed. The authors noted that, even though costs cannot be extrapolated to other areas that have different socioeconomic realities and where prices are not necessarily subsidised as in Chile, the significant cost-savings of the ambulatory treatment strategy are probably universal. The study examined children with FN who are at low risk for IBI and this was reflected in the authors' conclusions. The authors did not present their results selectively and their conclusions reflected the scope of the analysis. The authors did not report any other limitations of their study.

Implications of the study
The authors reported "results from this study have been used to support a recent change in national recommendations for children with cancer, fever, and neutropenia". They suggested "a prerequisite before recommending implementation of an outpatient management program in different settings is to have an experienced medical team that can assure close follow-up of patients and a rapid response for those patients who are not doing well at home".

Source of funding
None stated.

Bibliographic details
Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Ambulatory Care; Antineoplastic Combined Chemotherapy Protocols /therapeutic use; Bacterial Infections /etiology /prevention & control; Child; Child, Preschool; Cost Savings; Female; Fever /chemically induced /economics /therapy; Health Care Costs /statistics & numerical data; Humans; Length of Stay; Male; Neoplasms /drug therapy; Neutropenia /chemically induced /economics /therapy; Patient Discharge; Risk Factors; Treatment Outcome

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