Oral versus initial intravenous therapy for urinary tract infections in young febrile children

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
Treatment with oral antibiotics alone was compared with intravenous (i.v.) treatment followed by oral antibiotics for young children with fever and urinary tract infection (UTI). Children receiving i.v. treatment were hospitalised and treated with cefotaxime (Claforan) at a dose of 200 mg/kg per day (in four divided doses) for 3 days or until the child had been afebrile for 28 hours, whichever was longer. The children then received a 14-day course of oral cefixime (Suprax; 8 mg/kg once daily), followed by prophylaxis with cefixime (4 mg/kg once daily) for 2 weeks until a voiding cystourethrogram (VCUG) was performed. Oral treatment alone consisted of cefixime for 14 days. The initial dose of 16 mg/kg cefixime, given in the emergency department on day 1, was followed by a daily dose of 8 mg/kg for 13 days (exceptions were reported).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised children aged 1 to 24 months with a rectal temperature of at least 38.3 degrees C, either at presentation or within 24 hours, and who were suspected of having a UTI due to the presence of pyuria and bacteriuria. The children were also required to have a positive urine culture. Several exclusion criteria were reported. For example, a negative urine culture, hypersensitivity to cephalosporins, and Gram-positive cocci on the stained urine.

Setting
The setting was a hospital. The economic study was carried out at the Children's Hospital of Pittsburgh, Columbus Children's Hospital, Fairfax Hospital for Children, and Children's Hospital in Boston, USA.

Dates to which data relate
The effectiveness and resource use data were gathered from January 1992 to July 1997. No price year was reported.

Source of effectiveness data
The effectiveness evidence came from a single study.

Link between effectiveness and cost data
The costing was performed prospectively on a sub-sample of patients involved in the effectiveness study.

Study sample
Power calculations were performed in the planning phase of the study. These showed that a sample of 128 children in each treatment group was required to detect an absolute difference of 15% in the incidence of renal scarring between the two groups, with a power of 0.80 and a statistical significance of 0.05. The initial sample of eligible children included 421 patients. Of these, 23 refused to participate and 76 were not enrolled (investigator not available, use of prior antibiotics, language barrier, primary care provider refuses or out-of-state residence). Of the remaining 322 enrolled patients, 13 had a negative urine culture, and 3 were deemed to be too sick to be involved. Thus, the final sample included in the effectiveness study comprised 306 patients, 153 in each group. The mean age in the oral group was 8.8 (± 5.9) months and 88.9% were female. The mean age in the i.v. group was 8.3 (± 5.6) months and 89.6% were female. No statistically significant differences between the two groups were found.

**Study design**
This was a randomised clinical trial that was carried out in four centres. The unit of randomisation was each clinical centre. The children were allocated to the study treatments within strata based on age (1 to 12 or 13 to 24 months) and duration of fever (less than 48 or at least 48 hours). The overall follow-up was 6 months. The loss to follow-up was 13 patients (8.5%) in the oral group and 6 patients (3.9%) in the control group.

The outcomes for inpatients were assessed on daily rounds and by contacting the parents at 48 hours after discharge and 10 days after study entry. The parents of children treated orally were contacted monthly by telephone and at 48 hours and 10 days after study entry. A follow-up outpatient visit was performed at about 14 days for all participants. All episodes of reinfection were recorded and the children were treated according to the protocol to which they were initially assigned. The assessment was also performed by renal scans. These were interpreted independently by two physician investigators who were unaware of the child's treatment assignment (single blinding).

**Analysis of effectiveness**
The basis of the analysis of the clinical study was intention to treat. The health outcomes used in the analysis were:

- the results of the 99mTc-dimercaptosuccinic acid (DMSA) renal scan and the VCUG performed at the beginning of the study and at the follow-up assessment,

- the occurrence of defervescence,

- the incidence of reinfection,

- the degree of scarring,

- bacteraemia, and

- compliance.

Logistic regression analysis was used to evaluate the impact of specific patient characteristics on the estimated outcome measures. The patients in the study groups were comparable at baseline in terms of their demographic and clinical characteristics.

**Effectiveness results**
There was no significant difference in any of the outcome measures used in the effectiveness analysis.

The incidence of renal scarring over the whole study period was 9.8% in the oral group and 7.2% in the i.v. group, (p=0.21). The authors reported there was "no significant difference between...the incidence of new renal scarring...or extent (severity) of scarring" between the treatment groups.

The results of the DMSA and VCUG were comparable between the two groups. The incidence of reinfection was also comparable.
The statistical analysis showed that only the degree of vesicoureteral reflux was significantly associated with a higher incidence of scarring, irrespective of the mode of treatment.

Further analyses suggested that children with bacteraemia tended to be younger and have a higher peripheral white blood cell count than those without bacteraemia.

Compliance was 85% (percentage of patients with detectable cefixime in urine specimens).

**Clinical conclusions**

The effectiveness analysis showed that the two treatments were equally effective in the treatment of young children with fever and UTI.

**Measure of benefits used in the economic analysis**

The two treatments were considered to show similar effectiveness. Thus, a cost-minimisation analysis was performed.

**Direct costs**

Discounting was not relevant since the costs were incurred in six months. The unit costs were not analysed separately from the quantities of resources used. The health services included in the economic evaluation were clinic visits, emergency department, laboratory, hospital room, nursing, medication, renal ultrasound, VCUG, DMSA renal scans, and miscellaneous resources. The cost/resource boundary adopted in the study appears to have been that of the hospital, although this was not explicitly stated. Resource consumption was estimated on the basis of a sub-sample of 40 patients enrolled at the Pittsburgh hospital, by selecting the fifth patient per treatment group. The unit costs were estimated from the actual charges observed at the study hospital. A cost-to-charge ratio was used to calculate the true costs of the services on the basis of the hospital's Medicare Cost Report. The price year was not given.

**Statistical analysis of costs**

The costs were treated deterministically.

**Indirect Costs**

The indirect costs were not included in the economic analysis. However, if economic productivity was used as a measure of the indirect costs, then such costs would not be relevant to the study since the participants were children.

**Currency**

US dollars ($).

**Sensitivity analysis**

Sensitivity analyses were not reported.

**Estimated benefits used in the economic analysis**

See the 'Effectiveness Results' section.

**Cost results**

The estimated total charges (costs) were $3,630 ($1,436) in the sub-sample of 20 patients in the oral group and $7,382 ($3,577) in the sub-sample of 20 patients in the i.v. group.
Synthesis of costs and benefits
The costs and benefits were not combined because this study was a cost-minimisation analysis.

Authors’ conclusions
The outpatient (oral) antibiotic treatment of young children with fever and urinary tract infection (UTI) was as effective as the inpatient (intravenous, i.v.) treatment. However, substantial cost-savings were observed with the oral treatment, as the charges and costs for inpatient therapy were "at least two fold higher than those for outpatient therapy”.

CRD COMMENTARY - Selection of comparators
The authors stated that oral therapy, parenteral (i.v. or intramuscular) therapy, or a combination of both, represented the present treatment options in the USA for children with fever and UTI. Thus, the selection of the interventions compared appears to have been appropriate. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness used a randomised trial, which was appropriate for the study question. The internal validity of the analysis was enhanced by several factors. For example, the use of preliminary power calculations, the intention to treat basis of the analysis, the baseline comparability of the study groups, the use of logistic regression analysis to evaluate the impact of several factors on the outcome results, and the explicit description of the method of randomisation. These characteristics of the design tend to minimise the likelihood that bias and confounding had any impact on the outcome measures. The external validity of the study was improved by the multi-centre setting of the clinical study. The study sample appears to have been representative of the study population.

Validity of estimate of measure of benefit
Since the two treatments were considered equally effective, the analysis was categorised as a cost-minimisation study.

Validity of estimate of costs
The perspective adopted in the study appears to have been that of the hospital. All the relevant categories of costs seem to have been included in the economic evaluation. A cost-to-charge ratio was appropriately used to evaluate the true cost of the resources used. The source of the cost data was reported. However, the costs were treated deterministically and sensitivity analyses were not performed. Thus, the cost estimates were specific to the study setting. The reproducibility of the study in other settings was limited because the price year was not mentioned and there were no specific details on the resource use and unit costs.

Other issues
The authors made several comparisons of their findings with those from other published studies and found their results were comparable. Where differences occurred in design, the authors discussed these appropriately and gave potential reasons. The issue of generalisability of the study results to other settings was not addressed and sensitivity analyses were not conducted. Thus, the external validity of the analysis was reduced. The study referred to children with fever and UTI who were selected using strict inclusion and exclusion criteria. Caution is therefore required when applying the results of the present study to all children with the same disease.

Implications of the study
The authors suggested that, as the long-term effects are studied, the outpatient treatment of young children with fever and UTI with oral cefixime should be recommended in clinical practice. They highlighted its safe and effective profile and the "substantial" reduction of health care expenditure to qualify this recommendation. Although further work was not explicitly discussed, the authors implied there was a need for studies assessing the long-term effects of oral treatment.
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Other publications of related interest

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