Sequential antimicrobial therapy: treatment of severe lower respiratory tract infections in 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
The use of sequential antimicrobial therapy (SAT) for the treatment of paediatric patients suffering from severe lower respiratory tract infections. The treatment was based on intravenous therapy followed by oral administration of antimicrobial drugs.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised all paediatric patients suffering from severe, lower respiratory tract infections.

Setting
The setting was a hospital. The study was carried out in the paediatric ward of Antrim Area Hospital, Northern Ireland.

Dates to which data relate
The effectiveness and resource use data were gathered between December 1994 and February 1996. The price year was not reported.

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

Link between effectiveness and cost data
The costing was undertaken both prospectively and retrospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations were not performed to establish the sample size. All children admitted to the paediatric ward of the Antrim Area Hospital were included in the study. Overall, the study sample comprised 89 children. No children were excluded from the analysis.

The SAT group comprised 45 children who were hospitalised between December 1995 and February 1996. The mean age was 3.3 years, and 48% were boys. Of these, 34 children were administered one agent and 11 received two agents.
The control group comprised 44 children who were hospitalised between December 1994 and February 1995. The mean age was 3.2 years, and 47.7% were boys. Of these, 23 children were given one agent, 19 received two agents, and 2 were treated with three agents. No other baseline characteristics were given, although the groups were compared statistically in terms of their body temperature, and creatinine and urea levels.

**Study design**

The study was a non-randomised controlled trial with historical controls, carried out in a single centre (Antrim Area Hospital). The intervention data were gathered between December 1995 and February 1996, whilst the control data were gathered between December 1994 and February 1995. SAT-treated children were followed for 4 to 6 weeks after their discharge from hospital. The length of follow-up was not given for the control group. The parents of the children in the SAT group were given a questionnaire on their child’s clinical progress after discharge.

**Analysis of effectiveness**

All the children included in the study were accounted for in the analysis. This implied that the analysis was performed on an intention to treat basis.

The two primary health outcomes were treatment success and treatment failure. Treatment success was defined as a major improvement or complete resolution of all signs and symptoms. Treatment failure was defined as the persistence or progression of signs and symptoms, the presence of adverse effects, active infection or death. The outcome measures were evaluated retrospectively (from hospital records) for the children in the control group, and prospectively (from the parents’ questionnaire) for the children in the SAT group. The length of hospital stay and the number of days of intravenous and oral antimicrobial therapies were also considered, but these were only used as resources in the cost analysis.

There were no statistically-significant differences between the groups with respect to age, gender, and clinical characteristics, (p=0.119 or p>0.119). However, the two groups did differ in the type of antibiotics used, although this difference was not tested statistically.

**Effectiveness results**

Both the SAT and control therapies were stated to be effective in terms of treatment success. However, no differentiation was made between "major improvement" and "complete resolution". In addition, the result for non-recurrence was only given for the SAT group.

The mean (geometric) duration of hospital stay was significantly longer in the control group (8.3 days) than in the SAT group (4 days), (p<0.001).

The mean (geometric) duration of intravenous antimicrobial therapy was greater in the control group (5.6 days) than in the SAT group (1.7 days), (p<0.001). Similarly, the mean duration of antimicrobial therapy was greater in the control group (7.9 days) than in the SAT group (4 days), (p<0.001).

The mean (geometric) duration of oral antimicrobial therapy was not statistically different between the control (2 days) and SAT (2.2 days) groups.

**Clinical conclusions**

Both of the interventions were equally effective with respect to the main outcome measure (treatment success). The secondary outcomes (duration of stay and therapy) were significantly reduced in the SAT group.

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

The main health outcome of treatment success was used in the effectiveness analysis. Since this was claimed to be equal in the two groups, the authors stated that a cost-minimisation analysis was performed.
Direct costs
Discounting was irrelevant since the duration of follow-up was 6 weeks after discharge. The quantity/cost boundary adopted was that of the hospital. The direct costs were the total antimicrobial costs, diagnostic test costs and hospital bed costs (based on the length of stay). The total antimicrobial costs were related to the drug acquisition costs and the hidden costs of consumables, staff time and waste disposal. The costs were estimated from actual prices and hospital records. The resource use data were gathered between December 1994 and February 1996. The resource quantity data were given only for the length of stay and the duration of antibiotic treatment. The price year was not reported, but prices were collected between 1995 and 1996.

Statistical analysis of costs
The differences in costs and days (treatment and hospital stay) between the study groups were statistically tested.

Indirect Costs
The indirect costs were not included.

Currency
UK pounds sterling (€).

Sensitivity analysis
No sensitivity analysis was carried out.

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

Cost results
The average antimicrobial acquisition costs and hidden costs were significantly lower in the SAT group, compared with the control group, (p<0.001). For the SAT group, the drug acquisition costs were 10.3 and the hidden costs were 6.7. The equivalent costs in the control group were 26 (drug acquisition) and 17.4 (hidden costs). The mean costs for all laboratory tests were 45 in the SAT group and 53.6 in the control group; this difference was statistically significant, (p<0.001). The average hospital bed costs were 1,105 in the SAT group and 2,366 in the control group; this difference was also statistically significant, (p<0.001). The mean potential savings per patient using the SAT protocol were 26.4 for the antimicrobial therapy, 8.6 for the laboratory tests, and 1,261 for the hospital stay. The overall savings of SAT therapy amounted to 1,296 per patient, (p<0.001).

Synthesis of costs and benefits
Not relevant.

Authors' conclusions
Sequential antimicrobial therapy (SAT) and long-term intravenous therapy were equally effective for the treatment of children suffering from severe lower respiratory tract infections. However, the SAT strategy was associated with substantial cost-savings, compared with long-term intravenous therapy.

CRD COMMENTARY - Selection of comparators
The selection of the comparator was clear; it represented institutional practice for the management of severe lower respiratory tract infections in paediatric patients. You should consider whether it represents a widely used technology in your own setting.
Validity of estimate of measure of effectiveness
The internal validity of the study may have been adversely affected by the lack of randomisation when allocating the patients to the treatment groups. Although the comparability of groups with respect to demographics and clinical conditions was shown statistically, the role of confounding variables and selection bias cannot be ruled out. Further, secondary health outcomes were reported, but these were not included in the analysis and were used only as resource use data.

Also, some confounding was not accounted for:

The length of follow-up was not given for the control group and was variable for the SAT group was variable, although this variation was not reported.

It was unclear what the final outcome was. It was deduced that all the children in the SAT group achieved complete resolution (no recurrence was reported), but the resolution statistics were not given for the control group.

The nature of the therapy was also varied in terms of the type of antibiotic used, which was not accounted for.

Finally, the claim of equal effectiveness was based only on resolution of signs and symptoms, and not time to resolution. There was evidence of differences in the length of hospital stay and the duration of antibiotic use, which contradicts the claim of equal effectiveness.

It would have been interesting if the authors had produced a summary benefit measure.

Validity of estimate of measure of benefit
Not applicable.

Validity of estimate of costs
The unit costs and quantities were, generally, not reported separately, and sensitivity analyses were not performed. Consequently, the pattern of resource use by treatment groups was unknown and the generalisability of the study was limited. In addition, the costs included were fairly specific to the study setting. It would have been useful to have adopted a societal perspective and included the indirect costs, which are mainly borne by the families of the hospitalised children. However, the inclusion of such costs might have partially increased the advantage of SAT over long-term intravenous therapy, since SAT is associated with shorter hospital stay.

Other issues
The findings of the analysis were similar to those reported in other studies. However, the generalisability of the study to other settings appears to have been limited. The effectiveness results were not reported fully. Also, the conclusions relating to the equal effectiveness of both strategies were questionable.

Implications of the study
SAT was associated with consistent health care cost-savings and should be recommended for paediatric patients hospitalised with severe respiratory tract infections. However, as has been clearly argued, there were serious methodological flaws on both the effectiveness and cost sides of the study.

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