Three day versus five day treatment with amoxicillin for non-severe pneumonia in young children: a multicentre randomised controlled trial

ISCAP study group

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 3 days versus 5 days of oral amoxicillin for curing non-severe pneumonia in children. Amoxicillin was administered at 31 to 54 mg/kg per day in three divided doses.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised children aged 2 to 59 months, with complaints of cough, rapid respiration, or difficulty in breathing. The exclusion criteria included signs of severe pneumonia or disease, other conditions requiring antibiotic treatment, clinically recognised congenital heart disease, and chronic systemic disorders. Also excluded were those with a history of repeated wheezing or asthma, those who had been hospitalised in the last 2 weeks, and those who had taken antibiotics in the last 2 days. Children who had measles in the last month, or had a history of penicillin allergy, were also excluded.

Setting
The setting was outpatient departments of referral hospitals. The economic analysis was conducted in India.

Dates to which data relate
The effectiveness and resource data were collected from August 2000 to December 2002. The price year was not reported.

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

Link between effectiveness and cost data
The costing was carried out prospectively on a sub-group of 1,000 children who did not respond to the treatment or who relapsed.

Study sample
The use of power calculations was reported. These suggested that 950 children in each group were required to test the equivalence hypothesis with a power of 90%. A total of 2,188 children were recruited and randomised. Of these, 1,095
received 3 days' amoxicillin and 1,093 received 5 days' amoxicillin.

Study design
The study was a randomised, double-blinded, placebo-controlled trial that was conducted in seven referral hospitals in India. The duration of follow-up was 12 to 14 days. The loss to follow-up was 5.4% by day 5 and 6.8% by day 12 to 14.

Analysis of effectiveness
The analysis of the clinical study was conducted on an intention to treat basis. The primary health outcomes used were the clinical cure rates, number of treatment failures and treatment adherence. Treatment failure was defined in three ways. First, as the development of chest indrawing, convulsions, drowsiness, or the inability to drink at any time. Second, as a respiratory rate above age-specific cut-off points on day 3 or later. Finally, as oxygen saturation by pulse oximetry of less than 90% on day 3. Nonadherence was defined as an intake of less than seven doses by day 3, and of less than 5 doses between days 3 and 5. The secondary health outcomes used in the analysis were the relapse rates on day 5 and the adverse reaction rate. The tertiary health outcomes used were microbiology outcomes and mothers "or caregivers" assessment. There were no substantial differences in the baseline characteristics of the treatment groups.

Effectiveness results
The clinical cure rate was 89.5% with 3 days of treatment and 89.9% with 5 days of treatment. The absolute difference was 0.4 (95% confidence interval, CI: -2.1 - 3.0; p not significant).

Among wheezers and non-wheezers, the clinical cure rates on day 5 were similar for 3 and 5 days' treatment. The cure rates were 90.7% for wheezers versus 89.1% for non-wheezers with 3 days' treatment, and 89.8% (wheezers) and 90.0% (non-wheezers), respectively, with 5 days' treatment.

There were 225 (10.3%) clinical failures.

Clinical failure was associated with:
- isolation of respiratory syncytial virus (adjusted odds ratio 1.95, 95% CI: 1.0 - 3.8),
- excess respiratory rate of greater than 10 breaths/minute (adjusted odds ratio 2.89, 95% CI: 1.83 - 4.55), and
- nonadherence with treatment at day 5 (adjusted odds ratio 11.57, 95% CI: 7.4 - 18.0).

Adherence to the treatment regimen was 94% for the 3-day treatment and 85% for the 5-day treatment.

Adverse reactions were similar in both treatment arms. There were no deaths, purpura or serious adverse effects of amoxicillin.

The relapse rate after day 5 was 5.3% with 3 days' treatment and 4.4% with 5 days' treatment. The absolute difference was 1.0 (95% CI: -1.0 - 3.0; p not significant).

On day 14, the isolation rates of S. pneumonia and H. influenza were 10.9% (n=325) and 6.9% (n=249), respectively. The rates did not differ according to the type of treatment.

There was no change in resistance of H. influenza over time. However, the proportion of S. pneumonia isolates resistant to co-trimoxazole rose significantly from 66.1 to 78.2%, (p=0.02), over 15 days in the 5-day amoxicillin treatment group.

There was no increase in the emergence of antimicrobial resistance in S. pneumonia or H. influenza in individual patients.

Of the 1,963 children assessed as clinically cured, mothers or caregivers reported that 51.2% were completely well.
47.8% were improved but still sick, 1.3% were the same, and 0.1% were worse. Of the 96 patients assessed as not cured, mothers reported that 4.2% were completely well, 63.5% were improved but still sick, 29.2% were the same, and 3.1% were worse, (p=0.001).

**Clinical conclusions**
Treatment with oral amoxicillin for 3 days was as effective as treatment for 5 days in children with non-severe pneumonia.

**Measure of benefits used in the economic analysis**
No summary benefit measure was used in the economic evaluation. In effect, a cost-consequences analysis was conducted.

**Direct costs**
The perspective of the payer was adopted. The total direct medical costs estimated were for drugs, investigations, hospitalisation, procedures and consultations, and out-of-pocket expenditures. The resource data were collected from children who did not respond to treatment or who relapsed. The unit costs were derived from actual prices from three randomly selected hospitals. Averaged unit prices were used in the analysis. The resource quantities and the costs were not reported separately and the price year was not reported. The costs were not discounted since the duration of follow-up was less than one year.

**Statistical analysis of costs**
A univariate analysis was performed to compare the direct medical costs in the two treatment groups. Student's t-test was used.

**Indirect Costs**
The indirect costs were not included. This was consistent with the perspective adopted.

**Currency**
Indian rupees (R). The costs were also evaluated in UK pounds sterling (£) and US dollars ($), but no conversion rates were given.

**Sensitivity analysis**
No sensitivity analysis was carried out.

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

**Cost results**
The mean direct medical cost of treating those who had not responded to treatment or who had relapsed was R272.79 in both treatment groups.

The average direct medical costs of treating 1,000 cases of non-severe pneumonia with amoxicillin would be R54,930 (790, $1,100) for 3 days' treatment and R62,430 (900, $1,250) for 5 days' treatment.

**Synthesis of costs and benefits**
Not applicable due to the cost-consequences approach taken.

**Authors' conclusions**

Treatment with oral amoxicillin for 3 days was as effective as treatment for 5 days in children with non-severe pneumonia. It was also cheaper, with increased adherence and possible decreased emergence of antimicrobial resistance.

**CRD COMMENTARY - Selection of comparators**

The reason for the choice of the comparators was clear. Amoxicillin has been recommended as a suitable alternative to co-trimoxazole. You should consider whether amoxicillin is a widely used treatment in your own setting.

**Validity of estimate of measure of effectiveness**

The basis of the analysis was a prospective, randomised, double-blinded study, which was appropriate for the study question. The use of power calculations was reported. It was unclear whether the study sample was representative of the study population, as children with asthma and with severe disease were excluded and the causes of infection were not investigated. The patients were shown to have been comparable at analysis, so confounding should be low. Selection bias is likely to have been low due to randomisation. The authors reported that the duration of follow-up (15 days) may have been too short to show any difference in outcomes between the two treatment regimens. Overall, the internal validity should be fairly good.

**Validity of estimate of measure of benefit**

There was no summary measure of benefit since, in effect, a cost-consequences analysis was conducted.

**Validity of estimate of costs**

The perspective of the payer was adopted and, as such, all the relevant categories of costs appear to have been included in the analysis. However, no unit costs or resource quantities were reported and only limited details of the methods of cost estimation were given. The cost estimates are likely to be specific to the Indian setting and sensitivity analyses were not performed. The price year was not reported. These facts hinder the reproducibility of the results in other settings. The costs were treated stochastically. Although the authors reported the total costs in rupees, UK pounds sterling and US dollars, no conversion rates were reported. No discounting was performed since the duration of follow-up was less than one year.

**Other issues**

The authors compared their outcome findings with those from other studies and described the differences in both methods and results. The generalisability of the results was not discussed. The authors highlighted some limitations of their study, which have been mentioned already. The authors do not appear to have presented their results selectively. Their conclusions reflected the scope of the analysis.

**Implications of the study**

The authors recommended the 3-day course of amoxicillin for treating community-acquired non-severe pneumonia in children, as this is equally effective as a 5-day course but is cheaper, with increased adherence and possibly decreased emergence of antimicrobial resistance.

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