

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

ISCAP Study Group

Abstract

Objective To assess the efficacy of three days versus five days of treatment with oral amoxicillin for curing non-severe pneumonia in children.

Design Randomised, double blind, placebo controlled multicentre trial.

Setting Outpatient departments of seven referral hospitals in India.

Participants 2188 children aged 2-59 months, 1095 given three days of treatment and 1093 given five days.

Intervention Oral amoxicillin 31-54 mg/kg/day in three divided doses.

Main outcome measures Treatment failure: defined as development of chest indrawing, convulsions, drowsiness, or inability to drink at any time; respiratory rate above age specific cut-off points on day 3 or later; or oxygen saturation by pulse oximetry <90% on day 3.

Results The clinical cure rates with three days and five days of treatment were 89.5% and 89.9%, respectively (absolute difference 0.4 (95% confidence interval -2.1 to 3.0)). Adherence to treatment regimen was 94% and 85% for three day and five day treatments, respectively. Loss to follow up was 5.4% by day 5. There were no deaths, 41 hospitalisations, and 36 minor adverse reactions. There were 225 (10.3%) clinical failures and 106 (5.3%) relapses, and rates were similar in both treatments. At enrolment, 513 (23.4%) children tested positive for respiratory syncytial virus, and *Streptococcus pneumoniae* and *Haemophilus influenzae* were isolated from the nasopharynx in 878 (40.4%) and 496 (22.8%) children, respectively. Clinical failure was associated with isolation of respiratory syncytial virus (adjusted odds ratio 1.95 (95% confidence interval 1.0 to 3.8)), excess respiratory rate of > 10 breaths/minute (2.89 (1.83 to 4.55)), and non-adherence with treatment at day 5 (11.57 (7.4 to 18.0)).

Conclusions Treatment with oral amoxicillin for three days was as effective as for five days in children with non-severe pneumonia.

Introduction

Co-trimoxazole is recommended for acute respiratory infections in India, with amoxicillin as a suitable

alternative because of its proved efficacy against *S pneumoniae* and *H influenzae*, the most common causes of community acquired pneumonia. A trial of oral co-trimoxazole in Bangladeshi children reported that three days of treatment cured 75% of cases of non-severe pneumonia with no subsequent treatment.¹ A randomised controlled trial from Pakistan showed that three days and five days of treatment with oral amoxicillin had equivalent cure rates in children with non-severe pneumonia.²

To confirm these findings, we conducted the present study. Our primary hypothesis was that three days of treatment with oral amoxicillin is as effective as five days' treatment for non-severe pneumonia. Our secondary hypothesis was that relapse rates would be the same in the two treatment regimens.

Participants and methods

This double blind, placebo controlled, randomised trial was conducted in the outpatient departments of seven referral hospitals in India. Participants were children aged 2-59 months with cough, rapid respiration, or difficulty in breathing. We defined non-severe pneumonia as a respiratory rate of ≥ 50 breaths per minute (for ages 2-11 months) or ≥ 40 per minute (for age 12-59 months). We excluded children who had signs of severe pneumonia or disease, other conditions requiring antibiotic treatment, clinically recognised congenital heart disease, chronic systemic disorders, a history of repeated wheezing or asthma, been hospitalised in the previous two weeks, taken antibiotics in the previous two days, measles within the previous month, or a history of penicillin allergy. Patients with fever or wheeze received symptomatic treatment before enrolment. Those whose fast breathing persisted were enrolled after their parents or guardian had consented.

Objectives

Our primary objective was to compare the proportions of children recovering after three days' treatment and five days' treatment. Secondary objectives were to compare the proportions who relapsed within the next

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6-14 days, the proportions who had resistant strains of *S pneumoniae* or *H influenzae* in nasopharyngeal cultures at enrolment and at 14 day follow up, and the direct medical costs of treating clinical failures and relapses, and to assess the proportion of participants whose nasopharyngeal aspirates was positive for respiratory syncytial virus at enrolment.

Intervention

All participants received scored dispersible tablets of amoxicillin 125 mg for the first three days. Amoxicillin was given thrice daily dissolved in 5 ml of water, and the effective dose per kilogram body weight varied from 31 to 54 mg/day. For the next two days participants received either amoxicillin or placebo.

Randomisation

Block randomisation was done for each participating site to avoid unblinding. For both treatment groups, tablets were placed in serially numbered opaque white envelopes, each of which contained a green envelope containing 11 doses of amoxicillin for three days and a blue envelope containing eight doses of either amoxicillin or placebo for the next two days.

Outcomes

Participants were followed up at three and five days after enrolment and between 12 and 14 days after enrolment. Mothers or care providers were asked to categorise their child as completely well, improved but still sick, the same, or worse at each follow up visit. Children who did not respond to treatment, developed adverse reactions to amoxicillin, or withdrew from the study were treated according to standard hospital guidelines.

Treatment failure was defined as development of chest indrawing, convulsions, drowsiness, or inability to drink at any time; respiratory rate above age specific cut-off points on day 3 or later; or oxygen saturation by pulse oximetry <90% on day 3. Participants who did not fail on assessment at day 3 or day 5 were considered clinically cured. Relapse was defined as recurrence of signs of pneumonia or severe disease after day 5 among those who had been clinically cured at that time.

Treatment adherence was assessed by pill count on follow up days. Non-adherence was defined as intake of less than seven doses by day 3 and of less than five doses between days 3 and 5.

Laboratory procedures—We tested for the presence of respiratory syncytial virus in nasopharyngeal aspirates at enrolment. Nasopharyngeal swabs were taken at enrolment and at 14 days follow up to isolate *S pneumoniae* and *H influenzae*.

Cost data collection—Participants who did not respond to treatment or who relapsed were followed to collect data on the medical resources they used. To calculate the costs of these resources, we randomly selected three private sector hospitals that cater to lower middle class in each city of Lucknow, Vellore, Mumbai, New Delhi, Nagpur, Chandigarh, and Trivandrum; obtained their prices; and averaged them over the participating sites. The total estimated cost was the aggregated cost of drugs, investigations, hospitalisation, procedures and consultations, and out of pocket expenditures.

Statistical analysis

Clinical data analysis—Our primary analyses were done on an intention to treat basis. We calculated the difference in clinical cure rate. We also performed per protocol analysis for participants with complete follow up and adherence to treatment. We compared baseline and other characteristics and therapeutic failures between the two treatment groups. We constructed a multivariate model to assess determinants of treatment failure.

Cost analysis—We analysed costs from the payer's perspective. We multiplied the units of each resource used by its average cost to calculate the total expenditure on that component of treatment. We compared direct medical costs in the two treatment groups.

Results

We recruited 2188 patients from August 2000 to December 2002 and randomised 1095 to three days of amoxicillin treatment and 1093 to five days of treatment. Loss to follow up was 5.4% by day 5, and 6.8% by day 14. There were no substantial differences in the baseline characteristics of the treatment groups (see bmj.com).

Adherence to treatment

The mean doses taken from the green and blue envelopes were 8.9 (SD 0.9) out of nine doses and 5.56 (SD 1.6) out of six doses, respectively, and were similar in both the groups.

Primary and secondary clinical outcomes

In our intention to treat analysis, clinical cure rates were 89.5% (980/1095) and 89.9% (983/1093) in the three day treatment and five day treatment groups, respectively (table 1), similar among wheezers and non-wheezers. In the per protocol analysis, the clinical cure rates were 94.9% (980/1033) and 95.8% (983/1026). There was also no difference between groups in the rate of relapse among those considered cured on day 5 (table 1).

Microbiology outcomes

A total of 513 (23.4%) patients tested positive for respiratory syncytial virus at enrolment, of whom 8.7% had wheeze. Table 2 shows the antimicrobial resistance pattern for the 878 isolates of *S pneumoniae* and 496 isolates of *H influenzae* cultured at enrolment. On day 14, isolation rates of *S pneumoniae* and *H influenzae* were 10.9% (n = 325) and 6.9% (n = 249), respectively, and did not differ by treatment type (table 2). While there was no change in resistance of *H influenzae* over time, the proportion of *S pneumoniae* isolates resistant to co-trimoxazole rose significantly from 66.1% to

Table 1 Comparison of outcome measures in 2188 children with non-severe pneumonia randomised to 3 days or 5 days of treatment with amoxicillin: intention to treat analysis. Values are numbers (percentages) of patients unless stated otherwise

	3 day treatment (n=1095)	5 day treatment (n=1093)	Difference (95% CI)
Primary outcome measures:			
Cure on day 5	980 (89.5)	983 (89.9)	0.4 (-2.1 to 3.0)
Relapse after day 5	58 (5.3)	48 (4.4)	1.0 (-1.0 to 3.0)
Secondary outcome measure:			
Cure on day 5 among wheezers	127/140 (90.7)	132/147 (89.8)	0.9 (-5.9 to 7.8)
Cure on day 5 among non-wheezers	853/957 (89.1)	851/946 (90.0)	0.7 (-2.1 to 3.4)

Table 2 Antimicrobial resistance of isolates of *Streptococcus pneumoniae* and *Haemophilus influenzae* from children with non-severe pneumonia randomised to 3 days or 5 days of treatment with amoxicillin. Isolates cultured from nasopharyngeal swabs taken at enrolment (day 0) and final follow up (day 14)

Antibiotic resistance*	No of resistant isolates/total tested (%)				P value of difference between treatments	
	Day 0		Day 14		At day 14	Change from day 0 to day 14
	3 day treatment	5 day treatment	3 day treatment	5 day treatment		
<i>S pneumoniae</i> :						
Co-trimoxazole	253/380 (66.6)	252/381 (66.1)	106/159 (66.7)	111/142 (78.2)	0.02	0.05
Chloramphenicol	21/418 (5.0)	14/419 (3.3)	9/163 (5.5)	6/142 (4.2)	0.6	0.89
Oxacillin	67/408 (16.4)	64/413 (15.5)	17/160 (10.6)	17/141 (12.1)	0.7	0.59
Erythromycin	15/421 (3.6)	9/418 (2.2)	2/161 (1.2)	4/142 (2.8)	0.3	0.14
<i>H influenzae</i> :						
Co-trimoxazole	118/217 (54.4)	133/218 (61.0)	74/129 (57.4)	64/106 (60.4)	0.64	0.65
Chloramphenicol	58/232 (25.0)	57/234 (24.4)	27/126 (21.4)	24/108 (22.2)	0.88	0.83
Erythromycin	69/230 (30.0)	65/232 (28.0)	39/126 (31.0)	31/108 (28.7)	0.7	0.97
Ampicillin	46/235 (19.6)	40/237 (16.9)	30/129 (23.3)	24/108 (22.2)	0.85	0.8

*Resistance based on zone of inhibition in mm. *S pneumoniae* resistant to oxacillin (<20), chloramphenicol (≤20), erythromycin (≤15), co-trimoxazole (≤15). *H influenzae* resistant to ampicillin (<18), chloramphenicol (<25), erythromycin (<15), co-trimoxazole (<10).

78.2% (P = 0.02) over 15 days in the five day amoxicillin treatment group.

Risk factors associated with clinical failure

Clinical failure was significantly associated with non-adherence at day 5 (adjusted odds ratio 11.57 (95% confidence interval 7.4 to 18.0)), and excess respiratory rate of > 10 breaths/minute (2.89 (1.83 to 4.55)), and nasopharyngeal swab positivity for respiratory syncytial virus (1.95 (1.0 to 3.8)). (See bmj.com for details.)

Association of clinical cure with caregivers' assessment

Of the 1963 patients assessed as clinically cured, mothers or carers reported that 1005 (51.2%) were completely well, 938 (47.8%) were improved but still sick, 26 (1.3%) were the same, and one (0.1%) was 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).

Cost analysis

Average direct medical costs of successful treatment with amoxicillin for three days and five days were 11 and 19 rupees, respectively. Cost data were available for most cases of treatment failure (n = 183, 82.03%) and relapse (n = 84, 79.2%). The mean direct medical cost of treating those who had not responded to treatment or had relapsed was 272.79 rupees (SD 514.2) in both treatment groups. We calculate that the average direct medical costs of treating 1000 cases of non-severe pneumonia with three days or five days of amoxicillin would be 54 930 rupees (£790, \$1100) and 62 430 rupees (£900, \$1250), respectively.

Adverse reactions

Adverse reactions were similar in both treatment arms. There were no deaths, purpura, or serious adverse effects of amoxicillin. There were 41 hospitalisations, with similar numbers in the three day and five day treatments (18 and 23, respectively).

Discussion

Treatment with oral amoxicillin for either three days or five days was equally effective for non-severe pneumo-

nia. Among children with complete follow up who adhered to treatment, cure rate was about 95%. From the numbers needed to treat, we calculate that 250 cases of non-severe pneumonia would need to be treated with five days of amoxicillin rather than three days for one additional cure.

Short courses of amoxicillin have been used to treat infections caused by organisms causing tonsillopharyngitis,³ urinary tract infections,⁴ and other common childhood infections.⁵ In addition, similar results to ours have been reported in a study from Pakistan.²

Strengths and limitations of study

The main strengths of our trial are that it was large, double blind, and multicentre and was conducted over two years covering all four seasons with a minimal loss to follow up and good adherence to treatment. Its limitations are that it was a hospital based study, causes of infection were not investigated, follow up was limited to only 15 days, and children with history of asthma were excluded.

Risk factors for treatment failure

Unlike the Pakistan study,² we did not find any difference of outcomes in children aged < 12 months compared with older children. Possible explanations may be the lower proportion of infants recruited by us and variation between our study sites. Since almost half of the children's mothers or carers did not agree with a doctor's assessment of cure in our study, parents may need appropriate counselling or else may seek treatment elsewhere.

In our study, 23% of patients tested positive for respiratory syncytial virus. Because we excluded patients with severe disease, we possibly missed many other infected children.⁶ The detection kit used in our study had a sensitivity of 83%. Detection of the virus in our study increased the probability of treatment failure.

As in other studies,⁷ our carrier rate for either *S pneumoniae* or *H influenzae* bacteria at enrolment was less than 50%. We found a significant rise in resistance of *S pneumoniae* to co-trimoxazole from enrolment until day 14 in children receiving five days of treatment, as has been reported elsewhere.⁸ Resistance to various antibiotic classes with different mechanisms may occur in the same strain, giving this strain

What is already known on this topic

Amoxicillin is effective in treating non-severe pneumonia in children

Isolation of infective bacteria from the nasopharynx can be used to monitor antimicrobial resistance in the community

What this study adds

Three days of treatment with amoxicillin is as effective as the standard five days in treating non-severe pneumonia

Almost three quarters of nasopharyngeal isolates of *Streptococcus pneumoniae* and *Haemophilus influenzae* were resistant to co-trimoxazole

biological advantages in the selection process. This phenomenon results in the use of one class of antibiotics promoting carriage of *S pneumoniae* resistant to another antibiotic class.⁹

Conclusions

A three day course of amoxicillin for treating community acquired non-severe pneumonia in children, is equally effective as a five day course but is cheaper with increased adherence and possibly decreased emergence of antimicrobial resistance. Our findings have local as well as global implications, because our study

has also confirmed findings from a recently published data from elsewhere.

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Risk factors, prevalence, and treatment of anxiety and depressive disorders in Pakistan: systematic review

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Abstract

Objectives To assess the available evidence on the prevalence, aetiology, treatment, and prevention of anxiety and depressive disorders in Pakistan.

Design Systematic review of published literature.

Studies reviewed 20 studies, of which 17 gave prevalence estimates and 11 discussed risk factors.

Main outcome measures Prevalence of anxiety and depressive disorders, risk factors, effects of treatment.

Results Factors positively associated with anxiety and depressive disorders were female sex, middle age, low level of education, financial difficulty, being a housewife, and relationship problems. Arguments with husbands and relational problems with in-laws were positively associated in 3/11 studies. Those who had close confiding relationships were less likely to have anxiety and depressive disorders. Mean overall prevalence of anxiety and depressive disorders in the community population was 34% (range 29-66% for women and 10-33% for men). There were no rigorously controlled trials of treatments for these disorders.

Conclusions Available evidence suggests a major social cause for anxiety and depressive disorders in Pakistan. This evidence is limited because of methodological problems, so caution must be exercised in generalising this to the whole of the population of Pakistan.

Introduction

Anxiety and depressive disorders constitute a substantial proportion of the global burden of disease, and are projected to form the second most common cause of disability by 2020.¹ Non-communicable diseases such as these present a particular challenge for low income countries, where infectious diseases and malnutrition are still rife, and where only a low percentage of gross domestic product is allocated to health services.² These

References w1-w20 are listed on bmj.com



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