

Is 3 days of amoxicillin as effective as 5 days or more in the treatment of non-severe pneumonia in children?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at

http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *Is 3 days of amoxicillin as effective as 5 days or more in the treatment of non-severe pneumonia in children?*

The WHO Pocketbook of Hospital Care for Children recommends for antibiotic therapy in non-severe pneumonia – Give cotrimoxazole (4 mg/kg trimethoprim / 20 mg/kg sulfamethoxazole twice a day) for 5 days or amoxicillin (25 mg/kg 2 times a day) for 3 days. (Pocketbook 4.2.3, pg 80)

INTRODUCTION

Pneumonia is a leading cause of morbidity and mortality in developing countries. Pneumonia claims the lives of around 19% of children worldwide and approximately 2.1 million are below the age of 5 years[1][2][19]. Pneumonia is also responsible for about 8.2% of all disabilities and premature mortality[2]. Several studies and reviews conducted in developing countries showed that most community acquired pneumonias (CAP) in children are bacterial in origin with *Streptococcus pneumoniae* and *Haemophilus influenzae* being the most common pathogens[3]. Based on these findings, 5 days of oral co-trimoxazole or amoxicillin was the first line treatment in an outpatient setting for non-severe pneumonia[4]. However the most recent Pocket book of hospital care for children[8] published by the WHO changed the guidelines to 3 days of amoxicillin or co-trimoxazole instead of 5. Shortening the conventional course of amoxicillin to 3 days would mean lower cost on poor developing countries, more antibiotics would be made available for outpatients, patient adherence would improve, lower prevalence of side effects and antibiotic resistance would be better controlled. Therefore we performed this systematic review to help shed light on this important global issue and validate the recent change in WHO guidelines.

METHODS

The Articles were identified through searching the Cochrane library, MEDLINE, EMBASE and global health. (Amoxycillin OR amoxicillin) AND (pneumonia) AND (three OR 3) AND (children) were searched as key word and were mapped to relevant subject headings. The titles and abstracts of identified articles were read by two independent sources and only two

RCTs that are relevant to this review were found. Both studies were graded as level of evidence (LOE) 1a based on the SIGN system [5], which places weight on the quality and body of evidence. Details of both studies can be found in table 1 below.

RESULTS

Treatment failure and relapse:

Study 1 reported treatment success in 79% of patients in the 3-day group and 80% in the 5-day group (difference 0.7, 95% CI – 1.8 to 3.2)[11]. In study 2, treatment success was 89.5 % and 89.9% in the 3 day and 5 day group respectively[12]. (Difference 0.4 95% CI -2.1 to 3.0). Therefore showing no significant difference in clinical outcome in both treatment regimes in both studies.

Study 1 showed that 1% of patients in the 3 days group and 1% of patients in the 5-day group relapsed (difference 0.1, 95% CI – 0.6 to 0.8)[11]. 5.3 % of patients and 4.4% of patients relapsed in the 3-day group and 5 day group respectively in study 2 [12]. (Difference 1.0, 95% CI –1.0 to 3.0). Both studies show no significant difference between relapse rates on 3 days or 5 days of oral amoxicillin.

Compliance to treatment

There is significant loss in adherence with two extra days of treatment. Study 1 showed that 2% of children were non-adherent to therapy in the 3-day group after 3 days of treatment while 5 % were non-adherent in the 5-day group after 5 days of treatment (odds ratio 2.9, 95% CI 1.6-5.2, p<0.0001). In study 2, 5.8 % of patients were non-adherent to therapy in the 3-day group after 3 days of treatment and 15.1% were non-adherent in the 5-day group after 5 days of treatment.[11][12]

Risk factors associated with clinical failure: Univariate and logistic regression analysis in both studies showed that a respiratory rate >10 breaths/min above age specific cut off and non adherence in the 5 day group are significantly associated with treatment failure.

Cost analysis:

A univariate cost -consequences analysis performed by study 2 of the direct medical costs of both groups showed that the average medical costs of treating 1000 cases of non-severe pneumonia with amoxicillin would be 54,930 Indian Rupees (equivalent to \$1,100, £790) for 3 days of treatment and 64,430 (\$1250, £900) for 5 days of treatment. The total direct medical

costs estimated were for drugs, investigations, hospitalization, procedures, and consultations, and out of pocket expenditures.

DISCUSSION

After carefully comparing the results of both studies, this review shows that 3 days of amoxicillin is as effective as 5 days in the treatment of non-severe pneumonia in children. Treatment failure and relapse rates were similar with both regimes. Although the difference in treatment failure rates were small and insignificant, it is important to note the overall treatment failure rates were high, nearly reaching 20% in study 1. Similar studies conducted over the last decade in developing countries[9][10]show that the treatment failure rates are increasing with time for both amoxicillin and co-trimoxazole which is concerning since these are the antibiotics recommended by the WHO for the first line treatment of non severe pneumonia in children. The WHO therapy failure criteria are quite sensitive and a recent paper has proposed alternate therapy failure criteria, which resulted in lower therapy failure rates [13]. An increase in antimicrobial resistance of *S. pneumoniae* and *H. influenzae* to amoxicillin and co-trimoxazole maybe an important factor. Study 2 showed that almost 75% of nasopharyngeal isolates of *S. pneumoniae* and *H. influenzae* were resistant to co-trimoxazole. However the evidence linking antibiotic resistance to treatment failure in pneumonia remains unclear [9][14][15][16]. Non-adherence in the 5-day group was also a vital factor influencing treatment failure in this review.

Although most community-acquired pneumonias are bacterial, viral pneumonias are also common and sometimes children can have mixed bacterial and viral infections[7][17][18]. Therefore these children will not respond very well to antibiotic resulting in high failure rates. Distinguishing between bacterial and viral pneumonias clinically or by radiological examination is difficult[6] and expensive, especially with the limited resources available in developing countries such as India and Pakistan.

Summary

The evidence in this review therefore supports the recent change in the WHO guidelines from 5 days of amoxicillin to 3 days in order to treat non-severe pneumonia [8]. This means cheaper costs for developing countries, higher levels of patient compliance, and possibly decreased emergence of antibiotic resistance. However the high treatment failure rates showed by this review highlight the need of research to improve the specificity of therapy failure criteria. In addition, there is insufficient evidence on adverse effects as well as direct medical costs of different antibiotic treatment regimes.

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Table 1: Included studies

Citation Design	Country Setting	Inclusion criteria	Sample size	Intervention
(1) MASCOT pneumonia study group et al Double blinded multicentre RCT	Pakistan Multicentre hospitals	Patients <5 years (2-59 months) Male/female, diagnosed with non-severe pneumonia according to the WHO criteria ^{5/35} . No patients with asthma/bronchitis or severe disease	2000	15mg/kg oral amoxicillin for 3 days. Half children got medicine for next 2 days and other half got placebo.
(2) ISCAP study group et al Double blinded multicentre RCT	India Multicentre hospitals	Patients <5 years (2-59 months) Male/female, diagnosed with non-severe pneumonia according to the WHO criteria ^{5/35} . No patients with asthma/bronchitis or severe disease.	2188	Oral amoxicillin 31-54mg/kg/day in three divided doses for 3 days. Half children got medicine for next 2 days and other half got placebo.

MASCOT: multicentre amoxicillin short course therapy