SYSTEMATIC REVIEW

Oral Antibiotics for Community–acquired Pneumonia with Chest-indrawing in Children Aged Below Five Years: *A Systematic Review*

RAKESH LODHA, SHIVANI RANDEV AND SUSHIL K KABRA

From Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India.
Correspondence to: Dr SK Kabra, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi 110 029, India.
skkabra@hotmail.com

Objectives: To determine the efficacy of oral antibiotics in under-five children with pneumonia and chest indrawing.

Methods: We included controlled clinical trials (randomized or quasi randomized) that compared the efficacy of oral antibiotics *versus* parenteral antibiotics for treatment of community- acquired pneumonia with chest-indrawing (severe pneumonia as defined by the World Health Organization's guidelines) in children below 60 months of age. Data were extracted and managed using RevMan software. Main outcome variables were: treatment failure rate, relapse rate, death rate, need for hospitalization, and severe adverse effects.

Results: We identified four randomized controlled trials involving 4400 children who were diagnosed to have severe pneumonia but were feeding well and not hypoxic. Baseline characteristics of children in the two treatment arms (oral and parenteral antibiotics) were similar. In two studies, oral antibiotics were administered on an ambulatory basis, while in two, oral antibiotics were used in hospitalized children. Failure rate in children receiving oral antibiotics was 13% (288/2208) while that in children receiving parenteral antibiotics was 13.8% (302/2183) (OR 0.93; 95% CI 0.78, 1.11). Failure rates were not affected by the type of oral antibiotic, or presence of wheeze. Relapse rates, hospitalization or serious adverse events were similar in the two groups.

Conclusion: Children with tachypnea with chest-indrawing without signs/symptoms of very severe pneumonia may be treated with oral antibiotics.

Key words: *Ambulatory treatment, Amoxicillin, Management, Outcome*.

Community-acquired pneumonia is the leading cause of under-five morbidity and mortality in developing countries. Out of the 6.3 million deaths worldwide in children under five years of age in the year 2013, pneumonia accounted for 14.9% of theses deaths.

To improve the case detection and to standardize the management, WHO proposed simple classification for severity of pneumonia. As per these guidelines, children with severe or very severe pneumonia had to be treated with parenteral antibiotics [2]. As per the guideline, all children with chest indrawing needed hospitalization for parenteral antibiotics. This approach may be associated with multiple problems [3]. Recent trials suggest that children with pneumonia and chest indrawing may be treated with oral antibiotics [4-6]. We planned systematic review of all the clinical trials evaluating oral antibiotics in under-five children having community-acquired pneumonia with chest-indrawing.

METHODS

All controlled clinical trials (randomized or quasi randomized) that compared the efficacy of oral antibiotics with parenteral antibiotics for treatment of community-acquired pneumonia with chest-indrawing (severe pneumonia) for children below 60 months of age were included. Severe pneumonia for the purpose of this review was defined as cough or difficult breathing for less than two weeks; and rapid breathing (defined as a respiratory rate of more than 50 breaths/min in children two months to 11 months old, and more than 40 breaths/min in children 12 to 59 months of age); and lower chest-indrawing [2]. There were no language, regional or socio-economic restrictions.

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Studies on children suffering from chronic pulmonary diseases, immunodeficiency disorders, neurological disorders affecting lung function, and cardiac disorders were excluded.

Types of interventions: Comparison of antibiotics, in which at least one arm includes oral antibiotics in hospital (inpatient or outpatient) or community-based setting. The other arm may be parenteral therapy alone or switch therapy in which initial parenteral treatment is followed by oral antibiotics to complete the course. The antibiotics used for the oral and parenteral routes could be different. Subgroup analyses were carried out for hospital-based

treatment/outpatient treatment and for type of oral antibiotics.

Outcome measures: Primary outcome measure was 'treatment failure' defined as the presence of any of the following: persistence of chest indrawing, at time of assessment within 2 weeks of enrolment in the study, convulsions, drowsiness or inability to drink at any time, respiratory rate above the age-specific cut-off point on completion of treatment, or oxygen saturation of less than 90% (measured by pulse oximetry) after completion of the treatment or mortality. Loss to follow-up or withdrawal from the study at any time after recruitment 'failure' in the analysis was also considered as Secondary outcome measures included: (*a*) '*relapse'*defined as recurrence of symptoms/signs during follow up period following an improvement in clinical signs and symptoms with treatment and declared as cured; (*b*) death; (*c*) need for hospitalization; and, (*d*) severe adverse effects.

Search strategy for identification of studies: We searched the Cochrane Central Register of Controlled Trials: issue 4 of 2015 (The Cochrane Library), MEDLINE (1966 to April 2015) and EMBASE (1980 to April 2015) by using appropriate terms (***Web Table* I**).

We also searched bibliographies of the articles that were selected for review to identify any additional trials not recovered by the electronic searches.

Methods of the review: Abstracts of all articles were read by two authors independently, and the relevant articles were selected. Full text articles of selected studies were obtained. For missing data, the corresponding author was contacted by e-mail. If there was no response in two weeks time, we used the available information. A scientist, not involved in the data extraction, concealed the identifiers of the study by covering the titles, names of the authors on the printed version of the articles, and assigned serial numbers to the studies.

Data of baseline characteristics, and primary and secondary outcome measures were extracted in a pretested performa by two authors, independently. Differences in the data were resolved by discussion with third author.

Statistical analysis: Analyses were carried out using RevMan program (version 5.2). We assessed heterogeneity using the RevMan software that gave I^2 values; we considered significant heterogeneity to be present if the I^2 value was more than 30%. In case of heterogeneity between the studies, efforts were made to explore the causes. Random effects model was used for all analyses. Following subgroup analyses were also performed: (*i*) Failure rates in children receiving oral amoxicillin in comparison to parenteral penicillin/ ampicillin; (*ii*) Failure rates in children receiving oral drug as cotrimoxazole in comparison to parenteral penicillin; and (*iii*) Failure rates in ambulatory *versus* hospitalized treatment regimen.

We planned to assess the publication bias by Funnel plot in case sufficient number of trials were available. Quality of included studies was assessed using the Cochrane Collaboration's 'Risk of bias' tool [7] by two authors independently.

RESULTS

We identified a total of 1979 articles for the period 1966 to April 2015. After reviewing the abstracts of these articles, full text articles of 12 studies were retrieved; of these, a total of 4 randomized controlled trials (RCTs) were identified for data extraction (***Fig.* 1**). Details of included studies are presented in ***Table* I**.

Of the four studies included, one was multi-country [4] [Colombia, Ghana, India, Mexico, Pakistan, South Africa (two sites), Vietnam, Zambia]; and one study each were carried out in Pakistan [5], Gambia [6] and Kenya [8]. Three studies used amoxicillin as the oral antibiotic and Penicillin/ampicillin as parenteral antibiotics [4,5,8] while one used co-trimoxazole as the oral antibiotic [6]. Eight studies were excluded [9-16]. Reasons for exclusion are

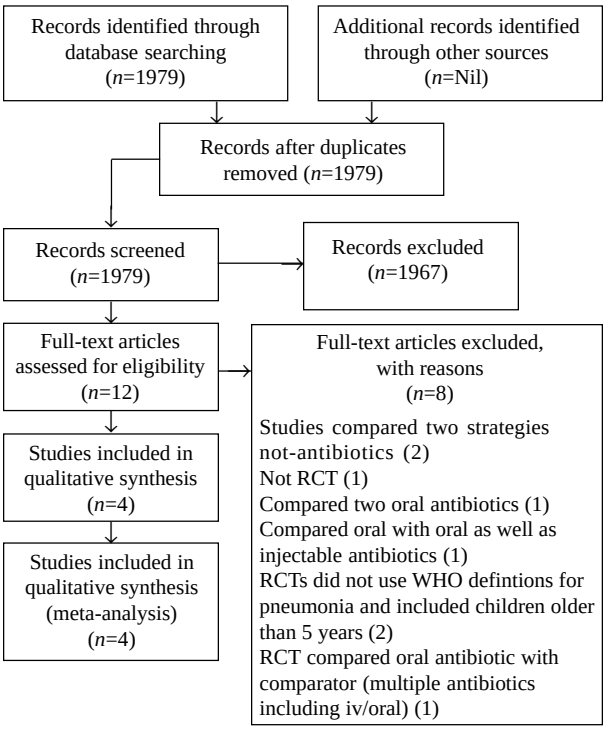

FIG.1 *PRISMA Flow Diagram for study selection.*

TABLE I DETAILS OF INCLUDED STUDIES

Addo-Yobo, et al. [4]	
Methods	This multicentre, randomized, open-label equivalency study carried out at nine sites [Colombia, Ghana, India, Mexico, Pakistan, South Africa (two sites), Vietnam, Zambia] with an aim to determine whether oral amoxicillin and parenteral penicillin were equivalent in the treatment of severe pneumonia in children aged 3-59 months.
Participants	1702 children aged between 3 months to 59 months of either sex with severe pneumonia based on case definition given by WHO.
Interventions	All patients were admitted for 48 hours. Patients received oral amoxicillin 45 mg/kg/day in four divided doses for 5 days or parenteral penicillin G 200000 IU /kg/day in four divided doses.
Outcome	Treatment failure was 19% in each group (161 patients, penicillin; 167 amoxicillin; risk difference -0.4%; 95% CI -4.2 to 3.3) at 48 h. Infancy (age 3-11 months; odds ratio 2.72; 95% CI 1.95 to 3.79), very fast breathing (1.94; 1.42 to 2.65), and hypoxia (1.95; 1.34 to 2.82) at baseline predicted treatment failure by multivariate analysis.
Hazir, et al. [5]	
Methods	Randomized, open-label equivalency trial was done at seven study sites in Pakistan.
Participants	2100 children of either sex between 3 months to 59 months of age with WHO defined severe pneumonia.
Interventions	Children either received parenteral ampicillin (100 mg/kg per day in four doses) for 48 h, followed by 3 days of oral amoxicillin (80-90 mg/kg per day; *n*=1012) in hospital or to home-based treatment for 5 days with oral amoxicillin (80-90 mg/kg per day in two doses; *n*=1025).
Outcome	1048 were randomly assigned to hospitalization and injectable ampicillin and 1052 to ambulatory treatment with oral amoxicillin. As per intention to treat analysis cumulative failure rates by day 6 in hospitalized and ambulatory treatment was 105/1048 (10.0%) and 89/1052 (8.5%) respectively with a risk difference of 1.6% (-0.9 to 4.0). Relapse rates by day 14 in hospitalized and ambulatory treatment group were 31/943 (3.3%) and 26/963 (2.7%) respectively with a risk difference of 0.6% (-0.9 to 2.1)
Campbell et al. [6]	
Methods	A quasi randomized controlled trial on children with cough with chest indrawing (WHO defined severe pneumonia) in rural Gambia. Children were assigned sequentially to one of the two treatment groups (Oral co-trimoxazole or injection of procaine penicillin).
Participants	134 children, aged 1 month to 4 years, who presented with acute respiratory illness for less than 1 week with signs of respiratory distress (intercostal indrawing or nasal flaring),.
Interventions	Children in group A received a 5-day course of oral co-trimoxazole on ambulatory basis. Those in group B received a single intramuscular injection of fortified procaine penicillin (procaine penicillin 4 mega units plus benzylpenicillin 1 mega unit per vial) and a 5-day course of oral ampicillin on ambulatory basis.
Outcome	There were no significant differences between the two groups in any of the symptoms, signs, or laboratory findings (e.g., length of illness, mean respiratory or heart rate, mean temperature, presence of auscultatory or radiological changes consistent with pneumonia, and blood culture isolation rate). There were no significant differences between the two groups in terms of final outcome at 2 weeks follow-up when assessed either by the mothers or the clinician.
Agweyu, et al. [8]	
Methods	An open-label, multicenter, randomized controlled noninferiority trial was conducted at 6 Kenyan hospitals. Eligible children aged 2-59 months were randomized to receive amoxicillin or benzyl penicillin and followed up for the primary outcome of treatment failure at 48 hours.
Participants	Children aged 2-59 months with severe pneumonia as defined in the 2005 WHO guidelines were recruited from 6 public hospitals across Kenya.
Interventions	Eligible children were randomized to oral amoxicillin at dose of 40-45 mg/kg twice daily or intravenous/ intramuscular benzyl penicillin at 50 000 IU/kg 4 times daily for a minimum of 48 hours.
Outcome	Treatment failure by day 5 postenrollment was 11.4% and 11.0% and rising to 13.5% and 16.8% by day 14 in the amoxicillin *vs* benzyl penicillin groups, respectively. Four patients died (overall mortality 0.8%) during the study, 3 of whom were allocated to the benzyl penicillin group. The presence of wheeze was independently associated with less frequent treatment failure.
Comments	Open label randomized controlled trial and included children with co- morbidity including malaria, diarrhea, wheeze, and a single convulsion in the presence of fever.

TABLE II GRADE PROFILE

Efficacy of oral antibiotics in under-five children with pneumonia and chest indrawing.

Patients: Children < 5 years age with pneumonia and chest indrawing

Intervention: Oral antibiotics

Comparison: Parenteral antibiotics

Outcome: Treatment failure

Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Parenteral antibiotic	With Oral antibiotics		Risk with Parenteral antibiotics	Risk difference with Oral antibiotics (95% CI)
Failure rate											
4400 (4 studies) 5 days	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	+++ High	302/2183 (13.8%)	288/2208 (13.04%)	OR 0.93 (0.78 to 1.11)	138 per 1000	8 fewer per 1000 (from 27 fewer to 13 more)

given in ***Web Table* II**. As the number of included studies was only four, the publication bias could not be assessed by funnel plot. Quality of studies is described in ***Web Fig.* 1**.

Baseline characteristics of included subjects: A total of four RCTs (4400 children less than 60 months of age) were included for analysis. All 4 RCTs enrolled children below 5 years of age; one of these included children from 1 month to 4 years of age [6]. Data on the number of children between 1-2 months were not available separately. Information on children below 1 year of age was available in 3 studies [4-6]; a total of 2389 out of 3873 children were below one year of age. The number of children below one year of age in oral and parenteral antibiotics group was 1205 and 1184, respectively. The proportion of infants was similar (OR 1.03; 95% CI 0.86, 1.22) in the two groups. Number of boys in oral antibiotic group and parenteral antibiotic group were 1314 and 1280, respectively (OR 1.04; 95% CI 0.92, 1.17).

Information on wheezing was available in three studies [4,5,8]. These excluded children with current wheeze with history of asthma and if their lower chest indrawing resolved with salbutamol inhalation. Information on those who had current wheeze that did not resolve with salbutamol inhalation was not available separately according to groups in one study [4]; however, information on numbers developing wheeze at 48 hours was available. Number of children with wheeze in amoxicillin group and penicillin/ampicillin group were 931 and 935, respectively (OR 1.03; 95% CI 0.79, 1.33)

Only one study [4] provided data on children with weight-for-age <–2Z. Number of children with malnutrition in those getting oral or parenteral antibiotics were 124 and 133, respectively (OR 0.91; 95% CI 0.69, 1.18).

Study by Addo-Yobo, *et al*. [4] excluded children who received antibiotics in recent past. Others [5,8] included children receiving antibiotics in recent past. Number of children in oral and parenteral groups who gave history of receiving antibiotics or their urine showed antimicrobial activities in urine were 268 and 152, respectively (OR 1.21; 95% CI 0.97, 1.50).

Etiological agents were identified in one study [4]. Respiratory Syncytial Virus (RSV) was isolated from nasopharyngeal aspirates of children getting oral or parenteral antimicrobials in 196/769 (25.5%) and 183/759 (24.1%), respectively (OR 1.05, 95% CI 0.83, 1.32). Nasopharyngeal cultures for bacterial pathogens were positive for *S. pneumoniae* and *H. influenzae* in 201/743 and 146/743, respectively in oral antibiotic group and same was 217/743 and 145/739, respectively in parenteral antibiotic group.

Three studies compared oral amoxicillin with ampicillin or penicillin [4,5,8]. One study compared oral cotrimoxazole with injectable procaine penicillin [6].

Treatment-failure rate: Failure rate in children receiving oral antibiotics was 288/2208 (13%) while that in children receiving parenteral antibiotics was 302/2183 (13.8%) (OR 0.93, 95% CI 0.78, 1.11) (***Fig.* 2**).

Among three studies [4,5,8] involving 4166 children (2145 in oral amoxicillin group and 2121 in parenteral

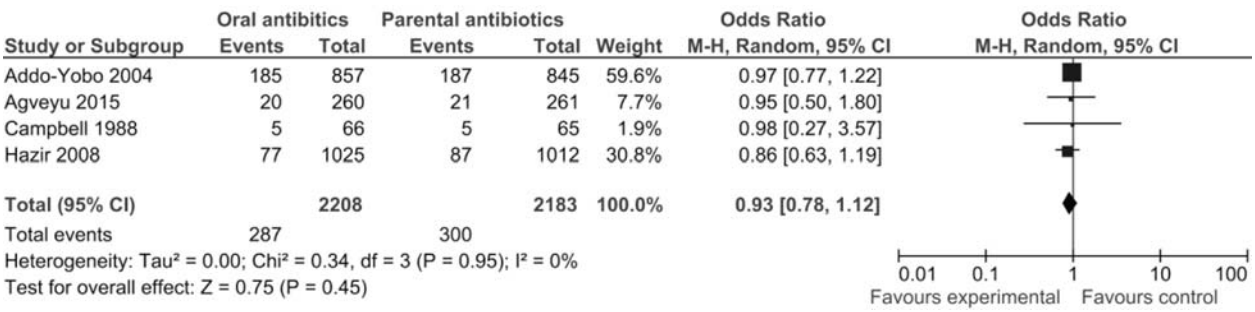

FIG. 2 *Forest-plot for Primary outcome of treatment failure rate.*

antibiotics i.e. penicillin/ampicillin, failure rates in children receiving oral amoxicillin or parenteral antibiotics were 282/2142 (13.2%) and 295/2118 (13.9%), respectively (OR 0.93; 95% CI 0.78, 1.12).

Oral cotrimoxazole was used in one study [6]. The failure rate was 6/66 (9.1%) and 7/65 (10.7%) in children receiving oral cotrimoxazole or intramuscular procaine penicillin, respectively (OR 0.83; 95% CI 0.26, 2.61).

In two studies [4,8], all enrolled subjects were admitted in beginning for atleast 48 hours. In one study [5], hospitalized children received injectable ampicillin while those receiving amoxicillin were treated on ambulatory basis. In one study [6], both the groups were treated on an ambulatory basis. The odds ratio of failure of treatment in the three studies was 0.97 [95%CI 0.77, 1.22], 0.86 [95% CI 0.63, 1.19], and 0.83 [95% CI 0.26, 2.61], respectively.

Relapse rates: Only one study reported relapse rates [5]. Number of patients who had relapse in oral antibiotics and parenteral antibiotics groups was 25/948 (2.6%) and 31/925 (3.4%), respectively (OR 0.78; 95% CI 0.46, 1.33).

Hospitalization: One study [4] was carried out in hospitalized children or at least they were admitted in hospital for 2 days. In one study [5] children receiving parenteral therapy were hospitalized at least for first two days; however, the study does not report number of children in the oral antibiotic group who required hospitalization; it suggests that those failed to treatment were given alternative therapy. One study was carried out on ambulatory basis [6]. In this study numbers requiring hospitalization in oral or parenteral antibiotic group were 3/66 (4.5%) and 2/68 (2.9%), respectively (OR 1.57; 95% CI 0.25, 9.72).

Death rates: Number of children who died in the oral antibiotics and parenteral antibiotics groups were 5/2208 (0.2%) and 15/1925 (0.8%), respectively (OR 0.3; 95% CI 0.11, 0.77).

Serious adverse events (SAE): SAE were specifically reported in one study [4]. They noted SAE in 30 children (8 in amoxicillin group and 22 in penicillin group). The SAE were deaths in 12, rash in 5, diarrhea in 5, allergy to penicillin in 2, anemia and malaria in one, severe malaria in 3 and unspecified events in 2. Thirteen of these SAE were thought to be either possibly or probably associated with the study drug, and treatment was discontinued or changed in 12 of the 13 cases – all improved subsequently. None of the deaths were attributed to study drug reaction.

Quality assessment: Three studies [4,5,8] were assessed to be of good quality except that they were not blinded (***Web Fig.* 1**). These three studies compared oral amoxicillin with parenteral antibiotics. The fourth study [6], comparing co-trimoxazole with parenteral antibiotic, had inadequate information regarding the sequence generation and allocation concealment; this was also an unblinded study. Using the GRADE framework, the available evidence is of 'High quality' (***Table* II**).

DISCUSSION

The results from this systematic review suggest that there is no significant difference in the outcome (failure rates and relapse rates) of pneumonia with chest indrawing in under-five children, between those treated with oral or parenteral antibiotics; the results were not influenced by treatment in hospital or treatment in community, the type of oral medications (amoxicillin or co-trimoxazole), etiological agents (RSV positive or negative) and presence of wheeze. Results suggest that children with pneumonia with chest indrawing (in absence of danger signs and signs of very severe pneumonia) can be treated with oral antibiotics. However, it is not possible to suggest a single antibiotic that is most effective. In present review, it was not possible to directly compare co-trimoxazole with amoxicillin.

All four included studies were carried out in low-to-

WHAT IS ALREADY KNOWN?

- Children below 5 years of age with severe pneumonia require hospitalization for treatment with intravenous antibiotics

WHAT THIS STUDY ADDS?

- Children below 5 years of age with severe pneumonia can be managed with oral antibiotics at home in absence of danger signs or signs of very severe pneumonia, with monitoring by health care workers.

middle income group of countries. Three studies were carried out in hospital (or partly in hospital) while one study was carried out completely on ambulatory basis, exclusion of which did not change the results. There were three more RCTs (that included children <60 months of age along with older children) comparing oral and parenteral treatment for severe pneumonia; these also suggest no difference in the failure rates [11,12,16]. However, the WHO definitions were not used in these studies. Two cluster-randomized controlled trials, carried out in rural Pakistan, compared home treatment of severe pneumonia with conventional treatment i.e. referral to hospital for parenteral antibiotics [9,10]. Both the studies concluded that community case management could result in a standardized treatment for children with severe pneumonia, reduce delay in treatment initiation, and reduce the costs for families and health-care systems. A multi-centric observational study [14] also reported similar results. Only one systematic review compared oral with parenteral antibiotic treatment [17] and included only one study [6]. As part of comprehensive reviews [18,19] on antibiotics for community acquired pneumonia in children, subgroup analyses were carried out to document comparison of oral *versus* parenteral antibiotics for treatment of severe pneumonia. In these reviews, three studies [4-6] were included and reported that failure rates were similar in the two groups. In the present review, we included four studies that compared oral and parenteral antibiotics in children below 60 months of age.

Mortality due to pneumonia may be affected by underlying illness like acquired immune deficiency syndrome (AIDS), congenital heart disease, severe malnutrition, and delayed intervention due to health-seeking behavior. Results of present review may not be applicable to countries with high rates of HIV infection. In one study [4] included in present review, after interim analysis of results, a modification in protocol was made to exclude children with suspected HIV infection due to higher mortality rates in countries with higher HIV infection rates. Therefore, the conclusions of present review may not be applicable to countries with high HIV infection rates.

The availability of vaccination against *S. pneumoniae* and *H. influenzae* (common organisms for community acquired pneumonia in under-five children) is expected to change the etiological agents as well as reduce mortality. This may change the approach to management of pneumonia. However, in most middle- and low-income group countries, the coverage of under-five children with these vaccines is low [20]. Therefore, the present strategies for management should be effective.

Present review has a limitation that the clinical diagnosis of pneumonia was not confirmed by other investigations in the included studies. However, it is a common practice to use only clinical criteria for the diagnosis and management of pneumonia in high burden settings.

Based on the results of the present review, we conclude that children with pneumonia with chest indrawing (severe pneumonia) from low- and middle-income countries and low rates of HIV infection may be managed with oral antibiotics at home in absence of danger signs or signs of very severe pneumonia, with monitoring by health care workers.

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