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Case Management of Childhood Pneumonia in Developing Countries

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Abstract

Pneumonia is a leading cause of morbidity and mortality in children worldwide. Appropriate management depends on accurate assessment of disease severity which for the majority of children in developing countries is based on clinical signs alone. This paper reviews recent evidence on clinical assessment and severity classification of pneumonia and reported results on the effectiveness of currently recommended treatments.

Methods: Potential studies for inclusion were identified by MEDLINE (1990 - 2006) search. The Oxford Center for Evidence Based Medicine (CEBM) criteria were used to describe the methodologic quality of selected studies.

Results: In the included studies the sensitivity of current definitions of tachypnea for diagnosing radiologic pneumonia ranged from 72% to 94% with specificities between 38% and 99%; chest indrawing had reported sensitivities of between 46-78%. Data provide some support for the value of current clinical criteria for classifying pneumonia severity with those meeting severe or very severe criteria being at considerably increased risk of death, hypoxemia or bacteraemia. Results of randomized controlled trials report clinically defined improvement at 48 hrs in at least 80% of children treated using recommended antibiotics. However, a limitation of these data may include inappropriate definitions of treatment failure. Particularly with regard to severe pneumonia issues that specifically need to be addressed are: the adequacy of penicillin monotherapy, or oral amoxicillin, or alternative antibiotics; the timing of introduction of high dose trimethoprim-sulfamethoxazole in children at risk of or known to be infected by HIV and the value of pulse oximetry.

Keywords

pneumonia; developing countries; clinical signs; case management

INTRODUCTION

Pneumonia accounts for one fifth of all childhood deaths worldwide, with approximately 2 million children dying each year.1 Several preventive interventions are or may soon be

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Authors' contributions

PA was responsible for conducting the literature searches, reviewing articles, assessing their quality, drafting and finalising the manuscript.

ME conceived of the idea for the review and was responsible for reviewing articles, assessing their quality, drafting and finalising the manuscript.

Conflicts of interest

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available to reduce this pneumonia-related mortality. Routine vaccination against *Haemophilus influenzae* Type B (HiB) has been associated with major declines in HiB morbidity.2-4 Similarly, a recent efficacy trial of a pneumococcal conjugate vaccine found 77% efficacy against invasive pneumococcal disease attributable to vaccine-serotypes, a 12% reduction in first episodes of severe pneumonia and a 16% fall in all cause mortality.5 However, the routine use of these vaccines in most developing countries is, and is likely to remain, hampered by their high price in the short to medium term.6

At present, identifying pneumonia cases and instituting appropriate antibiotic therapy is the primary strategy to reduce mortality caused by pneumonia with good evidence of effectiveness.7 Indeed, even if children benefit from both HiB and pneumococcal conjugate vaccines pneumonia will remain a major cause of morbidity and considerable mortality and thus a significant challenge to health systems. In The Gambia there were 13.4 episodes of severe pneumonia per 1000 child years in children receiving both vaccines.5 However, current case management strategies were developed more than 15 years ago and have remained largely unchanged since.8 The strategy promotes classification of a child presenting with cough or difficulty breathing as either no-pneumonia or three grades of severity: pneumonia, severe pneumonia and very severe pneumonia. This classification is intended to guide decisions on referral, antibiotic therapy, need for oxygen and intensity of monitoring, thus offering a system of prioritizing and rationalizing resource use through agreed, national policies.9

It is our experience, however, that health workers in Kenya use a variety of antibiotics in the treatment of outpatient pneumonia including cephalosporins and macrolides that are strongly promoted by the pharmaceutical industry as better or ‘stronger’ antibiotics (playing on concerns of widespread resistance to older antibiotics). For children admitted to the hospital a distinction between severe and very severe pneumonia is rarely made with the majority of children receiving therapy recommended for very severe cases.10 As the Ministry of Health in Kenya was interested in preparing and disseminating evidence based guidelines for care of children attending hospital we undertook to review the evidence supporting the case management approach to pneumonia, focusing on evidence that has emerged since the WHO guidelines were first disseminated in 1990. We anticipated that a review of such evidence might also contribute to highlighting key research needs and current and future challenges for case management both nationally and internationally.

METHODS

Search strategy and quality review

This review intended to answer questions on the performance of clinical signs in identifying pneumonia and classifying its severity. Further we intended to establish how currently recommended antibiotics perform in the treatment of pneumonia in children. Potential studies for inclusion were identified by direct searches of MEDLINE database through PubMed by use of clinical queries targeting the years 1990 to date. For areas where little or no new information exists (e.g. antibiotic treatment of very severe pneumonia) we provide information from earlier studies before 1990. The following combinations of search terms were used:

Clinical signs—pneumonia AND child* AND (raised respiratory rate OR fast breathing OR tachypnoea OR indrawing OR recession OR nasal flaring OR auscultat* OR crackle OR sign); severe pneumonia AND (risk OR predict*) AND death AND child*;

Hypoxaemia—Hypoxaemia AND predict* AND clinical signs

Antibiotics—pneumonia AND child* AND (penicillin OR amoxicillin OR chloramphenicol OR cephalosporin OR gentamicin OR cotrimoxazole)

(An asterix (*) is the truncation sign used in searching PubMed)

The specific searches on therapy were intended to identify available evidence based on recent randomized trials. However, where there were no randomized trials we briefly report findings of previous literature reviews. To ensure a comprehensive review, supplementary searches were conducted in the Cochrane library, the World Health Organization library database, and reference lists of selected studies. Each author independently reviewed the titles and available abstracts from the retrieved articles, selecting for further review those that appeared to evaluate clinical assessment or antibiotic treatment of pneumonia in children aged 1 month to 5 years. For antibiotic studies we did not exclude studies that included children outside this age bracket but studies performed in developed countries or trials of treatments not currently recommended in WHO guidelines were excluded.

The methodologic quality of the selected articles was assessed using the Oxford Center for Evidence Based Medicine (CEBM) levels of evidence, which ranks studies in a hierarchy, based on methodologic validity, with systematic review graded as level 1 (strong) evidence and expert opinion as level 5 (weak) evidence.

DEFINITIONS OF DISEASE CATEGORIES FOR PNEUMONIA

In the case management approach children are clinically identified as having pneumonia or not, the severity of the pneumonia classified and treatment appropriate to the degree of severity provided. The guidelines recommend cough or difficult breathing as the entry criteria for a diagnosis of pneumonia.9 If these entry criteria are met pneumonia is defined as tachypnea (respiratory rate ≥ 50 breaths per minute in an infant, or ≥ 40 breaths per minute in children one year or older); children with cough or difficult breathing and chest indrawing are considered to have severe pneumonia; and presence of a danger sign specifically central cyanosis, or severe respiratory distress or inability to drink in a child with cough or difficult breathing is classified as very severe pneumonia.

CLINICAL FEATURES OF PNEUMONIA IN CHILDREN

A problem in summarizing the evidence from available research is the lack of consistency in definitions of pneumonia that are used as the gold standard. In recent studies attempts have been made to provide more objective, generalisable and reliable criteria that include radiology and a combination of radiology and clinical data. However, not infrequently the gold standard has been a physician's or pediatrician's opinion. It is also important to realize that the clinical case definitions have tended to ensure high sensitivity while seeking to preserve specificity as much as possible. The clear imperative being to avoid failing to treat significant bacterial pneumonia. Although in traditional clinical practice diagnosis of pneumonia has been based on auscultation, signs detected by observation are associated with better inter-rater agreement (kappa values 0.3 and 0.46-0.6 respectively).11,12

The ability of clinical signs to predict radiologic pneumonia

The utility of simple clinical signs like rapid breathing and chest indrawing to diagnose pneumonia in infants and young children has been well established. 13-15 Table 1 summarizes recent formal studies that have measured sensitivities and specificities of clinical signs for radiologic pneumonia either at the time of presentation or during the course of hospitalization. 16-21

The reported value of adding another clinical sign to respiratory rate or chest indrawing such that two signs are a requirement for defining disease status in pneumonia has been variable. In Mexico, Palafox *et al*17 found that tachypnea, chest indrawing and crackles were the clinical signs that, alone or combined, showed a sensitivity of greater than 40% for identifying pneumonia. The combination of tachypnea and chest indrawing improved specificity (69%) but sensitivity (68%) was relatively low. Further combinations of crackles with tachypnea or chest indrawing or a combination of these three signs improved specificity (80-84%), but had low sensitivity (43-46%). (See table 1)

Predicting severity of disease and mortality in ALRI using clinical signs

A prime goal of clinical assessment is the detection of severe disease episodes on the assumption that these children are most likely to benefit from treatment. It is commonly accepted that death, as the most severe consequence of disease, is an important gold standard outcome. An alternative and plausible gold standard for the presence of severe disease is the presence of hypoxemia, a clear indication for supportive, inpatient therapy and a condition likely to be on the causal pathway to mortality.22,23 Further possible gold standards for severe disease include the presence of confirmed bacteraemia in association with pneumonia,24 and a senior clinical opinion that inpatient management is necessary.

Prediction of mortality and bacteraemia—Early studies from Papua New Guinea documented failure to feed or inability to drink and cyanosis to be significant and independent risk factors of mortality in ALRI.25,26 In practice, most of the children who are unable to drink or feed will have impaired consciousness or lethargy, which the WHO also recommends for identification of children with very severe pneumonia.9

In a subsequent study conducted in India,27 ALRI mortality was related to severity of WHO classification; none of the children with a diagnosis of pneumonia died while 10 (8.7%) children with severe pneumonia and 8 (47%) with very severe pneumonia died. Independent and significant predictors of mortality in this series included inability to feed, weight for age Z score <−3, and a short duration of fever. Similarly, Pepin *et al*28 found that mortality was highest among children who satisfied the severe pneumonia definition. Among the children considered to have severe pneumonia the number of deaths was higher in those who fulfilled the very severe disease definition (31/132 v 12/106; P=0.02). However, the very severe disease definition did not predict death when used in children who did not also qualify for the diagnosis of severe pneumonia (defined by the presence of indrawing). A recent study conducted among acute paediatric admissions found that simple clinical syndromes based on WHO IMCI guidelines identified 80% of children with an invasive bacterial infection and 93% of subsequent inpatient deaths.29 It should be noted that in this study young infants, children with severe malnutrition and children with signs also suggesting meningitis could not also have a diagnosis of pneumonia. Among children with a pneumonia syndrome the prevalence of invasive bacterial infection with very severe pneumonia was 11% while for severe pneumonia it was similar to that among inpatients with signs of pneumonia (6% versus 6.7%), but case fatality was greater: 15 out of 1037 (1.5%) children with pneumonia, 52 out of 1740 (3.5%) with severe pneumonia and 56 out of 296 (19%) with very severe pneumonia died. No attempt was made to examine whether additional or alternative clinical signs could improve the performance of syndrome definitions.

Hypoxemia

The frequency of hypoxemia is about 5 and 8 times higher in children with ARI in emergency departments and inpatient wards, respectively, than in cases cared for in out-patient clinics.30 It is also associated with a two- to five-fold increase in the risk of death from pneumonia.23,31-34 It is therefore important that hypoxemia is detected early and

accurately and oxygen administration initiated immediately to those needing it. Although hypoxemia is defined by varying thresholds of oxygen saturation depending on altitude (ref Lozano) current general guidelines suggest oxygen administration to a child with a measured oxygen saturation < 90% 90ref Blue book). Where oxygen saturation is not available current guidelines recommend that oxygen should be administered to all children with very severe pneumonia and those with a respiratory rate ≥ 70 breaths per minute amongst those with severe pneumonia [ref is WHO Blue book].

Accuracy of clinical signs for detecting hypoxemia—The unavailability of pulse oximetry in resource-poor settings has prompted several studies to assess the accuracy of clinical signs for detecting hypoxemia defined by pulse oximetry cut-offs. Recently, three studies from Nepal,35 India, 36 and Papua New Guinea37 confirmed the findings of an earlier review 38 reporting that no single clinical sign can predict hypoxemia with sufficient accuracy and reliability. In a study conducted among 150 children with pneumonia in Nepal 35 chest indrawing was the best predictor of hypoxemia (SpO_2< 90%) with 69% sensitivity and 83% specificity. On univariate analysis studies consistently demonstrate that central cyanosis,35-37 grunting 35,37 or inability to breastfeed35 are statistically associated with hypoxemia. However, it is noteworthy that a sign like cyanosis is highly specific for hypoxemia (specificities of 84-100% across studies32,33,36,37,39) making it useful for confirming hypoxemia but it's low sensitivity (9-42% in the same studies) means that inability to detect cyanosis does not rule out hypoxemia. The implication of the low sensitivity of signs of hypoxemia in the clinical setting is that some children with severe pneumonia who need oxygen will not receive it if administration is only based on clinical evaluation in accordance with current guidelines. However, therapy based on signs with very high sensitivity for identifying hypoxemia would be associated with low specificity resulting in frequent inappropriate administration of oxygen, a resource often expensive and in limited supply in low income countries.

ANTIBIOTIC MANAGEMENT OF PNEUMONIA

Non-severe pneumonia

For children with non-severe pneumonia, the WHO recommends treating the child as an outpatient using oral trimethoprim-sulfamethoxazole(TMP-SMX) or, as second line, oral amoxicillin for 5 days.9 However, a recent IMCI technical update recommends administering oral antibiotics for 3 days in children in non-HIV endemic areas.40 Recent data supporting these new recommendations are now summarized. Data describing the clinical efficacy of the regimen in different settings and the definitions of treatment failure commonly used are presented in Table 2.41-49

Treatment frequency—The pharmacokinetics of a 12 hourly regimen for amoxicillin (25 mg/kg/dose) was compared to 8 hourly dosing (15 mg/kg/dose) in Brazilian children 3 months to 5 years of age admitted to hospital with non-severe pneumonia.50 The mean plasma amoxicillin concentrations were generally higher after the 25mg/kg dose than after 15mg/kg dose, and remained above a given MIC of ≥1.0 g/ml for over 50% of the dosing interval in the majority of the children after both regimens.

The twice-daily regimen for amoxicillin was piloted in a randomized trial of 1459 children aged 2-59 months in Pakistan.43 A regimen that consisted of 25 mg/kg amoxicillin was compared to TMP-SMX (4 mg/kg TMP and 20 mg/kg SMX), both given twice daily for 5 days. Both amoxicillin and TMP-SMX provided similarly effective therapy with clinical cure rates of 83.9% and 81.1% respectively.

Duration of treatment—Two studies on duration of antibiotic treatment and outcomes from India (n=2188) and Pakistan (n=2000) showed similar treatment outcomes for children receiving 15 mg/kg oral amoxicillin every 8h for either 3 days or 5 days. 42,47 The clinical efficacy of 3- day and 5-day amoxicillin regimens were similar with reported treatment failure rates of 10.5% versus 10.1% in one study and 21% versus 20% in the other. In both studies rates of relapse were similar for both treatment regimens. For TMP-SMX, results of a multicenter study carried out in Bangladesh and Indonesia, among 2022 children with non-severe pneumonia, showed the overall 15-day cure rate was similar in the 3-day group (83.9%) and the 5-day group (84.3%).51

The comparative trials of amoxicillin and TMP-SMX discussed above 43,48 have recently been examined in a meta-analysis as part of a Cochrane Review52 that reports an increased treatment failure rate if treatment is with TMP-SMX (OR=1.33; 95% CI=1.05-1.67). However, this meta-analysis includes a sub-group of children with severe pneumonia from one study who fared worse if treated with TMP-SMX.48

Severe pneumonia

In the treatment of severe pneumonia in hospitalized children the policy option adopted by many low-income countries is for initial parenteral treatment with benzylpenicillin before changing to oral amoxicillin when the child improves (Table 3).

A multicenter study undertaken in 8 developing countries in Africa, Asia and South America compared the efficacy of oral with intravenous antibiotics for 1702 children admitted with severe pneumonia and able to tolerate oral medication.44 The trial showed that oral amoxicillin (45mg/kg/day in three doses) and injectable penicillin (200 000 IU/kg per day in four doses) are equivalent in terms of a primary outcome of treatment failure at 48h - 19% in both groups; Table 2. A sub-analysis of this study reported failure of standard WHO antimicrobial therapy among children with mild or asymptomatic HIV and severe pneumonia in two sites with high HIV prevalence in Africa.53 One hundred and six (23%) out of the 406 participants with known HIV status were infected; 34 (32.1%) HIV infected children failed therapy compared with 76 (21.2%) uninfected children (Adjusted Odds ratio 1.88; 95%CI 1.11-3.17). Notably, the 48 hour failure rates between HIV infected and uninfected children did not differ by treatment assignment.

Very severe pneumonia

Chloramphenicol is recommended for the treatment of children with very severe pneumonia in low income settings with benzylpenicillin and gentamicin given in combination as an alternative (Table 3). The use of chloramphenicol alone is supported by data from Papua New Guinea where Shann *et al*46 randomized 748 children with severe pneumonia to receive either chloramphenicol alone (25 mg/kg 6 hourly) or chloramphenicol plus penicillin (250 000 to 500 000 units 6 hourly). The treatment failure rate was lower in the chloramphenicol alone group, though this difference did not attain statistical significance [risk difference, 4·8%±5·2%(±95% CI)].

A more recent randomized trial of chloramphenicol (25 mg/kg every 6 hours) compared with benzylpenicillin (50 mg/kg every 6 hours) plus gentamicin (7·5 mg/kg daily) among 1116 children with severe or very severe pneumonia also in Papua New Guinea found no difference between the treatment groups in regard to mortality, treatment failure, or readmission.45 Treatment failure was considered a primary outcome only if it required a change of antibiotic. More children treated with chloramphenicol than penicillin plus gentamicin represented with severe pneumonia within one month of hospital discharge (50/559 versus 32/557 children; p=0·03). HIV infection was identified as one of the factors

underlying treatment failure. In a report of an unpublished study of another trial conducted in 7 countries with 958 children the combination of ampicillin plus gentamicin was said to be superior to use of chloramphenicol alone. (Relative risk of therapy failure, 1.5; 95% CI: 1.1-2.1).40

Defining treatment failure

Most recent antibiotic treatment studies conducted in developing countries have examined treatment failure as a primary outcome. Based on findings during clinical assessment after completing a period of therapy about 10 to 20 percent of children were classified as treatment failures (Table 2). Concerns have been raised recently over the appropriateness of the criteria used for defining treatment failure in these studies. 41,49 These definitions generally comprised of two factors: the clinical criteria for determining therapy success or failure and the time allowed before this assessment is done.

Clinical criteria for treatment failure—To be classified as improved on day 2, WHO guidelines require “slower breathing, less fever, eating better”; 8,9,54 these are non specific and could be clarified further. The operational definition for “slower breathing” used in most of the studies was a decrease in respiratory rate of more than 5 breaths per min or a return to normal range for age. It should be noted that children who had a decrease in respiratory rate less than 5 breaths per minute compared with their admission evaluation were considered “the same”, representative of a treatment failure and had their treatment changed, along with those who worsened (developed severe pneumonia). In the trials very few children were “worse”; most of the children who required treatment change were “unchanged” (table 2). The high treatment failure rates could therefore have been caused by these very conservative criteria and Rasmussen *et al*41 noted that if improvement had been defined as a decrease in respiratory rate of more than 3 or 4 breaths per minute the failure rate would be lower. A more recent study49 that considered only children classified as “worse” to have failed therapy reported day 5 failure in 20 (4.5%)of the children randomized to receive double dose amoxicillin and 25 (5.7%) children receiving standard dose amoxicillin for non severe pneumonia. The difference in treatment failure rates between the standard and double dose groups was not statistically significant (P=0.55).

Timing of clinical assessment—According to treatment guidelines the child treated as an outpatient or inpatient should be reviewed by the clinician if deteriorating or if not improving after 48 hours on treatment and changed to the second-line antibiotic.8,9 In a study41 that evaluated these WHO criteria for treatment failure re-evaluation on day 2 was appropriate since 68/76 (89·4%) of those who became worse were detected on day 2. However, in the same study the majority of the children with non-severe pneumonia who according to the guidelines should have had their therapy changed at 48 hrs, but did not, recovered on initial therapy. The treatment failure definition therefore overestimated clinical failure significantly. Similarly, the definition used in severe pneumonia is likely to overestimate treatment failure rates: Addo-Yobo *et al*44 observed that the majority of children described as having failed treatment at 48 hours based on the presence of persistent chest indrawing only resolved their illness soon thereafter. It seems therefore that while follow up at 48 hours and continuous monitoring of children on treatment for pneumonia is important, decisions regarding treatment change might be delayed in children described as being the same while the change should be immediate in those children whose condition is deteriorating.

Conclusions

Although there are difficulties with the standard definition of pneumonia, recent data do not suggest that the current WHO criteria for pneumonia can be easily improved. Current

definitions of severe and very severe disease are associated with increased mortality and other markers of biologically severe illness supporting their continued use in the absence of improved definitions. Treatment with recommended antibiotics remains effective in at least 80% of cases where studies have been done. Reasonable changes in the definitions of treatment failure for pneumonia would suggest that these treatment success rates are conservative. There has been little work on treatment failure definitions in severe or very severe pneumonia.

Further reduction of the burden of pneumonia morbidity and mortality is a priority, and there is an urgent need to implement interventions of proven efficacy including HiB and pneumococcal vaccines. Even when these interventions are implemented, however, there will be a need for evidence based case management guidelines. Issues that need to be addressed to develop these strategies for the next decade include:

1) Development of clinically appropriate definitions of treatment failure for each severity classification to provide some standard basis for assessing results of trials.

2) Adequately powered comparative studies with clinically important endpoints of penicillin monotherapy with oral amoxicillin or alternative antibiotics in the treatment of severe pneumonia in African children.

3) Adequately powered comparative studies, with clinically important endpoints, of broad spectrum regimens for the treatment of very severe pneumonia.

4) The value and cost-effectiveness of routine pulse oximetry in determining the use of oxygen in children presenting with severe or very severe pneumonia.

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TABLE 1

Studies reporting sensitivity and specificity of signs in diagnosing radiological pneumonia

Author	**March et al18**	**Palafox et al19**	**Cherian et al20***	**Falade et al21***	**Lozano et al22**	**Singhi et al23**
Location	**Brazil**	**Mexico**	**India**	**The Gambia**	**Colombia**	**India**
Level of evidence**	**1b**	**1b**	**1b**	**1b**	**1b**	**1b**
Definition of radiologic pneumonia	Opacity or pleural effusion on CXR	Presence of macro- or micro-nodular infiltrates or condensation in the lung	Pulmonary consolidation, infiltrates or pleural fluid or air in pleural space	Definite radiological consolidation or radiograph compatible with pneumonia plus crackles	Presence of alveolar or interstitial infiltrate in the chest radiograph.	Interstitial or alveolar infiltrates, lobar or segmental consolidation and air bronchograms
Age group studied	0-6 months	0-59 months	0-71 months	2-59 months	< 36 months	2-36 months
No. of children studied	76	110	758	742	200	854
Tachypnoea	77/39	74/67	81/86 (Normal) 78/76 (Stunted) 86/82 (Wasted) 85/86 (Stunted and wasted)	79/65(well nourished) 61/79(malnourished)	76/71	91/94 (2-6 months) 83/96 (7-11months) 94/98 (12-35months) 72/97 (≥ 36months)
Chest indrawing	47/80	71/59	78/97 (Normal) 80/99 (Stunted) 88/97 (Wasted) 85/100 (Stunted and wasted)	27† (well nourished) 17† (malnourished)	81/36	
Nasal flaring				19† (well nourished) 19† (malnourished)	56/53	89/90 (2-6 months) 88/98 (7-11months) 84/99 (12-35months) 75/99 (≥ 36months)
Crackles		46/79			80/55	
Tachypnoea and indrawing		68/69				95/91 (2-6 months) 89/92 (7-11months) 94/96 (12-35months) 76/95 (≥ 36months)
Tachypnoea and crackles		46/83				

*Sensitivities and specificities based on nutritional categories

**Validating cohort studies with good reference standards

†Values indicate sensitivity; specificity not reported

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TABLE 2

Outcomes defining treatment failure and rates of therapy failure in recent treatment studies *

Reference	Age (number of children enrolled in study)	Setting & year of publication	Treatment given	Definition of treatment failure	No. of children with outcome constituting treatment failure (%)				
					Need to change antibiotic/no improvement	Death	Loss to follow up / withdrawal	Other reasons	Total failure rates
Non-severe pneumonia									
Hazir et al52	2-59 months (876)	Outpatient, Pakistan	Standard or double dose oral amoxicillin for 3 days	Only children classified as worse ie developed lower chest indrawing or any other danger sign (Cyanosis, inability to drink, abnormally sleepy, convulsions)	61(6.96)	-	-	-	61 (6.96) [25 (5.7) in standard and 35 (7.9) in double dose groups]
Rasmussen at al 44	2-59 months (1144)	Outpatient, Pakistan; 2005	Standard or double dose oral cotrimoxazole	Need to change therapy (condition same or worse), death, loss to follow up	198 (17·3)	1 (0·001)	32 (2·8)	-	230 (20·3)
Agarwal et al50	2-59 months (2188)	Outpatient, India; 2004	Three- or five-day treatment with oral amoxicillin	Development of chest indrawing, drowsiness, convulsions or inability to drink, Sao_2 <90% on day 3; increased respiration on/after day 3, withdrawal.	96 (4·4)	-	129 (5·9)	-	225 (10·3)
MASCOT45	2-59 months (2000)	Outpatient, Pakistan; 2002	Three- or five-day amoxicillin	Treatment change up to 5 days after enrollment (due to persisting fast breathing on day 3-5), developed severe pneumonia/disease, death, no improvement.	338 (16·9)	1	32 (1·6)	40 (2)	411 (20·6)
CATCHUP46	2-59 months (1459)	Outpatient, India; 2002	Twice daily amoxicillin or cotrimoxazole	Loss to follow up, death, antibiotic change	219 (15)	1	30 (2·1)	6 (0·004)	256 (17·5)
Study enrolling patients with non severe pneumonia and severe pneumonia									

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Reference	Age (number of children enrolled in study)	Setting & year of publication	Treatment given	Definition of treatment failure	No. of children with outcome constituting treatment failure (%)				
					Need to change antibiotic/no improvement	Death	Loss to follow up / withdrawal	Other reasons	Total failure rates
Strauss et al51	2-59 months (595)	Outpatient and inpatient wards, Pakistan; 1998	Oral cotrimoxazole or oral amoxicillin	One or more of: oxygen saturation 87% or less for more than 30 minutes when the child is calm, prolonged tachypnoea (≥ 2h), presence of any danger sign, no improvement after 48h therapy or deterioration in the opinion of a senior clinician.	11(1.8)	1		111(18.7)[†]	122 (20.5) [Cotrimoxazole 92 (23) Amoxicillin 30 (15); Odds ratio (95% CI) 1.67 (1.06-2.63)]
Severe pneumonia									
Addo-Yobo et al47	3-59 months (1702)	Inpatient, International multi center; 2004	Parenteral penicillin or oral amoxicillin	Any of the following (up to or at the first 48 h): Danger signs, low SaO_2, persisting indrawing, serious adverse drug reaction, received another antibiotic, newly diagnosed comorbidity, consent withdrawal, discharge against medical advice, death	310(18·2)	7(0·4)	11(0·6)	-	328(19)
Very severe pneumonia									
Duke et al48	1-59 months (1116)	Inpatient, Papua New Guinea; 2002	Chloramphenicol or penicillin and gentamicin	Presence of 4 or more of the following (after 5 days of completed treatment): fever; tachypnoea or apnoeas; moderate or severe chest indrawings; chest crepitations or bronchial breath sounds; SaO2 not improved from admission;	119(10·7)	7(0·6)	-	82(7·3)	208(18·6)

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Reference	Age (number of children enrolled in study)	Setting & year of publication	Treatment given	Definition of treatment failure	No. of children with outcome constituting treatment failure (%)				
					Need to change antibiotic/no improvement	Death	Loss to follow up / withdrawal	Other reasons	Total failure rates
				worsening radiologic changes on CXR. OR death OR readmission within 1 month.					
Shann et al49	(748)	Inpatient, Papua New Guinea; 1985	Chloramphenicol alone or chloramphenicol and penicillin	Death or withdrawal for change of antibiotic	9(1·2)	110(14·7)	-	-	119(15·9)

Figures in parentheses are percentages unless indicated otherwise.

*All studies graded as level 1b evidence (Oxford CEBM)

†Study did not classify children who failed treatment according to outcomes constituting therapy failure

TABLE 3

Recommended antibiotic treatment for children with pneumonia11

Drug	Dose	Frequency (× daily)	Duration (days)
Oral treatments: Non severe pneumonia			
Amoxicillin	15 mg/ kg	3	5
Cotrimoxazole	4mg/ kg trimethoprim 20 mg/ kg sulfamethoxazole	2	5
Short course regime			
Amoxicillin	25 mg/ kg	2	3
Cotrimoxazole	4mg/ kg trimethoprim 20 mg/kg sulfamethoxazole	2	3
Intravenous treatments: severe pneumonia			
Benzyl penicillin	50 000 units/ kg	4	Until child improves *
Intravenous treatments: Very severe pneumonia			
Chloramphenicol	25 mg/kg	3	Until child improves †
Benzyl penicillin plus gentamicin	50 000 units/ kg (benzyl penicillin); 7.5 ml/ kg (gentamicin)	4 (penicillin) 1 (gentamicin)	10

* Then switch to oral amoxicillin for 5 days

† Then continue orally 3 times a day for a total course of 10 days