ORIGINAL ARTICLE

Comparison of standard versus double dose of amoxicillin in the treatment of non-severe pneumonia in children aged 2–59 months: a multi-centre, double blind, randomised controlled trial in Pakistan

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Arch Dis Child 2007;92:291–297. doi: 10.1136/adc.2005.092494

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Accepted 7 March 2006
Published Online First
17 March 2006

Introduction: WHO pneumonia case management guidelines recommend oral amoxicillin as first line treatment for non-severe pneumonia. Increasing treatment failure rates have been reported over a period of time, which could possibly be due to increasing minimum inhibitory concentrations of *Streptococcus pneumoniae* and *Haemophilus influenzae* for amoxicillin. Microbiological data show that this resistance can be overcome by increasing amoxicillin dosage. Based on this data, we examined whether we can improve the clinical outcome in non-severe pneumonia by doubling the dose of amoxicillin.

Methods: A double blind randomised controlled trial was conducted in the outpatient departments of four large hospitals in Pakistan. Children aged 2–59 months with non-severe pneumonia were randomised to receive either standard (45 mg/kg/day) or double dose (90 mg/kg/day) oral amoxicillin for 3 days and then followed up for 14 days. Final outcome was treatment failure by day 5.

Results: From September 2003 to June 2004, 876 children completed the study. 437 were randomised to standard and 439 to double dose oral amoxicillin. 20 (4.5%) children in the standard and 25 (5.7%) in the double dose group had therapy failure by day 5. Including the relapses, by day 14 there were 26 (5.9%) cumulative therapy failures with standard and 35 (7.9%) with double dose amoxicillin. These differences were not statistically significant ($p=0.55$ and $p=0.29$, respectively).

Conclusion: Clinical outcome in children aged 2–59 months with non-severe pneumonia is the same with standard and double dose oral amoxicillin. Non-severe pneumonia can be treated effectively and safely with a 3 day course of a standard dose.

The WHO acute respiratory infection (ARI) standard case management guidelines recommend oral cotrimoxazole or oral amoxicillin for the treatment of non-severe pneumonia¹ and have effectively reduced deaths from pneumonia.² Several clinical efficacy studies have demonstrated an increase in treatment failure rates with oral amoxicillin from 12% in 1991–92 to 19% in 2000–01 in Pakistan.^{3–5} Similar trends have been reported from India,⁶ Bangladesh and Indonesia.⁷ The reasons for this increase in failure rate are not entirely clear, but antimicrobial resistance could be one possibility. In vitro resistance of *Streptococcus pneumoniae* and *Haemophilus influenzae*, the commonest bacteria causing childhood pneumonia, has been reported from Pakistan^{8–12}; however, for pneumonia the direct relationship of laboratory resistance to clinical failure is debatable.^{3 13–15}

Increasing the amoxicillin dose to achieve higher minimum inhibitory concentrations can result in a more complete eradication of bacteria.^{16 17} A high-dose 3 day amoxicillin course was reportedly as effective as a 5 day standard dose course for the treatment of otitis media.¹⁸ The American Academy of Pediatrics believes that by recommending empiric initial treatment of acute otitis media with high-dose oral amoxicillin (80–90 mg/kg/day), antimicrobial resistance to pneumococci can be overcome.¹⁹

To our knowledge, no clinical trial has studied this issue as regards the clinical outcome in childhood pneumonia. Thus, in a multi-centre, double blind, randomised controlled trial we compared a standard dose (45 mg/kg/day) course of oral

amoxicillin with a double dose (80–90 mg/kg/day) course for the treatment of non-severe pneumonia in children less than 5 years of age.

METHODS

Study design

A multi-centre, double blind, randomised trial was conducted in the outpatient departments of four hospitals in Pakistan: Children's Hospital, Islamabad; Children's Hospital, Lahore; Nishtar Hospital, Multan; and Rawalpindi General Hospital, Rawalpindi. The trial was approved by the Institutional Ethics

Table 1 Classification of acute respiratory infection (ARI) in children presenting with cough and/or difficult breathing¹

Acute respiratory infection	Symptoms
No pneumonia (cough and cold)	RR: <50 (infants 2–11 months) RR: <40 (children 12–59 months) No LCI
Non-severe pneumonia	RR: ≥50 (infants 2–11 months) RR: ≥40 (children 12–59 months) No LCI
Severe pneumonia	LCI with or without rapid breathing
Very severe disease	Unable to drink, convulsions, abnormally sleepy or difficult to wake, stridor in calm child or clinically severe malnutrition

LCI, lower chest indrawing; RR, respiratory rate per minute.

Table 2 WHO ARI case management guideline definitions compared with clinical outcome definitions used in this study

	WHO criteria ¹	This study
Clinical resolution	Not specified but assumes that respiratory rate (RR) is less than age specific range*	RR less than age specific range*
Improved	RR below the age specific range without LCI or danger signs†	RR more than 5 breaths/min lower than baseline recording
Same	RR above the age specific range without LCI or danger signs†	RR above the age specific range but ± 5 breaths/min to the Developed LCI or any of the danger signs†
Worse	Developed LCI or any of the danger signs	Development of any sign of pneumonia between day 6 and 14 after fast breathing has disappeared
Relapse	Not specified	All children classified as "Clinical resolution", "Improved" or "Same"
Therapy success	Only children classified as "Clinical resolution" or "Improved"	Only children classified as "Worse"
Therapy failure	All children classified either as "Same" or "Worse"	

*Respiratory rate/min: 2–11 months ≥ 50 , 12–59 months ≥ 40 ; †central cyanosis, inability to drink, abnormally sleepy, convulsions. LCI, lower chest indrawing.

Review Board of Pakistan Institute of Medical Sciences, Islamabad.

Patients

Children aged 2–59 months with cough and difficult breathing were screened and classified using a standard WHO algorithm¹ for ARI case management (table 1). We only included children with non-severe pneumonia and excluded those with underlying chronic illness, a history of three or more episodes of wheeze or acute bronchial asthma and who had used any antibiotic during the previous 48 h. To ensure good follow-up, only children who lived within the municipal limits of urban regions and within walking distance in rural regions were enrolled. All care givers gave verbal, witnessed informed consent.

Procedures

Children were randomised to receive either a standard dose (45 mg/kg/day) or a double dose (90 mg/kg/day) divided into

three equal doses of oral amoxicillin for 3 days and sent home. Oral salbutamol and paracetamol were given when needed.

Randomisation

The randomisation scheme was generated by an individual not associated with patient care at the Children's Hospital, Islamabad with uneven blocks of two, four and six. Oral amoxicillin in the dosage of 125 mg/5 ml and 250 mg/5 ml was provided by Novartis Pharma (Karachi, Pakistan). Both preparations had identical packaging, taste, smell and colour.

Null hypothesis

Therapy outcome with the double dose should be no different from that with the standard dose of amoxicillin when used for 3 days for the treatment of non-severe pneumonia in 2–59 month old children. The study outcome was treatment failure by day 5 (table 2).

Respiratory rate was counted twice for 1 min each within 5 min when the child was quiet, feeding or asleep. We used the

Figure 1 Trial profile.

Table 3 Baseline characteristics of all patients in the two treatment groups (n = 876)

Baseline characteristics	Standard dose (n = 437)	Double dose (n = 439)
Demographic variables		
Sex, male (%)	284 (65.0%)	276 (62.9%)
Age in months		
Mean ($\pm$ SD)	12.6 ($\pm$ 11.5)	12.3 ($\pm$ 10.9)
Median (IQR)	8.0 (5–16.5)	8.0 (5–15.0)
Age categories in months		
2–5	145 (33.2%)	132 (30.1%)
6–11	128 (29.3%)	142 (32.3%)
12–23	92 (21.1%)	98 (22.3%)
24–59	72 (16.5%)	67 (15.3%)
History		
Duration of illness in days		
Mean ($\pm$ SD)	2.8 ($\pm$ 1.63)	2.8 ($\pm$ 1.70)
Median (IQR)	3.0 (2.0–3.0)	2.0 (2.0–3.0)
Duration of illness categories		
0–3 days	334 (76.4%)	342 (77.9%)
Median (IQR)	2.0 (2.0–3.0)	2.0 (2.0–3.0)
4 days or more	103 (23.6%)	97 (22.1%)
Median (IQR)	5.0 (4.0–6.0)	5.0 (4.0–6.0)
Fever	346 (79.2%)	340 (77.4%)
Cough	436 (99.8%)	436 (99.3%)
Difficult breathing	366 (83.8%)	375 (85.4%)
Vomiting	79 (18.1%)	71 (16.2%)
Breast feeding, yes	284 (64.9%)	279 (63.5%)
Breast feeding with age categories		
2–5 months	129 (45.4%)	121 (41.9%)
6–11 months	111 (39.1%)	115 (39.8%)
12–23 months	42 (14.8%)	42 (14.5%)
24–59 months	2 (0.7%)	1 (0.3%)
Past history of wheeze	14 (3.2%)	20 (4.6%)
Signs on examination		
Wheezing, yes	179 (40.9%)	190 (43.2%)
Wheezing with age categories		
2–5 months	75 (41.9%)	72 (37.9%)
6–11 months	55 (30.7%)	63 (33.2%)
12–23 months	31 (17.3%)	35 (18.4%)
24–59 months	18 (10.1%)	20 (10.5%)
Temperature in °C		
Mean ($\pm$ SD)	37.2 ($\pm$ 0.4)	37.2 ($\pm$ 0.54)
Median (IQR)	37.2 (37–37.2)	37.2 (37–37.3)
Temperature categories		
$\leq$ 37.7°C	376 (86.0%)	372 (84.7%)
Median (IQR)	37.2 (37–37.2)	37.2 (37–37.2)
> 37.7°C	61 (14.0%)	67 (15.3%)
Median (IQR)	37.7 (37.7–38.1)	37.8 (37.7–38.4)
Respiratory rate/min with age categories		
2–11 months		
Mean ($\pm$ SD)	57.5 ($\pm$ 6.6)	57.4 ($\pm$ 6.5)
Median (IQR)	55.0 (53.0–60.0)	55.5 (53.0–60.0)
12–59 months		
Mean ($\pm$ SD)	47.9 ($\pm$ 5.7)	48.6 ($\pm$ 6.5)
Median (IQR)	46.5 (44.0–50.0)	46.0 (44.2–51.7)

37.7°C = 100°F. IQR, interquartile range.

average value of the two readings. If the difference between the two readings was >5 breaths per minute, we took a third reading. The average of the two readings with a difference of <5 breaths per minute was selected. A wheezy child was given three doses of nebulised salbutamol 15 min apart and reassessed. Febrile children were given paracetamol before assessment. All study physicians responsible for data collection were trained in standard WHO ARI case management guidelines and in the study methodology used at the Children's Hospital, Islamabad. A senior paediatrician at each site supervised all procedures.

Follow-up of patients

The study physicians reassessed all enrolled children at first follow-up (day 3), second follow-up (day 5) and third follow-up (day 14) visits. Day of enrolment was counted as day 0. Patients who did not attend for follow-up on the specified date

were assessed the next day at the child's home. If the child was not available on that day, one or more attempts were made before declaring the child as lost to follow-up.

Study definitions

WHO definitions for treatment failure were modified (table 2).

Current WHO standard ARI case management guidelines classify all children who are the same and have not improved on first follow-up as treatment failure¹ and recommend changing the antibiotic to a second line drug. As a departure from these guidelines we stopped treatment in all patients who were categorised as same and followed them until day 14.

Final outcome was assessed on day 5. Children were categorised as clinical failure if they still had a respiratory rate above the age-specific range, had developed severe pneumonia or had very severe pneumonia/disease. All other children were labelled as clinical resolution.

Therapy change

Children with clinical failure by day 5 or those with a relapse by day 14 were treated with an appropriate second line antibiotic.

Patients who developed severe pneumonia or very severe disease (table 1) were referred for hospitalisation. All patients in whom treatment was changed were re-assessed after 48 h and followed up until well.

Adherence

All bottles had a sticker with nine squares and the care giver was instructed to tick a square each time a dose was administered and asked to bring back the medicine bottle on day 3 follow-up. All bottles were inspected at follow-up and any remaining drug was measured with specially designed adherence cards. The patient was judged adherent if s/he had taken 80% of the required dose and the amount of remaining drug matched the number of squares ticked.

Laboratory investigations

Chest radiographs were obtained for all patients at enrolment and read by the paediatric radiologist at the Children's Hospital, Islamabad according to the WHO Pneumonia Vaccine Trialists Group training program for the standardised diagnosis of radiological pneumonia.²⁰

Sample size

The sample size was designed to show no difference in clinical outcome in the two treatment arms and was calculated by using the EPI Info 6.04d database program (Centers for Disease Control and Prevention, Atlanta, GA, USA). A standard formula to estimate difference was used.²¹ Results of a previous similar trial⁴ showed a 19.0% clinical failure rate with a standard dose of amoxicillin using the WHO treatment failure definition.¹ We assumed that with our modified treatment failure definition, the treatment failure rate would not be more than 17.0% with standard dose and 10.0% with double dose amoxicillin. For an α of 0.05, β of 0.20 and assuming 5% loss to follow-up, the estimated sample size was 843 children.

Data collection and analysis

Autocopying case report forms were used for data collection and one copy was sent to the coordinating centre for data entry. Based on the randomisation sequence, each record had a unique identification number. Data were entered twice and validated. The EPI Info 6.04d database program and SPSS 11.0 (SPSS, Chicago, IL, USA) were used for analysis. Primary outcome was analysed by intention to treat and other analysis was carried out per protocol. The baseline characteristics of the two treatment arms and those who failed therapy versus those

Table 4 Baseline characteristics of treatment failures and relapses

Baseline characteristics	Treatment failures		Relapses	
	Standard dose (n = 20)	Double dose (n = 25)	Standard dose (n = 6)	Double dose (n = 10)
Sex, male	13 (65.0%)	17 (68.0%)	5 (83.3%)	6 (60.0%)
Age in months				
Mean ($\pm$ SD)	7.6 ($\pm$ 6.3)	9.4 ($\pm$ 8.3)	9.2 ($\pm$ 5.6)	8.4 ($\pm$ 8.3)
Median (IQR)	5.5 (4.0–7.0)	6.0 (4.0–14.0)	7.5 (4.5–16.0)	6.0 (3.0–9.5)
Age categories in months				
2–5	10 (50.0%)	12 (48.0%)	2 (33.3%)	4 (40.0%)
6–11	6 (30.0%)	6 (24.0%)	2 (33.3%)	5 (50.0%)
12–23	3 (15.0%)	5 (20.0%)	2 (33.3%)	0 (0.0%)
24–59	1 (5.0%)	2 (8.0%)	0 (0.0%)	1 (10.0%)
History				
Duration of illness in days				
Mean ($\pm$ SD)	2.6 ($\pm$ 1.2)	2.7 ($\pm$ 1.2)	2.6 ($\pm$ 1.2)	4.00 ($\pm$ 3.1)
Median (IQR)	3.0 (2.0–3.0)	3.0 (2.0–3.0)	2.5 (1.7–4.0)	3.0 (2.0–5.2)
Duration of illness categories				
0–3 days	17 (85.0%)	20 (80.0%)	4 (66.7%)	6 (60.0%)
4 or more days	3 (15.0%)	5 (20.0%)	2 (33.3%)	4 (40.0%)
Fever	14 (70.0%)	19 (76.0%)	5 (83.3%)	9 (90.0%)
Cough	20 (100.0%)	24 (96.0%)	6 (100.0%)	10 (100.0%)
Difficult breathing	15 (75.0%)	23 (92.0%)	5 (83.3%)	9 (90.0%)
Vomiting	6 (30.0%)	3 (12.0%)	2 (33.3%)	1 (10.0%)
Breast feeding, yes	14 (70.0%)	18 (72.0%)	5 (83.3%)	8 (80.0%)
Breast feeding with age categories				
2–5 months	7 (50.0%)	10 (55.5%)	1 (20.0%)	4 (50.0%)
6–11 months	6 (42.8%)	6 (33.4%)	2 (40.0%)	4 (50.0%)
12–23 months	1 (7.2%)	2 (11.1%)	2 (40.0%)	0
24–59 months	0	0	0	0
Past history of wheeze	1 (5.0%)	3 (12.0%)	0 (0.0%)	0 (0.0%)
Signs on examination				
Wheezing, yes	10 (50.0%)	15 (60.0%)	6 (100.0%)	5 (50.0%)
Wheezing with age categories				
2–5 months	5 (50.0%)	8 (53.3%)	2 (33.3%)	2 (40.0%)
6–11 months	2 (20.0%)	3 (20.0%)	2 (33.3%)	2 (40.0%)
12–23 months	3 (30.0%)	3 (20.0%)	2 (33.3%)	0
24–59 months	0	1 (6.7%)	0	1 (20.0%)
Temperature in °C				
Mean ($\pm$ SD)	37.1 ($\pm$ 0.3)	37.3 ($\pm$ 0.5)	36.4 ($\pm$ 1.9)	37.3 ($\pm$ 0.7)
Median (IQR)	37.0 (36.8–37.2)	37.2 (37.0–37.3)	37.1 (35.6–37.5)	37.1 (36.6–37.1)
Temperature categories				
$\leq 37.7^\circ\text{C}$	19 (95.0%)	21 (84.0%)	6 (100.0%)	8 (80.0%)
$> 37.7^\circ\text{C}$	1 (5.0%)	4 (16.0%)	0 (0.0%)	2 (20.0%)
Respiratory rate/min with age categories				
2–11 months				
Mean ($\pm$ SD)	56.9 ($\pm$ 4.2)	56.5 ($\pm$ 4.1)	58.1 ($\pm$ 4.9)	56.4 ($\pm$ 6.9)
Median (IQR)	55.2 (54.5–59.8)	55.7 (53.8–58.0)	56.0 (55.1–63.2)	59.5 (53.2–62.0)
12–59 months				
Mean ($\pm$ SD)	52.5 ($\pm$ 4.0)	49.0 ($\pm$ 5.87)	54.5 ($\pm$ 4.94)	48.0 ($\pm$ 0.0)
Median (IQR)	53.5 (48.2–55.7)	49.5 (43.0–53.5)	54.5 (51.0–58.0)	48.0 (48.0–48.0)

who recovered were compared. We used χ^2 test with Yates correction for categorical variables and independent sample *t* test for continuous variables. Estimates of odds ratio, 95% confidence intervals and *p* values were reported for categorical variables; only two-tailed *p* values were reported for continuous variables. A multivariate model was constructed to examine determinants of treatment failure by forward stepwise logistic regression in all patients. For this purpose, the continuous variables such as age, duration of illness and temperature were recoded to categorical variables. Variables with a *p* value of 0.1 were included in the model. Statistical significance was taken at the 5% level.

RESULTS

From September 2003 to June 2004, 900 children were enrolled. We randomly allocated 450 children each to the standard and double dose amoxicillin. After exclusion of 13 cases (two bottles broken and 11 lost to follow-up) from the standard dose group and 11 cases (one bottle broken and 10 lost to follow-up) from double dose group, 876 children completed the treatment for 3 days and were successfully followed up until day 14 (fig 1).

Baseline characteristics of the two groups are shown in table 3. There were 277 children aged 2–5 months (31.6%). In the infant group (<1 year old), 476 (87.0%) children were breast-fed and 265 (48.4%) children had wheeze at the time of enrolment.

At first follow-up (day 3), treatment was stopped in 424 (97.0%) children in the standard group and 421 (95.9%) in the double dose group (fig 1). This difference was not statistically significant. Out of 31 (3.4%) children declared as therapy failure, 11 had lower chest indrawing and four had developed danger signs. In remaining 16 children the antibiotic was changed by the study physician because in his/her opinion the children looked unwell although they did not meet the study therapy failure criteria.

At second follow-up (day 5), 417 of the 424 children in the standard dose group and 414 of the 421 children in the double dose group were declared clinically resolved (fig 1). This difference was not statistically significant. Of 14 (1.6%) children who failed therapy according to the protocol, one was classified as having severe pneumonia, one developed danger signs and the remaining 12 had a respiratory rate above the age specific cut-off value.

Table 5 Comparison of therapy success and failure by baseline characteristics of all patients (n=876)

Baseline characteristics	Therapy success (n=815)	Therapy failure (n=61)	OR (95% CI)	p Value
Sex, male	519 (63.7%)	41 (67.2%)	1.17 (0.65 to 2.11)	0.67
Age in months				
Mean ($\pm$ SD)	12.7 ($\pm$ 11.4)	8.6 ($\pm$ 7.3)		0.01
Median (IQR)	8.0 (5.0–17.0)	6.0 (4.0–10.0)		
Age categories in months				
2–5	249 (30.5%)	28 (45.9%)	3.80 (1.23 to 13.0)	0.01
6–11	251 (30.8%)	19 (31.1%)	2.55 (0.80 to 9.0)	0.13
12–23	180 (22.1%)	10 (16.4%)	1.88 (0.53 to 7.2)	0.43
24–59	135 (16.6%)	4 (6.6%)	–	
History				
Duration of illness in days				
Mean ($\pm$ SD)	2.8 ($\pm$ 1.7)	2.9 ($\pm$ 1.7)		0.75
Median (IQR)	2.0 (2.0–3.0)	3.0 (2.0–3.0)		
Duration of illness categories				
0–3 days	629 (77.2%)	47 (77.1%)		
Median (IQR)	2.0 (2.0–3.0)	2.0 (2.0–3.0)		
4 days or more	186 (22.8%)	14 (22.9%)	1.01 (0.52 to 1.94)	0.89
Median (IQR)	5.0 (4.0–6.0)	4.5 (4.0–5.0)		
Fever	639 (78.4%)	47 (77.1%)	0.92 (0.48 to 1.80)	0.93
Cough	812 (99.6%)	60 (98.4%)	0.22 (0.02 to 5.62)	0.66
Difficult breathing	689 (84.5%)	52 (85.2%)	1.06 (0.49 to 2.36)	0.97
Vomiting	138 (16.9%)	12 (19.7%)	1.20 (0.59 to 2.41)	0.71
Breast feeding, yes	518 (63.6%)	45 (73.8%)	1.61 (0.87 to 3.03)	0.14
Breast feeding with age categories				
2–5 months	228 (44.0%)	22 (48.9%)		0.62
6–11 months	208 (40.2%)	18 (40.0%)		0.56
12–23 months	79 (15.2%)	5 (11.1%)		0.40
24–59 months	3 (0.6%)	0 (0.0%)	–	
Past history of wheeze	30 (3.7%)	4 (6.6%)	1.84 (0.53 to 5.72)	0.43
Signs on examination				
Wheezing, yes	333 (40.9%)	36 (59.0%)	2.08 (1.19 to 3.66)	0.01
Wheezing with age categories				
2–5 months	130 (39.1%)	17 (47.2%)	2.35 (0.49 to 15.4)	0.40
6–11 months	109 (32.7%)	9 (25.0%)	1.49 (0.28 to 10.4)	0.89
12–23 months	58 (17.4%)	8 (22.2%)	2.48 (0.45 to 18.0)	0.42
24–59 months	36 (10.8%)	2 (5.6%)	–	
Temperature in °C				
Mean ($\pm$ SD)	37.3 ($\pm$ 0.45)	37.1 ($\pm$ 0.78)		0.07
Median (IQR)	37.2 (37–37.2)	37.2 (33.9–37.2)		
Temperature categories				
$\leq 37.7^\circ\text{C}$	694 (85.2%)	54 (88.5%)		
Median (IQR)	37.2 (37–37.2)	37.1 (36.8–37.2)		
$> 37.7^\circ\text{C}$	121 (14.8%)	7 (11.5%)	0.74 (0.30 to 1.75)	0.59
Median (IQR)	37.8 (37.7–38.3)	38.3 (37.7–38.8)		
Respiratory rate/min with age categories				
2–11 months				
Mean ($\pm$ SD)	57.5 ($\pm$ 6.7)	57.4 ($\pm$ 4.8)		0.88
Median (IQR)	55.0 (53.0–60.0)	56.0 (54.5–60.0)		
12–59 months				
Mean ($\pm$ SD)	48.1 ($\pm$ 6.1)	50.7 ($\pm$ 5.2)		0.13
Median (IQR)	46.0 (44.0–50.0)	50.7 (46.7–55.2)		

At third follow-up (day 14), six children in the standard dose group and 10 in the double dose group had relapsed. The difference was not statistically significant. Of 16 relapsed children, 11 had a respiratory rate above the age specific cut-off value and one child had lower chest indrawing. Four children received an antibiotic prescribed by a general practitioner between day 6 and 14 although clinical information necessitating this change of therapy was not available for the analysis. The characteristics of relapsed children are given in table 4. The cumulative failure rates at day 5 and 14 with the standard dose were 4.6% (n=20) and 5.9% (n=26), respectively, as compared with 5.7% (n=25) and 7.9% (n=35) with the double dose (fig 1). No deaths were reported in enrolled children.

A comparison of the baseline characteristics of children in the treatment failure and treatment success groups is shown in table 5. Logistic regression analysis of all patients showed that treatment failure was associated with age 2–5 months (OR 1.42, 95% CI 1.07 to 1.87, p=0.01) and presence of wheeze at the time of enrolment (OR 1.84, 95% CI 1.07 to 3.15, p=0.02).

Of 891 chest radiographs analysed, 61 (6.8%) showed evidence of end point pneumonia.²⁰

DISCUSSION

Our results show that doubling the amoxicillin dose did not affect the clinical outcome of non-severe pneumonia in 2–59 month old children. Had antimicrobial resistance resulted in high clinical failure rates for non-severe pneumonia in Pakistan,^{3–5} increasing the dose^{16–17} would have resulted in better outcomes in the higher dose group. From our data it seems that this was not the case. We believe that clinical outcome with a short course of high-dose amoxicillin and with an adequate sample size was evaluated for the first time in the treatment of childhood pneumonia. In a previous study, a high-dose (90 mg/kg/day), 5 day course of oral amoxicillin had shown reduced prevalence of resistant pneumococci at the end of therapy as compared to a 40 mg/kg/day dose course of 10 days, together with improved adherence.²² However, that

study did not report any clinical outcomes. No microbiological testing was carried out in our study. Our results also show a good clinical outcome for non-severe pneumonia with a 3 day course of amoxicillin. The number of children who showed signs of deterioration by day 14 was small, thereby strengthening the argument for treating non-severe pneumonia for only 3 days.⁴⁻⁶

Other reasons for higher therapy failure rates could be either viral aetiology or the presence of wheeze in children categorised as having non-severe pneumonia using WHO case management guidelines. The WHO recommends presumptive antibiotic therapy for the category of non-severe pneumonia¹ without making any distinction between viral and bacterial aetiology. Data show that a significant proportion of childhood pneumonia could be viral in origin,²³⁻²⁷ although a mixed viral and bacterial infection is also seen fairly often in developing countries.^{11, 28} Therefore, it is not unreasonable to assume that a number of children in our study had viral pneumonia, and so response to antibiotic therapy cannot be taken as a true estimate of the efficacy of an antibiotic or its dosage. This problem could have been resolved if we had had a third arm in which children received only placebo, but this was not possible due to ethical reasons.

Wheeze was identified as a significant predictor of treatment failure. Wheeze has a significant association with respiratory syncytial virus (RSV), bronchiolitis^{29, 30} and hyperreactive airway disease. Antibiotic therapy is unlikely to benefit children with wheeze due to these conditions.^{30, 31} WHO guidelines recommend giving two cycles of inhaled bronchodilators at 15 min interval to all children presenting with audible wheeze and fast breathing.^{1, 32} Children who respond to inhaled bronchodilators are sent home on oral bronchodilators only. This practice reduces antibiotic prescription by more than half in children with wheeze.³³ However, up to two thirds of children with auscultatory wheeze may not have audible wheeze^{33, 34} and will not be identified by health workers using the current WHO guidelines.¹ Many of the children will be classified as having pneumonia. Not only will they receive antibiotics unnecessarily, but their non-response to first line antibiotics means they are treated as treatment failures and are given unnecessary second line antibiotics. This could lead to an increase in antimicrobial resistance in addition to increasing costs for the national IMCI (Integrated Management of Childhood Illness) or ARI control programmes in low resource settings. It is unrealistic to expect community health workers to use auscultation to assess wheeze, but in many countries the case management guidelines are used at the health facility level by physicians or nurses. They are more qualified and should be encouraged to use a stethoscope to identify wheeze. Furthermore, use of metered dose inhalers with spacer devices and nebulisers should be encouraged for the delivery of rapidly acting bronchodilators at the health facility level. Besides helping children with wheeze, such practices will further rationalise antibiotic use.

Children aged less than 1 year were a high risk group for treatment failure in our study, as has been shown elsewhere.^{4, 5, 10} It is important to advise the care givers of these high risk children to return to the health facility at the appearance of the earliest signs of deterioration.

In conclusion, non-severe pneumonia can be treated safely and effectively with a standard dose of oral amoxicillin for 3 days. There is a need to improve specificity for assessment of pneumonia. Greater emphasis is needed on improving the management of children with wheeze. Children less than 1 year of age are a high risk group and more vigilance is required both at the health care provider and health care giver level to prevent adverse outcomes.

What is already known on this topic

- There are reports of rising treatment failure rates with oral amoxicillin, the currently recommended first line drug for non-severe pneumonia in children
- Existing microbiological data demonstrate that in vitro resistance to amoxicillin can be overcome by increasing the dosage

What this study adds

- Doubling the dose of amoxicillin does not improve the clinical outcome in childhood pneumonia
- Non-severe pneumonia can be treated effectively and safely with a 3 day course of standard dose oral amoxicillin

ACKNOWLEDGEMENTS

Oral amoxicillin, in the dosage of 125 mg/5 ml and 250 mg/5 ml, was provided by Novartis Pharma, Karachi, Pakistan.

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