RESEARCH BRIEF

Predictors of Treatment Failure in Hospitalized Children [3-59 months] with Severe and Very Severe Pneumonia

DIPTY L JAIN, VIJAYA SARATHI AND SARVESH JAWALEKAR

From the Department of Pediatrics, Government Medical College, Nagpur, India.

Correspondence to:
Dr Vijaya Sarathi, Assistant Professor, Department of Pediatrics, Government Medical College, Nagpur, India.
drvijayasarathi@gmail.com
Received: August 01, 2012;
Initial review: August 27, 2012;
Accepted: February 14, 2013.

We conducted this case-control study in children (age 3-59 mo) to study the risk factors for failure of standard treatment in severe and very severe community acquired pneumonia. One hundred and eighty one children were enrolled in the study among whom 31 (20.4%) had treatment failure. The independent risk factors for treatment failure by 48 hours using multivariate analysis were: infancy, measles immunization not given by 9 months, severe malnutrition, very fast breathing at baseline, hypoxemia at baseline, and bacteremia.

Keywords: *Children, Pneumonia, Treatment failure, Predictors*

World Health Organization recommends management of children with acute respiratory illness [ARI] solely based on clinical signs for the initiation of empiric antibiotic therapy [1]. Use of empiric antibiotic therapy based on these guidelines has been estimated to reduce pneumonia-specific mortality by 35-40% and overall mortality by 24% in children of 0-4 years of age [2]. Still ARI is the most common cause of under-five mortality [3]. Most of these deaths are associated with treatment failure. All five deaths in the study by Hazir, *et al.* [4] were defined to have treatment failure and antibiotics have been revised. It emphasizes the need for early identification of those at high risk for treatment failure so as to treat them with aggressive therapy. We conducted this study to recognize the risk factors for treatment failure in hospitalized children with community acquired pneumonia (CAP).

METHODS

This case control study was conducted over a period of two years, at Government Medical College Hospital, Nagpur. The study was approved by the institutional ethics committee and a written informed consent was obtained from parents/guardians of all participants. The study included children of age between 3-59 months, hospitalized with history of fever, cough and difficulty in breathing. Tachypnea was defined as respiratory rate ≥50/min in 2-11 months and ≥40/min in 12-59 month old children. Chest wall indrawing was defined as inward movement of lower chest wall on breathing in. Severe pneumonia was defined as tachypnea and chest wall indrawing. Very severe pneumonia was defined as tachypnea, chest wall indrawing and either central cyanosis or inability to drink. Very fast breathing was defined as respiratory rate ≥20/min above the cutoff used to define tachypnea. Severe malnutrition was defined as weight for height/length *Z* score ≤3. Hypoxemia was defined as oxygen saturation <90% in room air. Hypoglycemia was defined as capillary blood glucose <60 mg/dL. Leucopenia was defined as leucocyte count <4000/μL. Children with history of hyper-reactive airway disease, congenital heart disease, congenital/ chronic respiratory disorder, immunocompromised status or those who have received antibiotic for more than 24 hours were excluded from the study. None of the participants were immunized with pneumococcal or H. influenzae vaccine.

Baseline evaluation included a detailed clinical assessment and laboratory investigations within the first hour of enrollment. All infants (2-12 months) were treated with intravenous cefotaxime (100 mg/kg/day) while older children (>1 year) were treated with intravenous ampicillin (100 mg/kg/day). Reassessment was done every 12 hourly till 48 hours after enrollment to watch for the occurrence of treatment failure by 48 hours [primary end-point of the study].

Treatment failure was defined as any of the following occurring by or at 48 hours:

1. No improvement or worsening of tachypnea or lower chest indrawing;

2. New appearance, no improvement or worsening of danger signs such as inability to drink, abnormal sleepiness, difficult to awake from sleep, stridor in a calm child, central cyanosis, and convulsions; or
3. Occurrence of complications (empyema, pneumothorax, lung abscess, meningitis, septicaemia, shock, respiratory failure).

Statistical analysis: The data were analysed with SPSS software (version no.16). Unadjusted and adjusted odd's ratios with 95% confidence intervals were calculated for the effect of each variable by using multiple logistic regression models. *P* value <0.05 was considered statistically significant.

RESULTS

A total of 181 cases (108 boys) were enrolled. Thirty seven (20.4%) children had treatment failure at 48 hours. Reasons for treatment failure and complications are listed in ***Table* I**. Mean duration of hospitalization was 9.0±3.2 days in children with treatment failure and 4.7±2.2 days in responders. By univariate analysis several risk factors were associated with treatment failure by 48 hours. These included infancy, lack of measles immunization by 9 months of age, severe malnutrition, very fast breathing at baseline, severity of pneumonia, hypoxemia at baseline, hypoglycemia, leucopenia and bacteremia. On multivariate regression analysis infancy, measles immunization not given by 9 months, severe malnutrition, very fast breathing at baseline, hypoxemia at baseline, and bacteremia significantly predicted treatment failure (***Table* II**). There were 9 (4.9%) deaths among which 4 occurred within 48 hours of hospitalization. All the children with later deaths had treatment failure by 48 hours and died despite revision of antibiotics.

DISCUSSION

This study reports treatment failure rate in infants and children with severe and very severe CAP and its predictors. Thirty seven (20.4%) children had treatment failure which was significantly predicted by infancy, severe malnutrition, very fast breathing at baseline, lack of measles immunization, hypoxemia at baseline, and bacteremia. Most of the identified predictors of (excluding pulse oximetry and blood culture) treatment failure in the present study are simple characteristics which can be assessed effectively even at primary health care centers.

Infancy was the strongest predictor of treatment failure and it was also associated with high fatality rate. A similar observation was also made by few previous

TABLE I REASONS TO DEFINE TREATMENT FAILURE

Treatment failure by specific causes	*Number of cases (n=31)*
Persistence or worsening of lower chest indrawing and/or tachypnea	10
Persistence / Appearance of danger signs	5
Hypoxemia [S_PO_2 < 90%]	7
Development of complications [n=9]	
Empyema/ Pneumothorax	6
Lung abscess	1
Meningitis	2

TABLE II PREDICTORS OF TREATMENT FAILURE

Covariates	*No of failures/ total with characteristic*	*Unadjusted Odds Ratio (95% CI)*	*Adjusted Odds Ratio (95% CI)*	*P value*
Age < 12 months	28 / 92	3.89 (1.71-8.83)	3.68 (1.02- 10.13)	0.001
Not received measles immunization	6 / 11	5.38 (1.54-18.76)	2.60 (0.79 - 9.36)	0.03
Severe malnutrition (Weight Z score ≤-3)	16/ 40	3.81 (1.74-8.35)	1.93 (0.53 - 5.57)	0.03
Very fast breathing at baseline	24 / 74	3.47 (1.63-7.4)	1.76 (0.41- 4.49)	0.048
Very severe pneumonia	12 / 31	3.16 (1.36-7.32)	–	–
Hypoxemia at baseline (S_PO_2 < 90%)	14/32	4.26 (1.86-9.75)	2.40 (0.80- 8.52)	0.03
Hypoglycemia (capillary blood glucose < 60 mg/dL)	6/23	1.45 (0.53-3.97)	1.33 (0.48-5.29)	0.14
Leucopenia (TLC < 4000)	7/18	2.82 (1.01-7.88)	1.77 (0.6-5.7)	0.06
Presence of bacteremia	9 / 15	7.39 (2.44-22.43)	2.56 (0.69-7.54)	0.02

** 170 included all infants younger than 9 months and children elder than 9 months and immunized with measles vaccine*

studies [4-7]. However, a large multicentre study (SPEAR) did not find infancy as a significant predictor of treatment failure [8]. Similar to our study malnutrition, very fast breathing at baseline, baseline hypoxemia, bacteremia were also found to be significant predictors of treatment failure in few previous studies [4,6-8]. Additionally, lack of measles immunization was found to be a new independent predictor of treatment failure in severe and very severe pneumonia. The increased frequency of treatment failure among those who did not receive measles vaccination at 9 months cannot be attributed to increased frequency of post measles complications since only one child had history of measles after the age of 9 months but before the hospitalization with CAP. This observation is likely to be due to barriers to health care and is favored by the fact that the average duration of pre-hospitalization illness was higher in those who did not receive measles vaccination by 9 months (4.8 days) compared to the rest of the study population (3.3 days). However, duration of illness was not a significant predictor of treatment failure.

The 15 bacterial isolates included pneumococci (*n* =6), *Hemophilus influenzae* (*n*=5), *Staplylococcus aureus* (*n*=2), and *Escherechia coli* (*n*=2) and five of these isolates were resistant to the corresponding first line antibiotic used in them. Four of these five had treatment failure; however, antibiotic resistance was not a significant predictor of treatment failure on multivariate analysis. The fact that the 40% of bacterial isolates responsible for CAP were pneumococci emphasizes the role for pneumococcal vaccination in the prevention of severe and very severe CAP in children.

The present study is limited by a small number of subjects. The study may have referral bias since many enrolled cases were referred from peripheral centers and generalizability of the results may be limited.

To conclude, failure of empirical antibacterial therapy of children with CAP is common in India. Infancy, lack of measles immunization, severe malnutrition, very fast breathing, hypoxemia at baseline and presence of bacteremia were the significant predictors of treatment failure in young children with CAP. Strengthening the immunization and nutritional supplementation services may improve the outcome in young children with CAP. Children with the above risk factors may be considered for aggressive antimicrobial therapy. There is a need for larger study to confirm these findings. There is also a need to study whether the outcome improves with initial aggressive treatment of these children with high risk factors for treatment failure.

Contributors: All the authors have contributed, designed and approved the study.
Funding: None; Competing interests: None stated.

REFERENCES

1. Bryce J, Boschi-Pinto C, Shibuya K, Black RE. WHO Child Health Epidemiology Reference Group. WHO estimates of the causes of death in children. Lancet. 2005;365:1147-52.
2. Sazawal S, Black RE. Effect of pneumonia case management on mortality in neonates, infants, and preschool children: a meta-analysis of community-based trials. Lancet Infect Dis. 2003;3:547-56.
3. Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. Bull World Health Organ. 2008; 86: 408-16.
4. Hazir T, Fox LM, Nisar YB, Fox MP, Ashraf YP, MacLeod WB. New outpatient short-course home oral therapy for severe pneumonia [NO-SHOTS] Study Group. Ambulatory short-course high-dose oral amoxicillin for treatment of severe pneumonia in children: a randomised equivalency trial. Lancet. 2008; 371: 49-56.
5. McNally LM, Jeena PM, Gajee K, Thula SA, Sturm AW, Cassol S, *et al.* Effect of, age, polymicrobial disease, and maternal HIV status on treatment response and cause of severe pneumonia in South African children. Lancet. 2007;369:1440-51.
6. Addo-Yobo E, Chisaka N, Hassan M, for the Amoxicillin Penicillin Pneumonia International Study [APPIS] group. Oral amoxicillin versus injectable penicillin for severe pneumonia in children aged 3 to 59 months: a randomised multicentre equivalency study. Lancet. 2004;364: 1141-8.
7. Fu LY, Ruthazer R, Wilson I, Patel A, Fox LM, Tuan TA, et al. Brief hospitalization and pulse oximetry for amoxycillin treatment failure in severe pneumonia. Pediatrics. 2006;118:e1822-30.
8. Asghar R, Banajeh S, Egas J, Hibberd P, Iqbal I, Katep-Bwalya M, *et al*. Multicentre randomized controlled trial of chloramphenicol vs. ampicillin and gentamicin for the treatment of very severe pneumonia among children aged 2 to 59 months in low resource settings: a multicenter randomized trial [SPEAR study]. BMJ. 2008;336:80-4.