Original Research Article

Predictors of treatment failure in severe pneumonia treated with Ampicillin in tertiary care center

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ABSTRACT

Background: Pneumonia affects 156 million children under five years every year and is the leading cause of mortality in this age group. It emphasizes the need to identify high risk factors for Treatment Failure so as to treat them aggressively. The objective of this study was to assess factors influencing treatment failure in severe pneumonia treated with Ampicillin.

Methods: Prospective observational study, in which 235 children with severe pneumonia between 2 months to 60 months were enrolled and started with intravenous Ampicillin as per WHO protocol. If no clinical improvement was seen after 48 hours, it was taken as treatment failure and managed accordingly.

Results: Among 235 children, 43(18.2%) did not respond to Ampicillin. Among treatment failure cases males were 20 (46.5%) and females were 23 (53.6%). All the following parameters were statistically significant(p<0.05). Majority of 23(53.4%) were between 2 to 12 months. 13(30.2%) were incompletely immunized. MAM were 23(53.4%) and 22(51.1%) cases had signs of Rickets. 34(79.1%) had Anemia out of which 22(64%) had moderate anemia. 39(90.6%) children had fever and hypoxia at admission.

Conclusions: Infancy, malnutrition, severity of anemia, rickets, lack of immunization, hypoxia at baseline were significant predictors of treatment failure in severe pneumonia. Strengthening immunization and improving nutritional status may improve the outcome. Children with above risk factors require vigilant monitoring.

Keywords: Ampicillin, Anemia, Hypoxia, Immunization, Moderate acute malnutrition, Pneumonia, Rickets, Severe treatment failure

INTRODUCTION

Pneumonia affects 156 million children under the age of five years every year across the globe and is the leading cause of mortality in this age group.[1] World health organization recommends management of children with acute respiratory illness based on clinical signs for the initiation of empirical antibiotic therapy.[1] Use of empirical 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] Most of these deaths are associated with

treatment failure. All five deaths in the study by Hazir T et al.[3] were defined to have treatment failure and antibiotics were revised. It emphasizes the need for early identification of those at high risk for treatment failure so as to monitor them vigilantly and treat with aggressive therapy.

Authors conducted this study to recognize the risk factors for treatment failure in hospitalized children with severe pneumonia with Ampicillin. The objective of this study was to assess factors influencing treatment failure in severe pneumonia treated with Ampicillin.

METHODS

A prospective observational study was conducted from November 2016 to May 2018, at Bangalore Medical College and Research Institute, Bangalore, India.

The study was approved by the institutional ethics committee and a written informed consent was obtained from parents/ guardians of all participants.

Inclusion criteria

- Age between 2-60 months
- Children hospitalized with history of cough, cold, hurried breathing and chest in drawing.
- Tachypnea was defined as respiratory rate ≥50 breaths/min in children aged 2-12 months and ≥40 breaths/min in children of > 12 months.[4]

Exclusion criteria

- Pneumonia with known case of CHD or congenital malformations of the respiratory tract
- Complicated pneumonia at onset like empyema/abscess/necrotizing pneumonia/pleural effusion
- Primary or secondary immunodeficiency
- Hospital acquired pneumonia
- Pneumonia with co-morbid illness like diabetes/ CKD/ nephrotic syndrome/ asthma/ chronic GERD
- Those allergic to penicillin
- Those who have received antibiotic for more than 24 hours
- Those with severe acute malnutrition.

Total of 235 children were included in the study. Baseline evaluation included a detailed clinical assessment and laboratory investigations within the first hour of enrollment.

The patients with severe pneumonia were started with intravenous Ampicillin 50 mg/ kg sixth hourly after giving test dose, according to WHO guidelines.

Outcomes were assessed after 48 hours of starting Ampicillin. If no improvement was seen after 48 hours, antibiotics were upgraded to second line and managed accordingly.

Fever was defined as an axillary temperature >37.5°C.[5] Hypoxia defined as spo2 <94% in right upper limb.[6] Anemia defined and classified as per WHO.[7]

If weight for height/length was between-2 to -3 SD or mid upper arm circumference in more than 6 months of age was between 11.5 and 13.5 cm, it was defined as moderate acute malnutrition.[8] None of the children were immunized with pneumococcal vaccine.

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

- No improvement or worsening of fever, tachypnea, lower chest indrawing or hypoxia
- New appearance of signs, 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
- Occurrence of complications (empyema, pneumothorax, lung abscess, meningitis, septicemia, shock, respiratory failure).

Statistical analysis

The data were analyzed with SPSS software (version no.16). Unadjusted and adjusted odds 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 235 cases were enrolled. Children who responded to Ampicillin were 192 (81.7%), forty-three (18.3%) children had treatment failure at 48 hours. Reasons for treatment failure and complications are listed in (Table 1).

Table 1: Reasons to define treatment failure.

Treatment failure by specific causes	Number of cases (n=43)
Persistence or worsening of tachypnea	31
Persistence or worsening of fever	27
Persistence or worsening of lung signs	24
Hypoxia at baseline	26
Development of danger signs	11
Development of complication	00

By univariate variate analysis several risk factors were associated with treatment failure by 48 hours.

These were age group less than 2 years, decreased activity, noisy breathing, incomplete immunization status, malnutrition, rickets, anemia, hypoxia at baseline, fever and irritability.

On multivariate regression analysis, infancy, incomplete immunization, malnutrition, increase in severity of anemia, signs of rickets, fever, hypoxia at baseline significantly predicted treatment failure (Table 2). None of the cases died during course of the treatment.

Table 2: Predictors of treatment failure.

Parameters		Responders (N=192)	Non responders (N=43)	P-value
		N (%)	N (%)	
Age (years)	2-12months	99 (51.60%)	23 (53.49%)	0.000*
	13-24months	74 (38.50%)	15 (34.88%)	0.000*
	25-36 months	13 (6.8%)	04 (9.30%)	0.871
	>36 months	6 (3.1%)	01 (2.33%)	0.961
Gender	Male	123 (64.10%)	20 (46.50%)	0.134
	Female	69 (35.96%)	23 (53.50%)	0.133
Decreased activity		54 (28.12%)	19 (44.19%)	0.260
Noisy breathing		5 (2.63%)	3 (6.98%)	0.789
Incomplete immunization		25 (13.01%)	13 (30.23%)	0.011*
MAM		27 (14.10%)	23 (53.49%)	0.003*
Signs of rickets		41 (21.40%)	22 (51.16%)	0.015*
Hypoxia		110 (57.30%)	39 (90.70%)	0.000*
Fever		104 (54.20%)	39 (90.70%)	0.000*
Irritability		03 (1.6%)	01 (2.33%)	0.967
Grading of anemia	Mild	74 (38.50%)	07 (16.28%)	0.026*
	Moderate	55 (28.60%)	22 (51.16%)	0.000*
	Severe	01 (0.5%)	05 (11.63%)	0.000*

*Significance at 5% level (p<0.05)
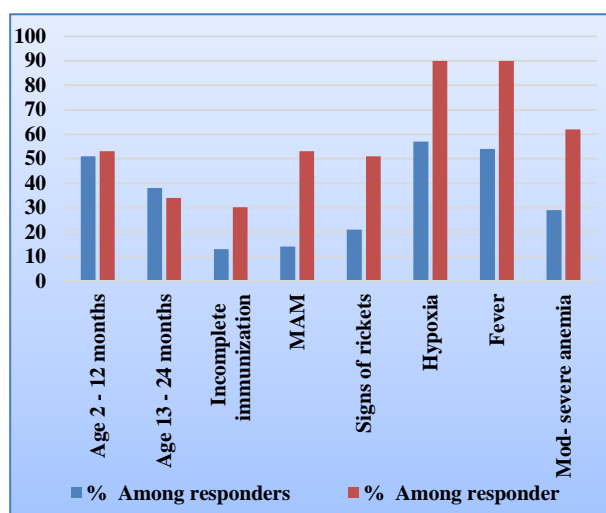
Figure 2: Percentage of predicting factors for treatment failure among responders and non-responders to Ampicillin.

DISCUSSION

This study describes and quantifies the treatment failure in infants and children with severe pneumonia treated with Ampicillin and its predictors. Forty-three (18.2%) children had treatment failure, which was predicted by younger age group, lack of immunization, malnutrition, rickets, anemia, hypoxia at baseline and fever.

Most of the identified predictors of treatment failure of the present study are based on clinical findings, can be easily assessed effectively even in primary health center. Infancy and age between 1-2 years, hypoxia at baseline, fever and increase in severity of anemia are the strongest predictors of treatment failure. Similar observations were also made in few previous studies.[4,9-11]

However, a large multi-center study (SPEAR) did not find infancy as a significant predictor of treatment failure.[12] Similar to present study, malnutrition and baseline hypoxemia were also found to be significant predictors of treatment failure in few previous studies.[4,10-12]

Additionally, in Jain et al, study, lack of measles immunization was found to be independent predictor of treatment failure in severe and very severe pneumonia.[13] In this study authors also included children who had not received H influenza (Hib) vaccine, so lack of Hib vaccination is also a risk factor along with measles. None of the children were immunized with pneumococcal vaccine, it also emphasizes the role of the pneumococcal vaccine in the prevention of community acquired pneumonia. Fever is also independent risk factor.

Haugen J et al, and Oduwole OA et al, studies found that vitamin D deficiency is associated with treatment failure in severe pneumonia, present study also had similar predictor which was indirectly measured by clinical signs of rickets.[14,15] Studies have also shown low Vitamin D levels is an independent risk factor for the development of pneumonia and increases the disease severity.[16-19]

Authors found that anemia and its increase in severity is risk factor for treatment failure, this result is comparable with study done by Moschovis PP et at, in which anemia at high altitude increases the risk of poor outcome with

severe pneumonia.[20] In present study found that cases of severe pneumonia were associated with anemia where as Sakka ASE et al, studied low hemoglobin levels as risk factors for severity of acute lower respiratory tract infections in Egyptian children.[19]

The present study is limited by referral bias since many enrolled cases were referred from peripheral centers and the results may be limited. For rickets, only clinical findings were included which were not proved with laboratory values.

CONCLUSION

Infancy and age less than 2 years, lack of immunization, malnutrition, increase in severity of anemia, rickets, fever and hypoxia at baseline were the significant predictors of treatment failure in young children with severe pneumonia.

Strengthening the immunization and nutritional supplementation with vitamin D and iron may improve the outcome in young children with severe pneumonia.

Children with above risk factors require vigilant monitoring. 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 and also whether acute correction of primary risk factors shortens the duration of illness reducing morbidity and hospital stay and whether it prevents future recurrences.

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