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ORIGINAL ARTICLE

PREDICTIVE FACTORS OF TREATMENT FAILURE FOR PEDIATRIC COMMUNITY-ACQUIRED PNEUMONIA C AND D IN 2-TO-59 MONTHS OF AGE

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

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ABSTRACT

Objective: To determine antibiotic treatment failure rate and predictors of treatment failure in children 2 to-59 months with Pediatric Community-Acquired Pneumonia-C (PCAP-C) and PCAP-D admitted at Makati Medical Center.

Methods: This prospective cohort study examined 100 children, 2-to-59 months with clinically diagnosed PCAP-C and PCAP-D. Baseline assessment was done on day 1 of hospital stay and follow-up assessments were done on days 3 and 7 or upon discharge for the outcomes of interest.

Results: One hundred children were included in the study and 98% had PCAP-C. This study identified a treatment failure rate of 17% among children with PCAP-C. There was no mortality. Malnutrition and low oxygen saturation on admission were significant predictors of treatment failure.

Conclusion: Antibiotic treatment failure rate was 17%. Malnutrition and hypoxia were significant predictors of treatment failure in children with PCAP-C.

KEYWORDS:

Pediatric Community-Acquired Pneumonia, severe pneumonia, lower respiratory tract infection, malnutrition, hypoxia

INTRODUCTION

Pneumonia is a leading cause of death accounting for 17% of all under-five deaths worldwide, or a loss of roughly 1.6 million lives. Around 90%-95% of these deaths occur in developing countries. According to the United Nations International Children's Emergency Fund (UNICEF), data back in September 2013 showed that majority of deaths occurred in sub-Saharan Africa and South Asia. Data from the Philippines in the same year showed that pneumonia was a top cause of infant mortality with a rate of 1.8/100,000 population; in children, 1-to-4 years mortality rate is 25.2 /100,000 population. [1] This trend was consistently observed over the last five years.

The etiology of pneumonia varies with age. For children less than two, the most common cause are viruses. In school-age children, bacterial pathogens such as *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* are more prevalent, followed by *Haemophilus influenzae* and *Chlamydia pneumoniae*. Other bacterial causes include *Staphylococcus aureus* and *Bordetella pertus*sis.

Treatment outcomes for pneumonia may vary depending on age, vaccination status, immunologic status, exposures, severity of disease, and the setting where the pathogen was acquired.

In a case-control study by Jain, et al involving children 3-to-59 months, most pneumonia deaths were associated with treatment failure.[2] Infancy, lack of measles immunization, severe malnutrition, tachypnea, hypoxemia at baseline, and presence of bacteremia were significant predictors of treatment failure.

A prospective longitudinal survey of children 2-59 months in 2009 by Agweya, *et al*, in Kenya found treatment failure rates ranging from 1.8% to 12.4% for severe pneumonia, and 21.4% to 39.3% for very severe pneumonia.[3] Treatment failure was defined as the development of severe pneumonia or death at any time, and the absence of improvement in the following for severe pneumonia: chest indrawing, measured temperature reduction of $\geq$ to 0.5 C, respiratory rate reduction of $\geq$ to 5 cycles/minute, identification of pathogen with *in vitro* resistance to antibiotics, and a senior clinician's decision to change antibiotic. For very severe pneumonia, treatment failure would mean all the conditions mentioned in severe pneumonia, plus deteriorating level of consciousness, the presence of lung abscess and/or bullae formation, inability to drink, and the requirement for supplementary oxygen on the second and fifth day of treatment. The study found that treatment failure rates varied due to non-adherence to treatment guidelines on pneumonia.

In the Philippines, there is paucity of research on predictors of treatment failure for PCAP-C and PCAP-D among children under five. One local prospective study was done by Lupisan, *et al*, in Bohol in 2007 suggested that for children aged 2-to-5 months, dense infiltrates on chest radiography and presence of bacterial pathogens in the blood would predict death.[4]

This study aimed to identify predictors of treatment failure in children less than five years with Pediatric Community-Acquired Pneumonia-C (PCAP-C) and PCAP-D admitted in a private tertiary hospital.

Specifically, this study determined whether the following factors are predictors of treatment failure: age, gender, immunization status (to *Haemophilus influenzae* type B (Hib) and *Streptococcus pneumoniae*), presence of associated symptoms suggestive such as vomiting or diarrhea suggestive of a viral etiology, exclusive breastfeeding for 6 months, care-seeking delays (more than three days), low

socioeconomic status (income below 30,000 per month) and choice of empiric antibiotic. It also determined whether low oxygen saturation (<92%), malnutrition (z-score of less than -2) and tachypnea are predictive factors of treatment failure.

If predictors for treatment failure are identified, timely changes in management choices to address these predictors for failure may be done. This will translate to a decrease in morbidity/mortality and subsequently improve the treatment outcome of patients with pneumonia.

MATERIALS AND METHODS

This prospective cohort study was conducted between September 1-October 24, 2016 at a private tertiary hospital in the Philippines.

Children, 2-to-59 months old, clinically diagnosed with pneumonia based on the presence of cough and/or dyspnea, or tachypnea for age, and with either wheezing or crackles on physical examination, were included. Patients were classified as PCAP-C if they had the following: respiratory rate ≥60/minute (3-12 months), ≥50/minute (1-5 years), ≥35/minute (above 5 years), intercostal and subcostal retractions, head bobbing, cyanosis, moderate dehydration, moderate malnutrition, and presence of pallor. Children were classified as PCAP-D if they had the following: respiratory rate > 70/minute (3-12 months), >50/minute (1-5 years), > 35/minute (above 5 years), supraclavicular, intercostal, subcostal retractions, grunting, apnea, cyanosis, head bobbing, severe dehydration, severe malnutrition and altered level of sensorium.

Excluded were children with any of the following conditions as these may affect the treatment outcome: on antibiotic therapy for 48 hours before admission, on anti-tuberculous medication, with asthma or any abnormal lung pathology i.e. Bronchopulmonary Dysplasia, Congenital Cystic Adenomatoid Malformation, with immunodeficiency disorder; with congenital heart disease or heart murmur; and with cardiac pathology based on electrocardiography or echocardiography.

Using the Raosoft sample size calculator with a margin of error of 5%, and confidence interval of 95% given the population size of 102 patients with PCAP-C and PCAP-D (from the census of September 1 to October 31, 2015), the minimum recommended sample size for both PCAP-C and PCAP-D was 81.

Treatment failure was defined as failure to improve or have normalization of the respiratory rate (RR + or – 5 cpm), oxygen saturation, (oxygen saturation < 92%), and temperature (temperature > 38), with the presence of pulmonary complications and/or presence of clinical danger signs (severe chest wall indrawing, grunting, inability to breastfeed or drink, lethargy and convulsion, or death within 72 hours from onset of treatment (PCAP Guidelines, Philippine Academy of Pediatric Pulmonologist, 2012).[5]

Baseline data were gathered from the patients' history, physical examination and oxygen saturation at room air were recorded using a portable pulse oximeter.

Methodology

After Institutional Review Board (I.R.B.) approval was secured, the investigator conducted an information session with the medical staff of the Department of Pediatrics of the Medical Center, where the objectives, purpose, and method of the study were discussed.

Informed consent was obtained prior to enrollment.

The pediatric resident on duty recruited and screened the patients in the pediatric

emergency room (E.R.) based on the inclusion criteria. The resident then classified the patients as PCAP-C or PCAP-D. When an overlap between the two categories was seen, the presence of a minimum of two clinical variables sufficed to classify the patient to a higher category (PCAP-D from PCAP-C). The same pediatric resident gathered information regarding patient's history and physical examination and laboratory results. The chest radiograph, if requested, was not used as an inclusion criterion since the diagnosis of pneumonia was based on clinical parameters.

Baseline clinical assessment and laboratory work-ups as ordered by the attending physician were performed at the E.R. prior to the administration of the first dose of antibiotics.

Clinical pneumonia was considered in patients with cough and/or respiratory difficulty, plus any of the following predictors: tachypnea in a patient aged 3 months to 5 years, fever at any age or oxygen saturation less than, or equal, to 92% at room air at any age in the absence of any co-existing illness (neurologic, musculoskeletal, or cardiac condition) that may potentially affect oxygenation (PCAP guidelines, 2012). Bacterial pneumonia was considered when the patient had high-grade fever but without wheezing for children less than 2 years old or for those more than two years old, with the following findings: alveolar consolidation on chest x-ray, and elevated serum C-reactive protein (C.R.P.), procalcitonin and/or elevated white blood cell count. The bedside nurse recorded the vital signs every four hours. Supportive therapy such as oxygen supplementation, antipyretics, and treatment with bronchodilators was given, as needed.

All treatment instituted as ordered by the attending physician was noted, whether they were part of the current treatment guidelines for pneumonia or not. Any changes to the current antibiotic treatment made by the attending physician were also recorded.

All patients who were diagnosed to have clinical pneumonia were followed up in the wards or ICU where the principal investigator measured the outcomes of a 72-hour treatment. The status of the patient was also noted on the seventh day of admission or on the day of discharge, whichever came first.

The subjects' clinical characteristics and socio-demographics were summarized in frequency tables using binary logistic regression analysis to determine predictors of antibiotic treatment failure of PCAP-C and PCAP-D. Predictors with a p-value of less than 0.05 on multivariate regression analysis were considered as significant independent predictors of antibiotic treatment failure.

RESULTS

Out of the 138 children admitted for pneumonia during the study period, 100 fulfilled the inclusion criteria and gave consent for the study. Thirty-eight were excluded due to previous antibiotic treatment for the current illness or ongoing treatment for tuberculosis or with concomitant asthma. Out of the 100 subjects, 98 had PCAP-C and 2 had PCAP-D. Sixty-three percent were male and 85% belonged to the middle class. Fifty-seven percent completed pneumococcal vaccination and 86% completed Hib vaccination. Intravenous cefuroxime was the antibiotic of choice for 70% of the patients.

Eighty-three percent had successful treatment outcomes while 17% were treatment failures. Children in the treatment failure group had a mean age of 19.5 months, while those in the treatment success group had a mean age of 22.7 months. Males predominated in both treatment success (61%) and treatment failure groups (71%). Most patients from the treatment failure group (88%) and the treatment success

group (84%) were from the middle class (88%). Breastfeeding rates for treatment failure group were 29% and 27% for treatment success group. Care-seeking delays were not seen in the treatment failure group (94%) and treatment success group (87%). Symptoms suggestive of viral etiology were seen in the treatment failure group (5%) and treatment success group (13%).

A lower pneumococcal vaccine completion rate was seen in the treatment failure group (29%) than the treatment success group (62%). A lower HiB vaccine completion rate was also seen in the treatment failure group (65%) than the treatment success group (90%). However, the differences in immunization rates between the two groups were not found to be statistically significant Oxygen saturation upon admission for the treatment failure group was 92.5% and 95% for the treatment success group.

Diagnostic procedures requested for both groups included chest radiographs and complete blood counts. Mean white blood count for treatment success and treatment failure groups were 10.5 and 9.7, respectively.

Table 1 shows the antibiotics used upon admission. Cefuroxime was the drug of choice for 70% of patients, followed by azithromycin (24%), and amoxicillin-clavulanate (11%).

Table 1. Antibiotics used for pneumonia) (N=100)

Antibiotics	Frequency	Percentage
Cefuroxime	70	70%
Azithromycin	24	24%
Co-amoxiclav	11	11%
Ampicillin-sulbactam	9	9%
Clarithromycin	9	9%
Amikacin	6	6%
Piperacillin-tazobactam	4	4%
Clindamycin	1	1%
Cefotaxime	1	1%

Table 2 shows that in the treatment success group, the antibiotics most commonly used were cefuroxime (50.6%) and a combination of cefuroxime and azithromycin (21%)

Table 2. Antibiotics used in Treatment Success Group (n=83)

Antibiotics	Frequency	Percentage
Cefuroxime	42	50.6%
Cefuroxime + Azithromycin	17	21%
Co-amoxiclav	5	6%
Piperacillin-tazobactam	3	4%
Ampicillin-sulbactam + Clarithromycin	3	4%
Co-amoxiclav + Clarithromycin	3	4%
Azithromycin	2	4%
Cefuroxime + Amikacin	2	4%
Ampicillin-sulbactam + Azithromycin	2	2%
Piperacillin-tazobactam + Azithromycin	1	1%
Ampicillin-sulbactam	1	1%
Ceftriaxone	1	1%
Co-amoxiclav + Amikacin	1	1%

Table 3 shows that in the treatment failure group, the antibiotics most commonly used were cefuroxime (41%) and a combination of ampicillin-sulbactam and clarithromycin (12%). Table 4 shows that persistence of tachypnea (47%), fever (18%) and chest retractions (18%) were the most common reasons for a change of the initial antibiotic regimen. Table 3 shows in those who did not respond to the first line drugs, treatment modifications made were the addition of a macrolide (47%) OR a shift to piperacillin-tazobactam (30%).

Table 3. Antibiotics used in Treatment Failure Group

First line Antibiotics used	Frequency	Percentage
Cefuroxime	7	41%
Cefuroxime + Amikacin	2	12%
Ampicillin-sulbactam + Clarithromycin	2	12%
Ampicillin-sulbactam	1	6%
Azithromycin	1	6%
Co-amoxiclav	1	6%
Co-amoxiclav + Azithromycin	1	6%
Clarithromycin	1	6%
Cefotaxime + Azithromycin	1	6%
Total	17	100%
Second line Antibiotics used	**Frequency**	**Percentage**
Added Azithromycin	5	30%
Added Clarithromycin	1	6%
Added Ampicillin-sulbactam	1	6%
Ampicillin-sulbactam + Amikacin	1	6%
Amikacin + Clarithromycin	1	6%
Cefuroxime	1	6%
Clindamycin	1	6%
Piperacillin-tazobactam + Azithromycin	1	6%
Vancomycin	1	6%
Piperacillin-tazobactam	4	24%
Total	17	100%

Table 4. Reasons for shifting antibiotics

Persistence of the following:	Frequency	Percentage
Tachypnea	8	47%
Fever	3	18%
Retractions	3	18%
Fever + tachypnea	1	6%
Fever + retractions	1	6%
Tachypnea + retractions	1	6%
Total	17	100%

Predictors of first-line antibiotic treatment failure are summarized in table 5a, 5b, and 5c. Using logistics regression analysis, significant predictors of treatment failure were malnutrition and low oxygen saturation upon admission.

DISCUSSION

This prospective cohort study evaluated the antibiotic treatment success and failure rates among patients 2-to-59 months old admitted to a tertiary hospital for PCAP-C and PCAP-D. The antibiotic treatment failure rate was 17%. Among all the variables studied, only malnutrition and hypoxemia upon admission were found to be significantly associated with treatment failure. Treatment failure was assessed and antibiotic regimen was altered due to continued tachypnea (47%), fever (18%) and chest retractions (18%). Though differences in pneumococcal (63% vs 29%) and Hib (40% vs 65%) vaccinations were seen among the treatment success and treatment failure groups, the differences were not statistically significant. The most common initial regimens used were cefuroxime and a combination of cefuroxime and amikacin. When treatment failure was assessed adjustments in the treatment made were the addition of a macrolide (47%) and a shift to a very broad-spectrum agent, piperacillin-tazobactam (29%). No specific antibiotic was found to be significantly associated with treatment failure.

Malnutrition was the strongest predictor of treatment failure. This is consistent with a case-control study by Jain, *et al*, where cefotaxime for infants and intravenous ampicillin for older children were used, which showed malnutrition to be the strongest predictor of treatment failure.[2] In a two-year longitudinal community-based study in Muntinlupa, Tupasi, *et al,* found that among children less than 5 years old, malnutrition, household crowding, parental smoking, and age less than 2 years were statistically associated with an increase in morbidity due to acute respiratory infection.[6]

Table 5a. Logistic regression analysis of predictors of treatment failure

		Odds Ratio	95% Confidence Interval		P-value
			Lower Bound	Upper Bound	
Age *(Mean, SD)*		0.999	0.947	1.054	0.977
Gender	Female	0.598	0.135	2.647	0.498
	Male	C			
Immunization status (Pneumococcal)	Complete	0.310	0.057	1.700	0.177
	Incomplete	1.666	0.161	17.255	0.669
	None	C			
Immunization status (Hib)	Complete	0.095	0.007	1.222	0.071
	Incomplete	0.280	0.017	4.521	0.370
	None	C			
Presence of other symptoms suggestive of viral etiology	Yes	0.729	0.068	7.841	0.794
	No	C			
Exclusively breastfed (at least 6 months)	Yes	3.763	0.748	18.940	0.108
	No	C			
Presence of care seeking delays (more than 3 days)	No	0.387	0.082	1.827	0.231
	Yes	C			
Socioeconomic status	Middle	5.211	0.489	55.532	0.171
	Upper	C			

Table 5b. Logistic regression analysis of predictors of treatment failure

		95% Confidence Interval		
	Odds ratio	Lower bound	Upper bound	P-value
Oxygen (Mean, SD)	0.836	0.706	0.989	0.037
Respiratory Rate (Mean, SD)	0.468	0.902	1.048	0.973
Malnutrition Yes No	6.253	1.128	34.673	0.036

Table 5c. Logistic regression analysis of predictors of treatment failure

Antibiotics	Odds ratio	P-value	Interpretation
Ceftriaxone	3.39E+09	1.000	Not significant
Piperacillin-tazobactam	2.15E+09	0.999	Not significant
Cefuroxime	20.709	0.065	Not significant
Co-amoxiclav	11.272	0.141	Not significant
Azithromycin	5.772	0.225	Not significant
Ampicillin-sulbactam	4.473	0.356	Not significant
Clarithromycin	1.012	1.000	Not significant
Amikacin	0.772	0.84	Not significant
Cefotaxime	1.98E-08	1.0	Not significant

A local study on fatal childhood pneumonia found that 32% of children, 86% of whom were infants, who died were undernourished. [7] A recent prospective observational study by Christi, *et al,* showed that among severely malnourished children, the range of bacterial pathogens causing pneumonia is different from the usual pathogens; gram-negative bacteria play a more significant role and are associated with higher mortality. [8] Such gram-negative organisms causing severe pneumonia were often resistant to penicillin, ampicillin, and gentamicin. Severely malnourished children were immunocompromised and might fail to show overt clinical signs of pneumonia due to depressed cell-mediated and humoral response.

Hypoxemia at baseline was also a significant predictor of treatment failure. Sudha, *et al*, in Nepal reported that among children 2-to-35 months, hypoxemia (defined as $\leq$ 90% oxygen saturation) upon admission, younger age, and radiographic consolidation were predictors of treatment failure. [9]

Although this study did not determine specific etiologies of pneumonia, hypoxemia is known to be commonly caused by *Streptococcus*

pneumoniae. This organism is widely considered to be the most common cause of community-acquired bacterial pneumonia. In this study, only 62% of the treatment success group and 29% from the treatment failure group completed pneumococcal vaccination. Although the difference was not statistically significant, this may potentially explain the significantly higher pulse oximetry reading in the treatment success group.

In this study, chest radiography had no role in the initial diagnosis of pneumonia. Nevertheless, radiographic findings were noted, and the majority had bronchopneumonia, followed by lobar infiltrates. In a two-year prospective longitudinal study done in Nepal, lobar consolidation was found to be an independent predictor of treatment failure at 48 hours, especially among penicillin recipients. [9]

When the initial regimen was assessed to be failing, the addition of a macrolide in 47% was the most common adjustment in treatment made. A local prospective study involving 82 in-patients, aged less than 5 years with pediatric community-acquired pneumonia, found that 26% of the sampled children had *Mycoplasma pneumonia infection* based on serologic testing. Among the patients who were mycoplasma IgM-positive, 100% were febrile and coughing, 24% were tachypneic, and 24% were hypoxemic upon admission. [10] In an earlier (2000) unpublished local retrospective study involving 58 children aged 1-18 years with community-acquired pneumonia admitted at Cardinal Santos Medical Center, 22% tested positive for mycoplasma IgM serology. [11] In a similar unpublished local retrospective study on 21 children aged 1-18 years with community-acquired pneumonia admitted at Makati Medical Center, 28% had a positive test for mycoplasma IgM serology; 100% of the mycoplasma IgM-positive patients were febrile and coughing.[12] These local data show that 22% to 28% of children with community-acquired pneumonia may have *Mycoplasma pneumoniae* as the pathogen, which justifies the addition of a macrolide when fever and/or tachypnea did not resolve despite initial antibiotic treatment.

Continued fever in 18% of children in the treatment failure group was a reason for a change in antimicrobial regimen. One probable reason for continued fever is if there are co-pathogens, particularly viruses causing the fever. In a prospective longitudinal cohort study involving 1,978 children less than 5 years old in Muntinlupa, it was found that among the 311 children who developed pneumonia, 33% were infected with a virus, respiratory syncytial virus (12.9%), parainfluenza (5.1%) and adenovirus (3.5%) being the most common causes. [6] However, our study cannot definitely identify viruses as a possible cause of the subjects' pneumonia, as no effort was made to identify specific bacterial or viral pathogens.

Our study indicated that no specific antibiotic was found to be significantly associated with treatment failure. According to the 2015 data gathered from the antimicrobial reference laboratory at the Research Institute for Tropical Medicine, 7.6%, 5%, and 0% of *S. pneumonia*e isolates collected from 22 sentinel hospitals nationwide were resistant to penicillin, erythromycin, and ceftriaxone, respectively. For *Haemophilus influenzae*, 8.9%, 3.4%, and 0% were resistant to ampicillin, ampicillin-sulbactam, and azithromycin, respectively. [13] With these relatively low resistance rates of presumed common respiratory bacterial pathogens, all antibiotic treatment given in the study subjects are adequate to treat the bacterial pathogens known to cause pneumonia.

CONCLUSION

The antibiotic treatment failure rate in patients with PCAP-C was 17%. Malnutrition and

hypoxia at baseline were significant predictors of antibiotic treatment failure in children with PCAP-C.

RECOMMENDATIONS

The use of pulse oximeter is a simple, cost-effective way to determine children at risk for treatment failure. This study recommends measurement of oxygen saturation and should always be done in children diagnosed to have pneumonia.

This study also recommends etiologic investigations for pneumonia e.g. viral agents such as influenza and RSV and serologic testing for Mycoplasma to determine the cause of continued fever and tachypnea especially in patients unresponsive to treatment.

LIMITATION

Because there are only two cases of PCAP-D, we are unable to give any significant conclusions about this group.

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